EU RMP	
Drug Substance	Dapagliflozin
Version Number	32
Succession Number	1
Data lock point	15 October 2025
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for FORXIGA™, EDISTRIDE™ (dapagliflozin)

The content of this RMP has been reviewed and approved by the QPPV.

Administrative Information

Rationale for submitting an updated RMP:

Completion of Cancer Post-Authorisation Safety Study (PASS) - D1690R00007: Comparison of the Risk of Cancer Between Patients with Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments (hereafter, the study is referred to as the 'Cancer PASS' in this document) and subsequent removal of important potential risks i.e. breast cancer, bladder cancer and prostate cancer, from the RMP.

Summary of significant changes in this RMP:

Part II Module SV
Post-authorisation exposure data updated.

Part II Module SVII
Important potential risks breast cancer, bladder cancer and prostate cancer are removed.

Part II Module SVIII
Important potential risks breast cancer, bladder cancer and prostate cancer are removed.

Part III
AE follow-up questionnaires for spontaneous reports of breast cancer, bladder cancer and prostate cancer are removed.
Additional pharmacovigilance activities: Cancer PASS removed.

Part V
Important potential risks breast cancer, bladder cancer and prostate cancer are removed.

Part VI
Important potential risks breast cancer, bladder cancer and prostate cancer are removed.
Cancer PASS completed and removed from the Post-authorisation Development plan.

Part VII
Annexes 2, 3, 4 and 8 updated based on the changes made in the body of the RMP

Other RMP versions under evaluation	Not applicable
Details of currently approved RMP	**Version Number:** v 31 **Assessment report date:** 05 September 2024 **Procedure number:** EMEA/H/C/2322/WS2733 (FORXIGA) EMEA/H/C/4161/WS2733 (EDISTRIDE)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
30-MSU	30 Month safety update
ACEi	Angiotensin-converting enzyme inhibitor
ADR	Adverse drug reaction
AE	Adverse event
AKI	Acute kidney injury
ALI	Acute liver injury
ARB	Angiotensin receptor blocker
aRMM	Additional Risk minimisation measure
ASIR	Age Standardised Incidence Rates
aTRH	apparent treatment-resistant hypertension
AUC	Area under the curve
BBN	N-butyl-N-(4-hydroxybutyl)-nitrosamine
CI	Confidence interval
CKD	Chronic kidney disease
C_{max}	Maximum plasma drug concentrations
COPD	Chronic obstructive pulmonary disease
CPN	Chronic progressive nephropathy
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
DALY	Disability adjusted life years
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease
DM	Diabetes Mellitus
eGFR	Estimated glomerular filtration rate (unit: mL/min/1.73 m^2)
EMA	European medicines agency
EPAR	European Public Assessment Report
ESRD	End-stage renal disease
EU	European union
GFR	Glomerular filtration rate
HIRD	Healthcare Integrated Research Database
HF	Heart failure
HfrEF	Heart Failure with reduced Ejection Fraction
IP	Investigational Product

Abbreviation/ Special term	Definition/Explanation
IRR	Incidence Rate Ratio
LT	Long-term
LVEF	Left ventricular ejection fraction
MRHD	Maximum recommended human dose
N	Number
NYHA	New York Heart Association
PASS	Post Authorisation Safety Study
PHARMO	PHARMO Data Network of the PHARMO Institute, part of Lumanity (the Netherlands)
PND	Postnatal day
PPV	Positive Predictive Value
PT	Preferred Term
PV	Pharmacovigilance
PY	Person-years
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious adverse event
SGLT2	Sodium glucose co-transporter 2
SGLT2i	Sodium glucose co-transporter 2 inhibitor
SmPC	Summary of Product Characteristics
ST	Short-term
SU	Sulphonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TCC	Transitional cell carcinoma
UACR	Urine Albumin-to-Creatinine Ratio
US	United States
UTI	Urinary tract infection

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Dapagliflozin
Pharmacotherapeutic group(s) (ATC Code)	A10BK01
Marketing Authorisation Holder	AstraZeneca AB
Medicinal products to which this RMP refers	1
Invented names in the European Economic Area (EEA)	FORXIGA, EDISTRIDE
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Human renal sodium-glucose co-transporter 2 (SGLT2) inhibitor
	Summary of mode of action: Dapagliflozin is a highly potent, selective, and reversible SGLT2 inhibitor. Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and diastolic function, and preserve renal function. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF, DELIVER and DAPA-CKD studies. Other effects include an increase in haematocrit and reduction in body weight. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose dapagliflozin has a low propensity to

Table I-1 Product Overview

	cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin. The SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	FORXIGA/EDISTRIDE Summary of Product Characteristics
Indications in the EEA	**Current:** <u>Type 2 diabetes mellitus</u> FORXIGA/EDISTRIDE is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: – as monotherapy when metformin is considered inappropriate due to intolerance. – in addition to other medicinal products for the treatment of type 2 diabetes. For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied see sections 4.4, 4.5 and 5.1 in SmPC. <u>Heart failure</u> FORXIGA/EDISTRIDE is indicated in adults for the treatment of symptomatic chronic heart failure. <u>Chronic kidney disease</u> FORXIGA/EDISTRIDE is indicated in adults for the treatment of chronic kidney disease.
	Proposed: Not applicable

Table I-1 Product Overview

Dosage in the EEA	**Current:** Tablets 5 mg and 10 mg
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Dapagliflozin propanediol 5 mg tablets are yellow, biconvex, round, film-coated tablets with "5" debossed on one side and "1427" debossed on the other side. Dapagliflozin propanediol 10 mg tablets are yellow, biconvex, diamond-shaped, film-coated tablets with "10" debossed on one side and "1428" debossed on the other side.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

II.1.1 Type 2 diabetes mellitus

Incidence

Determining the annual incidence of T2DM is challenging due to a high rate of undiagnosed cases (IDF Diabetes atlas 2021). Nevertheless, the estimated incidence of diabetes mellitus (DM) in the adult population has increased by more than 100% from 1990 to 2017, while the age standardised incidence rates (ASIR) increased from 2.34 to 2.85/1000 persons during the same period (Liu et al 2020). In the European region the ASIR of DM in 2017 ranged between 2.5 and 3.1/1000 persons (Liu et al 2020). According to the CDC report, the incidence of DM in the US population during 2018-2019 was 5.9/1000 persons (CDC 2023).

In the paediatric population, countries with a high incidence of T2DM in 2021 included China (7.35/1000) and India (3.97/1000), while Germany had the lowest incidence (0.001/1000) (Wu et al 2022).

Prevalence

T2DM is the most common form of diabetes, accounting for approximately 90% of all diabetes diagnoses. In 2021, one in every 10 adults (aged 20-79 years), estimated as 537 million globally, had diabetes mellitus. This number is projected to reach 643 million by 2030, and 783 million by 2045. An estimated 44% of adults living with diabetes (240 million people, overwhelmingly T2DM) in 2021 were undiagnosed (IDF Diabetes atlas 2021).

The prevalence of T2DM in the population aged 10 - 19 years in 2017 was 0.67/1000 persons (Perng et al 2023). Globally, the T2DM prevalence is reported to be highest among adolescents in Brazil (33 per 1000) and lowest in Denmark and Germany (0.06 and 0.01 per 1000, respectively). England and Wales had a prevalence of 2.9 per 1000 (Perng et al 2023, IDF Diabetes atlas 2021). However, comparisons should be made with caution as the population and the diagnostic criteria were not identical across the studies.

Demographics of the population in the authorised indication and risk factors for the disease

Over two-thirds of people with diabetes live in urban areas and three out of four are of working age (20 to 65 years). In 2021, 360 million people with diabetes lived in urban areas, whereas 177 million lived in rural areas – the prevalence in urban areas being 12.1% and in rural areas 8.3%. The prevalence of diabetes among urban population is expected to increase to nearly 600 million in 2045 (13.9%), which is primarily driven by global urbanisation and aging population (IDF Diabetes atlas 2021). It is estimated that 81% of patients with diabetes mellitus live in low- and middle-income countries. In 2021, there were about 17.7 million more men than women living with diabetes mellitus. The prevalence of diabetes is expected to increase in both genders.

In the US population under the age of 20 years, T2DM is more prevalent among African Americans than in American Indian/Hispanic/non-Hispanic white (1.80 vs. 1.63/1.03/0.20 per 1000, respectively), with a female predominance across all races (0.82 vs. 0.51 per 1000) (Perng et al 2023). Similar female predominance in the incidence of T2DM among youth was also observed worldwide including in EU the region (IDF Diabetes atlas 2021).

The causes of T2DM are not completely understood but there is a strong link with overweight and obesity, and increasing age, as well as with ethnicity and family history. T2DM results from a combination of multi-gene predisposition and environmental triggers. T2DM is increasingly seen in children and younger adults owing to rising levels of obesity, physical inactivity and inappropriate diet (IDF Diabetes atlas 2021).

The main existing treatment options

Management of T2DM is aimed at achieving glycaemic control and minimizing cardiovascular risk factors. These include healthy lifestyle, promoting healthy diet, regular physical activity, healthy body weight, avoidance of risk behaviour, e.g., smoking and alcohol abuse, and medication if the recommended metabolic target is not achieved (ElSayed et al 2023).

Antidiabetic medications treat T2DM by lowering glucose levels in the blood. There are different classes of antidiabetic drugs, which include but are not limited to insulin, biguanides (metformin), thiazolidinediones, sulphonylureas (SUs), alpha-glucosidase inhibitors,

dipeptidyl peptidase-4 inhibitors, SGLT2 inhibitors, and glucagon-like peptide-1 receptor agonists (ADA 2022). Most patients eventually require a combination of agents to achieve glycaemic targets (Matthews et al 2019, Prattichizzo et al 2020).

While there is a wide array of glucose-lowering medications approved for adults with T2DM, children and adolescents have limited options with insulin and metformin being the first drugs approved for children. Subsequently, injectable glucagon-like peptide-1 receptor agonists (GLP-1 RA) liraglutide, exenatide and dulaglutide have been approved for use in children 10 years of age or older by the U.S. Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) (Shehadeh et al 2023, Wu et al 2022). Oral SGLT2 inhibitor dapagliflozin has also been recommended for children ≥10 years of age with uncontrolled T2DM by the EMA (Tamborlane et al 2022). More recently, empagliflozin was approved by both US FDA and EMA and the empagliflozin/metformin FDC by US FDA for children ≥10 years of age.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

T2DM is a progressive disease and contributes to serious comorbid conditions. Macrovascular and microvascular complications arising from diabetes include cardiovascular disease, diabetic nephropathy, peripheral neuropathy, retinopathy (blindness), and amputation. Worldwide, diabetes is the fourteenth largest cause of disability adjusted life years (DALYs), accounting for about 2.8% of global DALYs in 2019 (GBD 2019: Diseases and Injuries Collaborators).

Diabetes increases the risk of mortality nearly two-fold and is associated with mean reduction in life expectancy of approximately 8 years in both men and women. In 2021, global mortality attributable to diabetes in the adult population aged 20 to 79 years was estimated at 6.7 million (IDF Diabetes atlas 2021). Currently, there are no population-based estimates of T2DM mortality in children or adolescents, however, T2DM in this age range is more aggressive than T1DM. Short-term mortality was found to be 1.5 times higher among the T2DM paediatric patients compared to their peers with T1DM over a follow-up of nearly 9 years (Perng et al 2023).

Important co-morbidities

The aetiology and natural history of T2DM is complex and it shares risk factors with cardiovascular and kidney diseases, so it can be difficult to distinguish whether associated conditions are risk factors, complications, or co-morbidities. Multiple chronic conditions are highly prevalent among patients with T2DM, nearly 40% have 3 or more comorbid conditions (Lin et al 2015). Hypertension, hyperlipidaemia, and obesity are very prevalent in adults with T2DM (Lin et al 2015, Reach et al 2013).

Heart failure is more common in the T2DM population than in those without, perhaps due in part to the high prevalence of hypertension and kidney disease in T2DM patients. Non-alcoholic fatty liver disease can arise due to metabolic disruptions associated with T2DM. As T2DM prevalence increases with age, other common diseases associated with increased age, such as COPD, arthritis, and cancers, are co-morbidities (Chen and Tseng 2013, Lin et al 2015).

Many of the co-morbidities and complications present in adults with T2DM are also present in children with T2DM. Co-morbidities in children with T2DM include hypertension, dyslipidaemia, nephropathy, non-alcoholic fatty acid liver disease, obstructive sleep apnoea, polycystic ovary syndrome, retinopathy, neuropathy, and mental health disorders (e.g., depression and disordered eating) (Shah et al 2022).

II.1.2 Heart Failure

Incidence

The incidence of heart failure (HF) varies widely ranging between 1 and 9 per 1000 person-years (PY) (Savarese et al 2022), with incidences of 3 to 5 per 1000 PY in Europe and 2.2 per 1000 in the US (McDonagh et al 2021). The age-adjusted incidence of HF in high income countries is stable or declining, reflecting better management, however, the overall incidence is increasing due to the ageing population (Groenewegen et al 2020, McDonagh et al 2021). Over the last 2 decades, the incidence of HF with LVEF < 40% has slightly decreased, while HF with LVEF > 40% was shown to increase (Tsao et al 2018). Nearly half of the incident HF-related hospitalisation in the US are attributed to HF with LVEF > 40 % (Benjamin et al 2019).

Prevalence

Over 64 million people, approximately 1% to 2% of the general adult population, are affected by HF worldwide (Groenewegen et al 2020, McDonagh et al 2021). The prevalence is increasing due to the aging population, global population growth, and better survival following diagnosis (Groenewegen et al 2020). Of all hospitalisations worldwide, 1% to 2% are due to HF (Groenewegen et al 2020) and readmissions are common (Cheng et al 2014, Cui et al 2020).

Demographics of the population in the authorised indication and risk factors for the disease

Both incidence and prevalence of HF increase with advancing age (Odegaard et al 2020, McDonagh et al 2021). Elderly women are overrepresented among patients with HF and LVEF > 40% (Romiti et al 2022), whereas HF with LVEF < 40% is more common in younger men (Lam et al 2019). US studies have reported a higher incidence of HF in African-

American patients, followed by Spanish-American, Caucasians, and Chinese-American patients (Tsao et al 2022).

The main existing treatment options

The current European and US guidelines recommend different treatment paradigms for HF across the LVEF spectrum (Heidenreich et al 2022, McDonagh et al 2021). Recommended treatment of HF with LVEF < 40% with effects on mortality and HF events includes 4 classes: renin-angiotensin system inhibitors, beta blockers, mineralocorticoid receptor antagonists, and SGLT2i (Heidenreich et al 2022, McDonagh et al 2021), where SGLT2i is recommended to reduce hospitalisation and cardiovascular mortality in symptomatic patients with chronic LVEF < 40% , regardless of the presence of T2DM.

The US guideline includes a new moderate (class IIa) recommendation for SGLT2i in patients with HF and LVEF >40% (Heidenreich et al 2022), but the European guideline does not yet include SGLT2i for this HF subpopulation (McDonagh et al 2021). Unlike the US guideline, the European guideline recommends SGLT2i in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalisations (McDonagh et al 2021).

Management of HF with LVEF > 40% is directed towards comorbidities and risk factors for development of HF, underlying cardiovascular disease, and symptomatic treatment of volume overload (Heidenreich et al 2022, McDonagh et al 2021).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

HF is a common, chronic, progressive disease, and despite substantial improvements in HF diagnosis over the last few decades, the overall prognosis remains poor with reduced quality of life, high healthcare consumption, and high mortality, with an estimated 5-year mortality rate after diagnosis of 50% (McDonagh et al 2021).

Studies among hospitalised patients with HF indicate a decline in rehospitalisation and mortality rates over the last 4 decades (Kimmoun et al 2021). However, the absolute number of hospital admissions for HF is expected to increase by approximately 50% in the next 25 years due to population growth, ageing, better survival, and the increasing prevalence of co-morbidities (Savarese and Lund 2017).

Important co-morbidities

Multimorbidity is a common feature in patients with HF, with over 85% of the patients having 2 or more co-morbid chronic conditions (Heidenreich et al 2022). In a recent systematic review, the most commonly recorded major comorbid disorders were hypertension, ischaemic heart disease, hyperlipidaemia, diabetes, chronic kidney disease and atrial fibrillation (Khan et al 2020). Co-morbidities are major contributors to high hospitalisation rates (Streng et al 2018,

Savarese et al 2022), with an 1.5 times higher risk in patients with diabetes, atrial fibrillation, obesity, and chronic kidney disease (CKD) (Mosterd and Hoes 2007). Women have a higher prevalence of co-morbidities leading to higher hospitalisation rates (Lawson et al 2019).

Patients with HF and LVEF < 40% are more likely to have ischemic cardiovascular co-morbidities, whereas patients with LVEF > 40% have a higher prevalence of atrial fibrillation, hypertension, and non-CV comorbidities (eg diabetes, obesity, and CKD) (Savarese and Lund 2017, McDonagh et al 2021).

II.1.3 Chronic Kidney Disease (CKD)

Incidence

The global incidence of CKD in 2016 was > 21 million (Xie et al 2018). The global incidence rate of stage 3 to 5 CKD was estimated at 288.53/100000 people (95% UI: 258.38, 319.24) in 2016 (310.13/100000 people when age-standardised) (Xie et al 2018). Despite increasing interest in the burden of CKD worldwide, there is evidence that a substantial number of CKD cases remain undiagnosed leading to underestimation of the true burden of disease (Bakris 2019; Hirst et al 2020; Wong et al 2018).

Prevalence

The global prevalence of stage 1–5 CKD has been reported as between 9.1 to 13.4% (GBD Chronic Kidney Disease Collaboration 2020; Hill et al 2016), and age-standardised prevalence for Central, Eastern and Western Europe was reported as 7.6%, 12.4%, and 5.4% respectively (GBD Chronic Kidney Disease Collaboration 2020). The prevalence of stage 3–5 CKD was estimated as 10.6% in 2016, translating into > 275 million cases globally (Hill et al 2016, Xie et al 2018).

Prevalence estimates for each stage of CKD vary, but the majority of patients with diagnosed CKD have early-stage disease, with a much lower proportion of patients progressing to kidney failure. For example, the global prevalence of stage 3 CKD (eGFR 30–59ml/min/1.73 m^2) is estimated to be between 3.6% to 7.6%, whereas estimates of the global prevalence of stage 5 CKD (eGFR < 15 ml/min/1.73 m^2) range from 0.1% to0.7% (GBD Chronic Kidney Disease Collaboration 2020, Hill et al 2016)

A 2020 systematic review identified ten studies across the USA, China, France, Italy and Spain that classified patients according to both GFR and albuminuria status (Murton et al 2021). Of patients with CKD stage 2–5, the prevalence of individuals with albuminuria stage A1 (UACR < 30 mg/g) was 27.4% to 56.4%, A2 (UACR 30 to 300 mg/g) was 2.9% to 10.0%, and A3 (UACR > 300 mg/g) was 0.4% to 3.2% (Murton et al 2021).

Demographics of the population in the authorised indication and risk factors for the disease

The prevalence of CKD increases with advancing age with a reported prevalence of 13.7% in those aged 30 to 39 years up to 34.3% for those aged 70 to 79 years (Hill et al 2016). The proportion of CKD prevalence is highest between the sixth and seventh decade of life (Xie et al 2018).

Whilst the prevalence of CKD tends to be higher in women, men experience more severe disease. For instance, a recent global burden of disease study reported a 1.3-fold higher age-standardised CKD prevalence among females than males, however, age-standardised incidence of dialysis and transplantation was 47% higher in males than females and age-standardised CKD mortality was 39% higher in males than females (GBD Chronic Kidney Disease Collaboration 2020).

Finally, CKD is more common in blacks than in whites, non-Hispanic Asians and Hispanics (Centers for Disease Control and Prevention 2020). Another study reported that Black Americans experienced a disproportionate burden of ESRD in United States with the risk of ESRD up to 5 times those of age-adjusted white counterparts, despite comparable rate of for early stage of CKD (Hsu et al 2003).

The main existing treatment options

Blockade of the angiotensin system with ACEi or ARB represents the mainstay of standard of care treatment for CKD in patients with T2DM and without diabetes. Cardiovascular risk and glycaemic control are pharmaceutically managed as necessary within this patient group (Inker et al 2014).

Recently, a member of the SGLT2 inhibitor class, canagliflozin, demonstrated a 30% cardiorenal risk reduction and a 34% risk reduction for renal adverse events in patients with diabetic nephropathy (Perkovic et al 2019). Following positive EMA (June 2020) assessment of phase III CREDENCE study, the canagliflozin product labelling has been extended to include evidence of canagliflozin's treatment benefits in treatment of DKD with T2DM patients.

Interventional studies assessing the use of ACEi or ARB for the treatment of diabetic kidney disease (DKD) (Lewis et al 2001, Brenner et al 2001) or SGLT2 inhibition on top of standard of care in patients with DKD (Perkovic et al 2019) indicate that patients treated with ACEi or ARB remain at risk of morbidity, mortality, and progression to ESRD. Additionally, a significant proportion of patients with CKD treated with standard of care (23% of patients with diabetes; 15% of patients without diabetes) display accelerated disease progression (decline in eGFR of > 4 mL/min/1.73 m^2 per year) (Go et al 2018).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The progression of CKD can be quantified using measures of changing eGFR and albuminuria over time, which describe the transition of patients with CKD between CKD stages. Patients with CKD are at increased risk of CV events, particularly as CKD progresses to later stages, and this is associated with a significant increase in mortality compared to the general population. For example, two 2016 meta-analyses reported that patients with CKD (eGFR < 60ml/min/1.73m^2) are at increased risk of both new-onset atrial fibrillation (HR 1.47 [95% CI, 1.21–1.78]) (Shang et al 2016) and myocardial infarction (relative risk 1.52 [95% CI 1.39 to 1.67] p = 0.00001), compared to the general population (Vashistha et al 2016). A 2019 systematic literature review identified 18 studies that quantified the risk of CV morbidity (myocardial infarction, stroke and heart failure) by CKD stage, and demonstrated that the risk of CV morbidity increases with both CKD stage and albuminuria progression; patients with stage 5 CKD and macroalbuminuria were shown to have an 11.4-fold increased risk of CV morbidity compared to patients with stage 1 CKD and normoalbuminuria (AstraZeneca 2019).

Patients with CKD are at a higher risk for CV-related and all-cause mortality compared to the general population. In 2017, CKD was associated with an age-standardised mortality rate of 15.9/100000 population (Hill et al 2016). A meta-analysis compiling data from 39 studies found that the relative risk for mortality in those with reduced kidney function, compared to those without, was significantly increased in 93% of cohorts (71% when adjusted for other established risk factors) (Tonelli et al 2006). Where suitable data were available, mortality risk increased exponentially with decreasing renal function (Tonelli et al 2006). All-cause mortality has been shown to increase with CKD stage; this is likely because patients at later stages of CKD have a greater number of, or more advanced, comorbidities.

Important comorbidities

CKD patients have high prevalence of hypertension (48-66%), diabetes (17% to 33%), ischemic heart disease (2% to 23%), hyperlipidaemia (11%), cerebrovascular disease (6% to 12%), heart failure (1% to3.5%) (Fraser et al 2015, Lee et al 2018, Tuttle et al 2019), however, data on the prevalence of CKD comorbidities according to the KDIGO 2012 categories are limited. Overall, the prevalence of comorbidities increases with albuminuria severity. In a Spanish hypertensive cohort, the prevalence of diabetes was higher in patients with CKD that had greater albuminuria severity; among patients with eGFR < 60mL/min/1.73 m^2, diabetes was present in 26%, 43%, and 53% of individuals with normoalbuminuria, microalbuminuria and macroalbuminuria, respectively (Ruiz-Hurtado et al 2016). In a French CKD cohort, the proportion of patients with atherosclerotic CV disease was higher in microalbuminuric (30.9%) and macroalbuminuric (34.4%) than normoalbuminuric (28.5%) patients (Villain et al 2020). In an analysis of US hypertensive patients, the prevalence of apparent treatment-resistant hypertension (aTRH) was found to increase with both worsening

GFR status and increasing albuminuria severity. In hypertensive patients with eGFR 45 to 59 mL/min/1.73 m^2, the prevalence of aTRH was 17.2%, 26.9%, 32.2% and 50.7% in groups with UACR < 10, 10 to 29, 30 to 299 and ≥ 300 mg/g, respectively. In those with eGFR < 45 mL/min/1.73 m^2, the corresponding figures were 22.5%, 24.5%, 32.8%, and 56.4% (Tanner et al 2013). Finally, a 2020 analysis of the US DISCOVER-CKD study found that patients with an eGFR of 25 to 75 ml/min/1.73 m^2 and an elevated UACR (200 to 5000 mg/g) had a higher prevalence of comorbidities such as T2DM, heart failure and hypertension compared to the overall cohort of patients with stage 3 to 5 CKD or kidney failure (Garcia Sanchez et al 2020).

II.2 MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of key findings from nonclinical data

Toxicity

Reproductive and Developmental toxicity: In rats, both maternal and developmental toxicities were observed at ≥ 2300x the maximum recommended human dose (MRHD). Maternal toxicity included mortality. Developmental toxicity consisted of increased embryo foetal lethality, reduced foetal body weights, and increased incidences of foetal malformations and skeletal variations. Based upon the exposure multiples, these effects are not considered relevant to humans.

Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, at a dose associated with maternal dapagliflozin exposures of 1415x MRHD. Additional findings included dose-related reductions in pup body weights at maternal dapagliflozin exposures of ≥ 249x MRHD. In a follow-up study in lactating pups, renal pelvic dilatation was associated with pup dapagliflozin exposures of 138x MRHD and dose-related reductions in pup body weights were observed at pup exposures ≥ 29x MRHD. These results suggest that lactational exposure to dapagliflozin affected renal maturation in rats.

Lactational exposure of dapagliflozin to weanling rats was also associated with glucosuria and reduced weight gain. In contrast to adult rats, new-born rats presumably lack compensatory fat stores and muscle mass with which to counter this increased excretion of glucose. Therefore, there is a risk that dapagliflozin could reduce weight gain in nursing infants whose mothers take dapagliflozin.

In a juvenile toxicity study, with dapagliflozin dosed to young rats from postnatal day (PND) 21 until PND 90, renal pelvic and tubular dilatations were observed at all dose levels; pup exposures at the lowest dose tested were ≥ 15x the MRHD. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the 1- month recovery period. Consequently, administration of dapagliflozin to weanling juvenile

rats and indirect exposure during late pregnancy are associated with renal pelvic and tubular dilatations in progeny, although the long-term (LT) functional consequences of these effects are unknown. Since human anatomic renal maturation occurs in the second and third trimesters of pregnancy while functional maturation continues for the first 2 years of age, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats is a potential risk for human renal maturation.

Dapagliflozin is secreted in milk in lactating rats, but it is not known whether it is secreted in human milk. The negative effects on body weight gain associated with lactational exposures in the rat suggest that dapagliflozin should be avoided in lactating mothers during the first 2 years of life.

Nephrotoxicity: In the 6-month study in rats, cortical and medullary tubular dilatation, medullary tubular reactive hyperplasia with mineralisation, and urothelial hyperplasia were observed at the high dose (≥ 2100x MRHD). In addition, minimal to slight tubular cysts and exacerbated chronic progressive nephropathy (CPN) were observed in high-dose female rats. After a recovery period, exacerbation of CPN persisted in female rats, but there were no other renal lesions. The renal lesions in rats do not represent a safety concern for humans.

Other toxicity-related information or data as applicable

Genotoxicity: Dapagliflozin was negative in the Ames mutagenicity assay and was positive in an *in vitro* clastogenicity assay but only in the presence of S9 activation and at concentrations ≥ 100 μg/mL. Importantly, dapagliflozin was negative when tested in vivo in rats at exposure multiples >2100x the MRHD. In these studies, the estimated or measured maximum plasma drug concentrations (C_{max}) approached or exceeded the 100 μg/mL level that produced cytogenetic alterations *in vitro*. Because *in vitro* cytogenetics assays are only intended to assist in hazard identification, while *in vivo* cytogenetics studies are used to confirm risk assessment, the weight of evidence supports that dapagliflozin is not genotoxic.

Carcinogenicity: An integrated review of the nonclinical data from the dapagliflozin programme, with additional perspective from the literature, was conducted to assess the biological plausibility and/or potential linkages between dapagliflozin and malignant tumours, especially bladder cancer.

There is no evidence that SGLT2 inhibition or dapagliflozin is a tumour initiator

- Dapagliflozin is not mutagenic and not clastogenic in vivo.
- Dapagliflozin did not induce tumours in 2-year rodent carcinogenicity studies. There were no urinary bladder tumours observed in these carcinogenicity studies.

- Dapagliflozin is highly selective for SGTL2 and there is no evidence for a linkage between its pharmacologic target or its mechanism of action (MOA) and an increased risk of tumours. SGLT2 is not expressed in either bladder or breast tissue.
- In a 15-month phenotyping study, there was no evidence of any difference in survival, body weights, clinical pathology parameters, or histopathologic findings observed between SGLT2 knockout mice and their wild-type counterparts. Despite a lifetime of glucosuria, there was no evidence of any alterations of renal function or proliferative changes observed in the kidneys or urinary bladders of SGLT2 knockout mice. This data strongly suggests that high levels of urinary glucose does not induce urinary tract tumours or accelerate age-related urinary tract pathology.

There is no evidence that dapagliflozin functions as a tumour promoter

- There were no increases in incidence or shortening of the latency period of background tumours following dapagliflozin administration relative to controls in either the mouse or rat 2-year carcinogenicity studies. This data supports our contention that dapagliflozin is not functioning as a non-specific tumour promoter in rodents.
- Risk factors for tumour promotion particularly for bladder tumours include, but are not limited to, immunosuppression, perturbations of hormonal balance, alterations in urinary pH and/or urinary composition leading to crystalluria and bladder irritation, cytotoxicity, local infection, inflammation, and/or cell proliferation. The common theme is interruption of intercellular communication and/or induction of cell proliferation acting as a stimulus for tumour promotion (Trosko et al 1983). Dapagliflozin was not associated with any of the above, except for a low incidence of inflammatory effects in chronic studies in rats and dogs, which did not translate to neoplastic changes.
- Tumour promotion typically occurs through increases in cell proliferation, but no hyperplastic or proliferative changes attributable to dapagliflozin were observed in the bladder (or any other tissue) in any of the toxicity studies, including 2-year rodent carcinogenicity studies (> 100× the MRHD) and a 12-month dog toxicity study (> 3000× the MRHD). The dog has been considered to be particularly sensitive to urinary bladder tumours (Clayson and Cooper 1970); thus, the absence of any hyperplastic changes at exposures that significantly exceeded human exposures strongly supports the absence of any bladder tumour risk with dapagliflozin (Maeshima et al 2009, Maeshima et al 2010).
- A 6-month bladder tumour initiation-promotion study in rats with dapagliflozin was initiated as a post-approval commitment by the US Food and Drug Administration. The objectives of the study were to determine the potential effect of dapagliflozin on the incidence and degree of invasiveness of urinary bladder carcinomas induced with N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN). BBN was administered twice weekly by oral gavage for 6 weeks followed by a daily dose of dapagliflozin from Week 8 to Week 34 for 26 weeks. The dose of dapagliflozin was selected to give an exposure of approximately 7x that of the maximum human therapeutic dose as well as polyuria and increased level of glucose in the urine. Uracil was included as a positive control agent and showed effects as a tumour promoter and early progressor. The results showed that dapagliflozin does not act as a promoter or progressor of bladder cancer.

There is no evidence that SGLT2 inhibition or dapagliflozin administration enhances tumour growth

- Data from the nonclinical toxicology studies with dapagliflozin, in which glucosuria was a common feature, suggest that the presence of glucosuria does not lead to hyperplasia or to bladder tumours. Also, an in vitro experiment with 5 cultured bladder cancer cell lines indicated that concentrations of glucose more than 11 mM were not associated with enhanced cell growth, and concentrations of glucose of 50 mM were cytostatic.
- The in vitro effects of dapagliflozin and its primary human metabolite, 3-O-glucuronide, on human transitional cell carcinomas (TCC) tumour cell growth were examined. Six human bladder TCC cell lines were treated with the parent drug or its 3-O-glucuronide metabolite at concentrations of up to 20 µg/mL (≥ 100x human C_{max} at the MRHD) under sub-optimal growth conditions to allow for detection of enhancements in growth. For all 6 TCC cell lines, in vitro exposure to dapagliflozin or dapagliflozin 3-O-glucuronide did not result in stimulation of bladder tumour cell proliferation.
- In a mouse xenograft study, dapagliflozin was administered daily by oral gavage to male and female nude mice bearing human TCC tumours. Administration of dapagliflozin did not significantly enhance the size of EJ1 or UMUC3 tumours in implanted nude mice at exposures ≤ 75× and ≤ 0.9× clinical exposures at the MRHD.
- for dapagliflozin and its 3-O-glucuronide metabolite, respectively. This experiment provides further support that dapagliflozin administration is not associated with the enhancement of urinary bladder tumour growth.

In conclusion, the data from the nonclinical studies indicate that SGLT2 inhibition and/or dapagliflozin is not a tumour initiator, promotor, or tumour growth enhancer and that there is no biological basis for an increased cancer risk with dapagliflozin.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

II.3.1 Subjects with T2DM

D1693C0001 DECLARE CV outcomes study exposure

There were 17160 subjects randomised in the DECLARE cardiovascular (CV) outcomes study, of whom 8574 were treated with dapagliflozin. Summary of exposure is presented in Table II-1 and Table II-2.

Table II-1 Extent of Exposure Summary for Study D1693C00001 DECLARE, Safety Population

	DAPA TOTAL (N = 8574)			ALL CONTROL (N = 8569)		
Duration of exposure (months)	**# of subjects entering interval**	**Patient-years within interval [a]**	**Cumulative patient-years (0-end of interval) [b]**	**# of subjects entering Interval**	**Patient-years within interval [a]**	**Cumulative patient-years (0-end of interval) [b]**
0 to ≤3	8574	2091.1	2091.1	8569	2092.8	2092.8
4 to ≤6	8394	2050.5	4141.6	8410	2048.4	4141.2
7 to ≤9	8236	2000.1	6141.7	8214	1989.4	6130.6
10 to ≤12	8042	1966.7	8108.4	7978	1948.6	8079.2
13 to ≤15	7903	1922.3	10030.7	7814	1896.2	9975.4
16 to ≤18	7735	1890.3	11921.0	7620	1860.6	11836.0
19 to ≤21	7611	1856.8	13777.8	7474	1819.0	13655.0
22 to ≤24	7475	1828.8	15606.6	7315	1788.0	15443.0
25 to ≤27	7359	1795.1	17401.7	7178	1742.7	17185.7
28 to ≤30	7225	1770.1	19171.8	7005	1709.2	18894.9
31 to ≤36	7121	3444.2	22616.0	6855	3297.7	22192.6
37 to ≤42	6878	3231.3	25847.3	6556	3071.8	25264.4
43 to ≤48	6300	2794.4	28641.7	5984	2640.6	27905.0
49 to ≤54	4413	1330.5	29972.2	4119	1224.7	29129.7
55 to ≤60	1173	207.0	30179.2	1075	187.7	29317.4
>60	38	1.2	30180.4	37	1.6	29319.0

The counts include all subjects who received at least one dose of study drug. Duration of exposure in months where month is defined as 30 days.

[a] Patient-years Within Interval is the sum over the subjects exposure within the interval to study medication expressed in years where subject exposure within interval is the Last dosing date in interval - First dosing date in interval plus 1 day.

[b] Cumulative Patient-years: 0 - End of Interval is the sum over the subjects exposure from day 1 of dosing through the end of the interval to study medication expressed in years, where cumulative subject exposure to end of interval is last dosing date in Interval - First dosing date plus 1 day. N is the number of treated subjects.

Table II-2 Demographic Characteristics Summary, Cumulative Subject Exposure by Age, Sex, and Race for D1693C00001 DECLARE, Randomised Subjects

	DAPA TOTAL (N=8582)	ALL CONTROL (N=8578)
Age range (years) (%)		

Table II-2 Demographic Characteristics Summary, Cumulative Subject Exposure by Age, Sex, and Race for D1693C00001 DECLARE, Randomised Subjects

	DAPA TOTAL (N=8582)	ALL CONTROL (N=8578)
18 – 64 years	4677 (54.5)	4681 (54.6)
≥65 years	3905 (45.5)	3897 (45.4)
Total	**8582**	**8578**
Male (%)		
18-64	3176 (37.0)	3080 (35.9)
≥65 years	2235 (26.0)	2247 (26.2)
Total	**5411**	**5327**
Female (%)		
18-64	1501 (17.5)	1601 (18.7)
≥65 years	1670 (19.5)	1650 (19.2)
Total	**3171**	**3251**
Racial group (%)		
White	6843 (79.7)	6810 (79.4)
Black or African-American	295 (3.4)	308 (3.6)
Asian	1148 (13.4)	1155 (13.5)
Other	296 (3.4)	305 (3.6)
Total	**8582**	**8578**

The race subgroup of other includes subjects with reported race of American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander; or Other.

Overall exposure in the adult T2DM clinical programme

The safety and tolerability of dapagliflozin were thoroughly documented and evaluated in the original submission for approval of dapagliflozin for treatment of T2DM, which has been supplemented over time with updated information on the safety and tolerability of dapagliflozin.

The cumulative duration of exposure for randomised subjects from development international birth date to 04 October 2018 is 37428 patient-years for dapagliflozin-treated subjects (N=16936) and 33666 patient-years for control subjects (N=13503), as presented in Table II-3.

Cumulative summary tabulation of dapagliflozin exposure by age/sex and by racial group from the completed Phase II/III/IV clinical studies in subjects with T2DM is presented in Table II-4.

Table II-3 Extent of Exposure Summary for Phase I/IIb/III/IV Studies – Short-term Plus Long-term Treatment Period Including Data After Rescue – T2DM Treated Subjects, Safety Population

	DAPA TOTAL (N=16936)			ALL CONTROL (N=13503)		
Duration of exposure (months)	**# of subjects entering interval**	**Patient-years within interval[a]**	**Cumulative patient-years (0-End of interval)[b]**	**# of subjects entering interval**	**Patient-years within interval[a]**	**Cumulative patient-years (0-end of interval) [b]**
0 to ≤3	16936	4040.1	4040.1	13503	3237.0	3237.0
4 to ≤6	14827	3460.4	7500.5	12233	2903.4	6140.4
7 to ≤9	12181	2948.7	10449.2	10703	2583.0	8723.4
10 to ≤12	11814	2824.8	13274.0	10320	2483.9	11207.3
13 to ≤15	10580	2393.7	15667.7	9539	2150.8	13358.1
16 to ≤18	9560	2326.0	17993.7	8587	2084.4	15442.5
19 to ≤21	9336	2269.7	20263.4	8352	2026.4	17468.9
22 to ≤24	9108	2208.4	22471.8	8137	1980.3	19449.2
25 to ≤27	8373	1865.2	24337.0	7774	1798.8	21248.0
28 to ≤30	7425	1818.5	26155.5	7188	1753.9	23001.9
31 to ≤36	7316	3536.1	29691.6	7034	3382.7	26384.6
37 to ≤42	7059	3316.0	33007.6	6722	3148.2	29532.8
43 to ≤48	6465	2874.4	35882.0	6133	2712.3	32245.1
49 to ≤54	4571	1337.7	37219.7	4257	1231.3	33476.4
55 to ≤60	1173	207.0	37426.7	1075	187.7	33664.1
> 60	38	1.2	37427.9	37	1.6	33665.7

The counts include all subjects who received at least one dose of study drug in completed studies. Duration of exposure in months where month is defined as 30 days.

[a] Patient-years within interval is the sum over the subjects exposure within the interval to study medication expressed in years where subject exposure within interval is the Last dosing date in interval - First dosing date in interval plus 1 day.

[b] Cumulative Patient-years: 0 - end of interval is the sum over the subjects exposure from day 1 of dosing through the end of the interval to study medication expressed in years, where cumulative subject exposure to end of interval is last dosing date in Interval - First dosing date plus 1 day.
N is the number of treated subjects.

Table II-4 Estimated Cumulative Subject Exposure to Dapagliflozin From Completed Clinical Trials in Subjects with T2DM by Age and Sex, Randomised Subjects

	DAPA TOTAL (N=16966)	ALL CONTROL (N=13523)
Age range (years)		
<18 years	24 (0.1)	0
18 – 64 years	11128 (65.6)	8262 (61.1)
≥65 years	5814 (34.3)	5261 (38.9)
Total	**16966**	**13523**
Male		
<18 years	9 (<0.1)	0
18-64	6640 (39.1)	5108 (37.8)
≥65 years	3305 (19.5)	3016 (22.3)
Total	**9954**	**8124**
Female		
<18 years	15 (<0.1)	0
18-64	4488 (26.5)	3154 (23.3)
≥65 years	2509 (14.8)	2245 (16.6)
Total	**7012**	**5399**
Racial group		
White	12766 (75.2)	10384 (76.8)
Black or African-American	625 (3.7)	507 (3.7)
Asian	3065 (18.1)	2184 (16.2)
Other	510 (3.0)	448 (3.3)
Total	**16966**	**13523**

The counts include all subjects randomised in completed studies as of 04 October 2018.

The race subgroup of other includes subjects with reported race of American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander; or Other.

II.3.2 Subjects with T2DM aged 10 years and above

Data from the studies D1680C00019 (T2NOW) and D1680C00017 (T2GO) have not been pooled. There are no suitable studies to pool the data from T2NOW with due to significant differences in study design.

D1680C00019 study exposure

245 subjects were randomised in study D1680C00019, of whom 81 received dapagliflozin. A summary of exposure is presented in Table II-5 and Table II-6.

Table II-5 Duration of Exposure To Study Drug Regardless of Rescue for Dapagliflozin and Placebo During the ST + LT Period Based on Actual Dose and Treatment Taken (Treated Subjects Data Set)

Characteristic	Statistic	Dapagliflozin 5mg (N = 81)	Dapagliflozin 10mg (N = 31)	Total dapagliflozin (N = 84)	Placebo (N = 76)
Duration of exposure (days)	Mean	264.5	210.2	332.6	320.6
	SD	122.76	77.52	88.25	100.02
	Min	50	24	50	6
	1st Quartile	103.0	140.0	359.0	265.5
	Median	359.0	259.0	364.0	363.0
	3rd Quartile	364.0	273.0	369.0	367.0
	Max	392	281	526	475
	Total treatment days	21422	6515	27937	24365
Duration of exposure (patient-years)	Total patient-years	58.7	17.8	76.5	66.7
Duration of exposure category (days) n (%)	1-90	2 (2.5)	3 (9.7)	3 (3.6)	3 (3.9)
	91-180	23 (28.4)	9 (29.0)	5 (6.0)	4 (5.3)
	181-270	10 (12.3)	9 (29.0)	5 (6.0)	12 (15.8)
	271-365	31 (38.3)	10 (32.3)	46 (54.8)	34 (44.7)
	> 365	15 (18.5)	0	25 (29.8)	23 (30.3)

Duration of exposure is defined as the date of last dose - date of first dose + 1.
Patient-years is calculated as the sum of exposure duration (days) for each subject divided by 365.25.
Percentages are based on the total number of subjects in the treatment group (N).
Subjects are included in each treatment column for which they took actual treatment. Subjects who were third randomised to Dapagliflozin 10mg monotherapy are included in the Dapagliflozin 10mg column.
Total Dapagliflozin subjects may be included in both Dapagliflozin 5mg and 10mg with duration of exposure calculated separately for each dose. This also includes subjects who were third randomised at Week 32/40 and who switched from placebo to Dapagliflozin.
Max = Maximum; Min = Minimum; N = Number of subjects in the treatment group or regimen in the analysis set; n = Number of subjects included in the analysis; SD = Standard deviation; ST + LT = Short term + Long term

Table II-6 Demographic Characteristics (Randomized subjects)

Demographic characteristics		Total Dapagliflozin (N=81)	Placebo (N=76)	Total (N=157)
Age (years)	n	81	76	157
	Mean	14.4	14.7	14.5
	SD	2.0	1.6	1.8
	Median	15.0	15.0	15.0
	Min	10	11	10
	Max	17	17	17
Age group (years) n (%)	≥10 and <15	38 (46.9)	35 (46.1)	73 (46.5)
	≥15 and <18	43 (53.1)	41 (53.9)	84 (53.5)
	Total	81	76	157
Sex n (%)	Male	32 (39.5)	32 (42.1)	64 (40.8)
	Female	49 (60.5)	44 (57.9)	93 (59.2)
	Total	81	76	157
Race n (%)	White	42 (51.9)	32 (42.1)	74 (47.1)
	Black or African American	7 (8.6)	3 (3.9)	10 (6.4)
	Asian	18 (22.2)	24 (31.6)	42 (26.8)
	Native Hawaiian or other Pacific Islander	0	3 (3.9)	3 (1.9)
	American Indian or Alaska Native	11 (13.6)	12 (15.8)	23 (14.6)
	Other	3 (3.7)	2 (2.6)	5 (3.2)
	Total	81	76	157
Ethnic group n (%)	Hispanic or Latino	45 (55.6)	34 (44.7)	79 (50.3)
	Not Hispanic or Latino	36 (44.4)	42 (55.3)	78 (49.7)
	Total	81	76	157
Country n (%)	Argentina	1 (1.2)	0	1 (0.6)
	Brazil	5 (6.2)	2 (2.6)	7 (4.5)
	Colombia	0	1 (1.3)	1 (0.6)
	India	3 (3.7)	4 (5.3)	7 (4.5)

Table II-6 Demographic Characteristics (Randomized subjects)

Demographic characteristics		Total Dapagliflozin (N=81)	Placebo (N=76)	Total (N=157)
	Israel	1 (1.2)	3 (3.9)	4 (2.5)
	Italy	5 (6.2)	2 (2.6)	7 (4.5)
	Malaysia	9 (11.1)	11 (14.5)	20 (12.7)
	Mexico	33 (40.7)	20 (26.3)	53 (33.8)
	New Zealand	2 (2.5)	1 (1.3)	3 (1.9)
	Philippines	3 (3.7)	2 (2.6)	5 (3.2)
	Poland	0	1 (1.3)	1 (0.6)
	Russian Federation	0	1 (1.3)	1 (0.6)
	South Korea	1 (1.2)	3 (3.9)	4 (2.5)
	Taiwan	1 (1.2)	1 (1.3)	2 (1.3)
	Thailand	0	1 (1.3)	1 (0.6)
	Turkey	1 (1.2)	7 (9.2)	8 (5.1)
	Ukraine	2 (2.5)	1 (1.3)	3 (1.9)
	United Kingdom	2 (2.5)	2 (2.6)	4 (2.5)
	United States of America	12 (14.8)	13 (17.1)	25 (15.9)
	Total	81	76	157
Geographic region n (%)	Asia/Pacific	19 (23.5)	23 (30.3)	42 (26.8)
	Europe	11 (13.6)	17 (22.4)	28 (17.8)
	Latin America	39 (48.1)	23 (30.3)	62 (39.5)
	North America	12 (14.8)	13 (17.1)	25 (15.9)
	Total	81	76	157

Percentages are based on the total number of subjects in the treatment group (N).

Max = Maximum. Min = Minimum. N = Number of subjects in the treatment group or regimen in the analysis set. n = Number of subjects included in the analysis. SD = Standard deviation.

D1690C00017 study exposure

Extent of exposure during the 24-week double-blind short-term period

There were 72 paediatric subjects randomised in the D1690C00017 study, of whom 39 were treated with dapagliflozin. Summary of exposure is presented in Table II-7 and Table II-8.

Table II-7 Duration of Exposure During the 24-week Double-blind Short-term Period Regardless Rescue Medication Initiation (Treated Subjects Set)

		Dapagliflozin 10mg (N=39)	Placebo (N=33)
Duration of exposure (days)	Mean (SD)	156.0 (37.7)	141.3 (55.3)
	Median	168.0	168.0
	Min, Max	9, 179	7, 202
	1st quartile, 3rd quartile	167.0, 171.0	141.0, 174.0
	Total treatment days	6084	4664
Duration of exposure (patient-year)	Total patient-years	16.7	12.8
Duration of exposure category (days) n (%)	1-7	0	1 (3.0)
	8-14	2 (5.1)	0
	15-28	0	3 (9.1)
	29-42	0	1 (3.0)
	43-56	0	0
	57-70	0	0
	71-84	0	0
	85-98	0	1 (3.0)
	99-140	4 (10.3)	2 (6.1)
	141-182	33 (84.6)	24 (72.7)
	>182	0	1 (3.0)

Percentage is using number of patients from the treated patients set in the treatment group as denominator.

Duration of exposure expressed in patient-year is calculated as sum of exposure duration (days) for each patient divided by 365.25.

Max maximum; Min minimum; N number of patients in treatment group; n number of patients in category or analysis; SD standard deviation.

Table II-8 Demographic Characteristics (Full Analysis Subject Set)

Demographic characteristic		Dapagliflozin 10mg (N=39)	Placebo (N=33)	Total (N=72)
Age (years)	Mean (SD)	16.1 (3.3)	16.2 (3.6)	16.1 (3.4)
	Median	16.0	16.0	16.0
	Min, Max	11, 23	11, 24	11, 24
Age group (years) n (%)	≥10 and ≤15	16 (41.0)	14 (42.4)	30 (41.7)
	>15 and <18	13 (33.3)	10 (30.3)	23 (31.9)
	≥18 and <25	10 (25.6)	9 (27.3)	19 (26.4)

Table II-8 Demographic Characteristics (Full Analysis Subject Set)

Demographic characteristic		Dapagliflozin 10mg (N=39)	Placebo (N=33)	Total (N=72)
	Total	39 (100)	33 (100)	72 (100)
Sex n (%)	Male	15 (38.5)	14 (42.4)	29 (40.3)
	Female	24 (61.5)	19 (57.6)	43 (59.7)
	Total	39 (100)	33 (100)	72 (100)
Race n (%)	White	28 (71.8)	16 (48.5)	44 (61.1)
	Black or African American	8 (20.5)	10 (30.3)	18 (25.0)
	Asian	0	1 (3.0)	1 (1.4)
	Native Hawaiian or other Pacific Islander	1 (2.6)	0	1 (1.4)
	American Indian or Alaska Native	2 (5.1)	3 (9.1)	5 (6.9)
	Other	0	3 (9.1)	3 (4.2)
	Total	39 (100)	33 (100)	72 (100)
Ethnic group n (%)	Hispanic or Latino	12 (30.8)	12 (36.4)	24 (33.3)
	Not Hispanic or Latino	26 (66.7)	21 (63.6)	47 (65.3)
	Total	38 (97.4)	33 (100)	71 (98.6)
Geographic Region n (%)	North America	16 (41.0)	16 (48.5)	32 (44.4)
	Latin America	7 (17.9)	9 (27.3)	16 (22.2)
	Europe	16 (41.0)	8 (24.2)	24 (33.3)
	Asia/Pacific	0	0	0
	Total	39 (100)	33 (100)	72 (100)
Country n (%)	Hungary	2 (5.1)	0	2 (2.8)
	Israel	8 (20.5)	5 (15.2)	13 (18.1)
	Mexico	7 (17.9)	9 (27.3)	16 (22.2)
	Russia	6 (15.4)	3 (9.1)	9 (12.5)
	United States	16 (41.0)	16 (48.5)	32 (44.4)
	Total	39 (100)	33 (100)	72 (100)

Percentage is using the number of patients from the FAS in the treatment group as denominator.

Max maximum; Min minimum; N number of patients in treatment group; n number of patients in category or analysis; SD standard deviation.

Extent of exposure during the 52-week short-term plus long-term period

The mean (SD) duration of exposure in the dapagliflozin/dapagliflozin group was 308.4 (107.8) days, with a total duration of exposure of 32.9 patient-years.

In the placebo/dapagliflozin group, in which patients switched from double-blind placebo to open-label dapagliflozin, the overall mean (SD) duration of exposure was 284.9 (139.0) days, with a total duration of exposure of 25.7 patient-years. This included exposure to dapagliflozin 10 mg during the open-label (LT) period. During LT the mean (SD) duration of exposure to dapagliflozin 10 mg was 188.1 (40.6) days, with a total duration of exposure of 12.9 patient-years.

Overall, the duration of exposure to dapagliflozin 10 mg was 45.8 patient-years, which is considered as adequate for the evaluation of safety during the ST + LT treatment period in this study.

D1690C00016 study exposure (Paediatric PK/PD study)

A total of 24 patients were administered a single oral dose of dapagliflozin: 8 patients each received 2.5, 5, or 10 mg. All subjects completed the study except 1 patient who discontinued from the study on Day 2 due to personal circumstances after receiving dapagliflozin 2.5 mg on Day 1.

The 24 treated patients with T2DM in Study D1690C00016 were predominantly white or black, with a mean age of 14.5 years (range 11 to 17 years). Per protocol requirement, at least 3 males and 3 females were dosed in each dose group and the 10 to 15 (years) age group and the 16 to 17 (years) age group each included at least 3 patients in each dose group.

II.3.3 Subjects with Heart failure

Four Phase III Heart Failure studies have been completed:

DAPA-HF trial (D1699C00001) was an event-driven randomised study in 4744 patients with HFrEF (with and without T2DM), of whom 2373 were randomised to dapagliflozin and 2371 to placebo, evaluating the effect of dapagliflozin 10 mg versus placebo in reducing the incidence of Cardiovascular death or worsening HF event (hospitalization for HF or equivalent HF event). The median duration of exposure to study drug was balanced between treatment groups: 17.8 months in the dapagliflozin group and 17.6 months in the placebo.

The 2 DETERMINE studies were parallel-group, randomised, double-blind, placebo-controlled studies in patients with LVEF > 40% (DETERMINE-preserved, D169EC00001) and LVEF ≤ 40% (DETERMINE-reduced, D169EC00002), including patients with and without T2DM, evaluating the effect of dapagliflozin 10 mg versus placebo on change in HF symptoms, physical limitation and exercise capacity. Patients were treated for 16 weeks, with

no post-treatment follow-up period. D169EC00001 and D169EC00002 included 504 and 313 patients respectively, of whom 253 and 156 were randomised to dapagliflozin.

DELIVER (D169CC00001) was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study in HF patients with LVEF > 40%, evaluating the effect of dapagliflozin 10 mg compared with placebo, given once daily in addition to background therapy, including treatments to control co-morbidities, in reducing the composite of CV death or an HF event (hospitalisation for HF or urgent HF visit). DELIVER included 6263 patients of whom 3131 were randomised to dapagliflozin and 3132 to placebo. The median duration of exposure to IP was similar between treatment groups: 26.9 months in the dapagliflozin group and 27.0 months in the placebo group.

A summary of the exposure in patients with HF is presented in Table II-9and Table II-10.

Table II-9 Extent of Exposure Summary For Heart Failure Studies - Safety Population

	DAPA TOTAL (N = 5902)			PLACEBO (N = 5901)		
Duration of Exposure (Months)	**# of Subjects Entering Interval**	**Patient-years Within Interval[a]**	**Cumulative Patient-years (0-End of Interval)[b]**	**# of Subjects Entering Interval**	**Patient-years Within Interval[a]**	**Cumulative Patient-years (0-End of Interval)[b]**
0 to ≤ 3	5902	1414.2	1414.2	5901	1414.8	1414.8
4 to ≤ 6	5608	1286.0	2700.2	5618	1288.0	2702.8
7 to ≤ 9	5009	1215.6	3915.8	5021	1216.9	3919.7
10 to ≤ 12	4839	1170.5	5086.3	4841	1168.1	5087.8
13 to ≤ 15	4634	1085.6	6171.9	4602	1077.0	6164.8
16 to ≤ 18	4137	937.8	7109.7	4093	928.8	7093.6
19 to ≤ 21	3454	762.6	7872.3	3418	755.9	7849.5
22 to ≤ 24	2706	597.5	8469.8	2670	597.2	8446.7
25 to ≤ 27	2143	448.9	8918.7	2154	450.2	8896.9
28 to ≤ 30	1573	332.6	9251.3	1575	329.0	9225.9
31 to ≤ 36	1150	397.3	9648.6	1137	392.7	9618.6
37 to ≤ 42	428	69.9	9718.5	418	71.2	9689.8
43 to ≤ 48	1	0.0	9718.5	0	0.0	9689.8

The counts include all subjects who received at least one dose of study drug. Duration of exposure in months where month is defined as 30 days.

[a] Patient-years Within Interval is the sum over the subjects exposure within the interval to study medication expressed in years where subject exposure within interval is the Last dosing date in interval - First dosing date in interval plus 1 day

[b] Cumulative Patient-years: 0 - End of Interval is the sum over the subjects exposure from day 1 of dosing through the end of the interval to study medication expressed in years, where cumulative subject exposure to end of interval is last dosing date in Interval - First dosing date plus 1 day. N is the number of treated subjects.

Studies included in the table are: D1699C00001, D169EC00001, D169EC00002, and D169CC00001.

Table II-10 Demographics Characteristics for Heart Failure studies - Age, Sex and Race for subjects exposed to IP – Randomized subjects

		Dapa 10mg (N=5913)	Placebo (N=5911)	Total (N=11824)
Demographic characteristic				
Age (years)	n	5913	5911	11824
	Mean	69.5	69.4	69.4
	SD	10.5	10.4	10.4
	Median	70.0	70.0	70.0
	Min	22	25	22
	Max	99	99	99
Age group (years) n (%)	18 - 64	1726 (29.2)	1715 (29.0)	3441 (29.1)
	≥ 65	4187 (70.8)	4196 (71.0)	8383 (70.9)
	Total	5913	5911	11824
Sex n (%)	Male	3849 (65.1)	3855 (65.2)	7704 (65.2)
	Female	2064 (34.9)	2056 (34.8)	4120 (34.8)
	Total	5913	5911	11824
Male Age group (years) n (%)	18 - 64	1274 (21.5)	1249 (21.1)	2523 (21.3)
	≥ 65	2575 (43.5)	2606 (44.1)	5181 (43.8)
	Total	3849	3855	7704
Female Age group (years) n (%)	18 - 64	452 (7.6)	466 (7.9)	918 (7.8)
	≥ 65	1612 (27.3)	1590 (26.9)	3202 (27.1)
	Total	2064	2056	4120
Race n (%)	White	4168 (70.5)	4172 (70.6)	8340 (70.5)
	Black or African American	245 (4.1)	221 (3.7)	466 (3.9)
	Asian	1237 (20.9)	1285 (21.7)	2522 (21.3)

Table II-10 Demographics Characteristics for Heart Failure studies - Age, Sex and Race for subjects exposed to IP – Randomized subjects				
		Dapa 10mg (N=5913)	Placebo (N=5911)	Total (N=11824)
Demographic characteristic				
	Other	263 (4.4)	233 (3.9)	496 (4.2)
	Total	5913	5911	11824

The race subgroup of other includes subjects with reported race of American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, or Other.

Studies included in the table are: D1699C00001, D169EC00001, D169EC00002, and D169CC00001.

II.3.4 Patients with Chronic Kidney Disease (CKD)

D169AC00001 DAPA-CKD outcomes study exposure

There were 4304 subjects randomised in the DAPA-CKD outcomes study, of whom 2152 were treated with dapagliflozin. A summary of the exposure is presented in Table II-11 and Table II-12.

Table II-11 Extent of Exposure Summary for Study D169AC00001 DAPA-CKD, Safety Population

	DAPA TOTAL (N = 2149)			PLACEBO (N = 2149)		
Duration of exposure (months)	**# of subjects entering interval**	**Patient-years within interval [a]**	**Cumulative patient-years (0-end of interval) [b]**	**# of subjects entering Interval**	**Patient-years within interval [a]**	**Cumulative patient-years (0-end of interval) [b]**
0 to ≤ 3	2149	518.4	518.4	2149	518.4	518.4
4 to ≤ 6	2059	490.6	1009.0	2055	487.4	1005.8
7 to ≤ 9	1946	475.2	1484.2	1932	470.3	1476.1
10 to ≤ 12	1906	464.0	1948.2	1876	456.5	1932.6
13 to ≤ 15	1863	452.4	2400.6	1827	443.3	2375.9
16 to ≤ 18	1822	443.1	2843.7	1778	435.2	2811.1
19 to ≤ 21	1772	428.4	3272.1	1745	420.1	3231.2
22 to ≤ 24	1692	388.8	3660.9	1654	379.8	3611.0
25 to ≤ 27	1415	314.0	3974.9	1357	299.0	3910.0
28 to ≤ 30	1125	228.3	4203.2	1071	217.8	4127.8
31 to ≤ 36	726	174.7	4377.9	700	164.0	4291.8
37 to ≤ 42	79	6.0	4383.9	64	4.3	4296.1

The counts include all subjects who received at least one dose of study drug. Duration of exposure in months where month is defined as 30 days.

[a] Patient-years Within Interval is the sum over the subject exposure within the interval to study medication expressed in years where subject exposure within interval is the Last dosing date in interval - First dosing date in interval plus 1 day.

[b] Cumulative Patient-years: 0 - End of Interval is the sum over the subject exposure from day 1 of dosing through the end of the interval to study medication expressed in years, where cumulative subject exposure to end of interval is last dosing date in Interval - First dosing date plus 1 day. N is the number of treated subjects.

Table II-12 Demographic Characteristics Summary, Cumulative Subject Exposure by Age, Sex, and Race for D169AC00001 DAPA-CKD, Randomised Subjects

	DAPA 10mg (N=2152)	PLACEBO (N=2152)	Total (N=4304)
Age (years)			
n	2152	2152	4304
Mean	61.8	61.9	61.8
SD	12.1	12.1	12.1
Median	63.0	64.0	63.0
Min	23	18	18
Max	93	91	93
Age range (years) (%)			
18 – 64 years	1170 (54.4)	1141 (53.0)	2311 (53.7)
≥65 years	982 (45.6)	1011 (47.0)	1993 (46.3)
Total	2152	2152	4304
Sex n (%)			
Male	1443 (67.1)	1436 (66.7)	2879 (66.9)
Female	709 (32.9)	716 (33.3)	1425 (33.1)
Total	2152	2152	4304
Male (%)			
18-64	768 (35.7)	768 (35.7)	1536 (35.7)
≥65 years	675 (31.4)	668 (31.0)	1343 (31.2)
Total	1443	1436	2879
Female (%)			
18-64	402 (18.7)	373 (17.3)	775 (18.0)

Table II-12 Demographic Characteristics Summary, Cumulative Subject Exposure by Age, Sex, and Race for D169AC00001 DAPA-CKD, Randomised Subjects

	DAPA 10mg (N=2152)	PLACEBO (N=2152)	Total (N=4304)
≥65 years	307 (14.3)	343 (15.9)	650 (15.1)
Total	709	716	1425
Racial group (%)			
White	1124 (52.2)	1166 (54.2)	2290 (53.2)
Black or African-American	104 (4.8)	87 (4.0)	191 (4.4)
Asian	749 (34.8)	718 (33.4)	1467 (34.1)
Other	175 (8.1)	181 (8.4)	356 (8.3)
Total	2152	2152	4304

The race subgroup of other includes subjects with reported race of American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander; or Other.

II.3.5 Subjects with T1DM

Although FORXIGA/EDISTRIDE is no longer indicated for use in T1DM, the exposure data in this patient population remain relevant for the characterisation of the safety concern 'Diabetic Ketoacidosis including events with atypical presentation'.

Since patients with T1DM are completely dependent on exogenous insulin, there is a higher background risk of DKA in these patients, as DKA is often precipitated by omissions of or inadequate insulin doses.

There were 1797 subjects randomised in the T1DM Phase III studies, of whom 1265 were treated with dapagliflozin. A total of 1155 subjects completed 24 weeks of treatment with dapagliflozin and 562 subjects were treated with dapagliflozin for > 360 days, for a cumulative exposure to dapagliflozin of 906.8 patient-years.

Of the 1265 subjects in T1DM Phase III studies, 1114 were from placebo-controlled studies MB102229 and MB102230 and were included in the T1DM short-term (ST) placebo-controlled Phase III pool. Summary exposure data for the T1DM ST placebo-controlled Phase III pool are presented in Table II-13 to Table II-15.

Table II-13 Duration of Exposure – T1DM ST Placebo-Controlled Phase III Pool

	Number of subjects (%)[a]	
Duration of exposure (days)	**DAPA 5 MG + INS (N=548)**	**DAPA 10 MG + INS (N=566)**
1-7	3 (0.5)	3 (0.5)
8-30	10 (1.8)	6 (1.1)
31-60	9 (1.6)	8 (1.4)
61-90	12 (2.2)	11 (1.9)
91-120	4 (0.7)	8 (1.4)
121-180	491 (89.6)	505 (89.2)
>180	19 (3.5)	25 (4.4)
Cumulative Exposure (Patient-Years)	**241.6**	**252.3**

[a] ST placebo-controlled Phase III pool (safety analysis set).

Table II-14 Age Group and Sex – T1DM

	Number of subjects T1DM[a]
Age	
<18 years	0
Adults (18 – 64 years)	1057
Elderly (≥65 years)	57
Sex	
Male	510
Female	604

[a] ST placebo-controlled Phase III pool (all doses).

Table II-15 Racial Origin – T1DM

Racial group	Number of subjects T1DM[a]
Asian	103
Black or African-American	23
White	975
Other	13
Total	1114

[a] ST placebo-controlled Phase III pool (all doses).

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Severe hepatic insufficiency and/or significant abnormal liver function

Reason for exclusion: Patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: There is scientific evidence to indicate that the safety profile of patients with severe hepatic insufficiency and/or significant abnormal liver function will not be different than that of the general target population. In the Phase 1 single-dose study of the pharmacokinetics and safety of dapagliflozin 10 mg (MB102027), adult subjects with hepatic insufficiency conforming to Child-Pugh classification A, B or C were compared with healthy subjects. Twenty-four subjects received dapagliflozin; 6 subjects for each of the hepatic function groups (normal healthy, and Child-Pugh Classes A, B and C). There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects. In patients with mild or moderate hepatic impairment, mean C_{max} and area under the curve (AUC) of dapagliflozin were up to 12% and 36% higher, respectively, compared with healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively.

Severe renal impairment

Reason for exclusion: The glucosuric efficacy of dapagliflozin is dependent on renal function. Patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data. For studies in CKD this exclusion criteria was not applied.

Is it considered to be included as missing information: No

Rationale: The DAPA-CKD outcomes study has provided evidence of beneficial use in this population. Since the glucose lowering effect of Dapagliflozin is dependent on renal function, the label (SmPC section 4.2) includes advice to consider use of additional glucose lowering treatment in patients with diabetes mellitus and eGRF below 45.

History of unstable or rapidly progressing renal disease

Reason for exclusion: Patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data. For studies in CKD this exclusion criteria was not applied.

Is it considered to be included as missing information: No

Rationale: DAPA-CKD outcomes study has provided evidence of beneficial use in this population. The label (SmPC Section 4.2) includes advice to consider use of additional glucose lowering treatment in patients with diabetes mellitus and eGRF below 45.

Volume depletion (Patients who, in the judgment of the investigator, might have been at risk for dehydration)

Reason for exclusion: In the original dapagliflozin clinical programme, patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: In the DECLARE CV outcomes study, T2DM patients were evaluated over a mean exposure to study drug of 48 months in 17143 patients. In this large study, where volume depletion was not an exclusion criterion, the numbers of patients with adverse events (AEs) suggestive of volume depletion were balanced between treatment groups and there was no evidence of an increased risk of AEs suggestive of volume depletion, including serious events, with dapagliflozin treatment. There was no imbalance in events of volume depletion in elderly patients, patients on loop diuretic or angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker (ACEi/ARBs). This population is therefore not relevant for consideration as missing information.

Congestive heart failure defined as New York Heart Association (NYHA) class III or IV, and/or left ventricular ejection fraction of ≤ 40%

Reason for exclusion: In the original dapagliflozin clinical programme patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of dapagliflozin and to ensure interpretability of data.

Is it considered to be included as missing information: Yes (NYHA class IV only)

DAPA-HF, DETERMINE-preserved, DETERMINE-reduced and DELIVER studies included in total 11824 patients. Of these, 3168 patients were in NYHA class III and 62 patients were in NYHA class IV.

II.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programmes are unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

II.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Exposure of special populations from completed clinical studies in subjects known to be exposed to dapagliflozin in the clinical development programmes is presented in Table II-16.

Table II-16 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

	T1DM[a]	T2DM[b]
Type of special population	**Exposure**	
Pregnant women	Not included in the clinical development programme	
Breast-feeding women	Not included in the clinical development programme	
Renal impairment (GFR [mL/min/1.73 m^2])		
<30	0	9
30 - <60	35	668
60 - <90	515	3113
Hepatic impairment (Child Pugh's A, B, C)	0	18

[a] ST placebo-controlled Phase III pool (all doses).

[b] All Phase 2b/3 pool, 30-MSU integrated safety database (all doses).

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented here is based on dapagliflozin monthly actual ex-factory sales volume from each local affiliate. These data represent all dapagliflozin formulations delivered to various distribution channels (eg, wholesalers, pharmacies, etc) worldwide.

The sales volume is provided as the number of tablets distributed. The estimated post-marketing patient exposure data is an approximation based on the assumption that each patient took 1 tablet (5 or 10 mg) once daily. The exposure is expressed in patient-years and is calculated by dividing the number of distributed daily doses by 365 days.

More detailed patient-level data (e.g., gender, ethnicity, age category, off-label use, specific populations etc) are not available.

II.5.2 Exposure

The regional cumulative sales figures are presented by patient-years in Table II-17.

Table II-17 Dapagliflozin Sales Quantity by Region

Region	Estimated exposure (patient-years)[a]
Europe	19661843
Rest of the World	67733790

[a] Cumulative exposure as of 30 September 2025, reference: Forxiga PBRER (Reporting period: 05 October 2024 to 04 October 2025).

The completed Observational Single-cohort Data Base Study of Dapagliflozin Utilisation in Europe (MB102134/D1690R00006) was conducted to describe the characteristics of European patients using dapagliflozin in routine clinical practice in Europe, with the main objective being to identify and enumerate patients who were prescribed dapagliflozin outside of the recommendations in the approved EU label. The study took place in a primary care setting and included patients newly prescribed dapagliflozin between January 2013 and December 2015 (Germany) or June 2016 (United Kingdom and Spain) by age, sex, dapagliflozin dose, country, selected co-morbidities, and selected concomitant medications. The final results on exposure are presented in Table II-18.

Table II-18 Exposure by Age Group and Sex at Inclusion in the Dapagliflozin Utilisation Study in Europe (MB102134/D1690R00006)

	Number of patients (%)[a]		
	United Kingdom n=8409	**Germany n=1715**	**Spain N=1692**
Age group (years)			
<45	837 (10.0%)	69 (4.1%)	103 (6.1%)
45 to 59	3413 (40.6%)	426 (25.3%)	514 (30.5%)
60 to 74	3709 (44.1%)	884 (52.4%)	917 (54.3%)
>75	450 (5.4%)	308 (18.3%)	154 (9.1%)
Missing	0	28	4
Sex			
Male	4875 (58.0%)	979 (57.2%)	968 (57.6%)
Female	3532 (42.0%)	734 (42.8%)	713 (42.4%)
Missing	2	2	11

[a] Percentages are of non-missing values

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential for drug abuse for dapagliflozin has not been studied. Based on its pharmacological properties, dapagliflozin is not likely to have a potential for drug abuse and no findings during the clinical programme indicate a risk for abuse, dependence, or misuse for illegal purposes.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of safety concerns in the initial RMP submission

Not applicable.

II.7.2 New safety concerns and reclassification with a submission of an updated RMP

II.7.2.1 New safety concerns

Not applicable.

II.7.2.2 Reclassification of safety concerns

AstraZeneca has revised the list of safety concerns for dapagliflozin following the results from Cancer PASS. As a result, the following safety concerns are removed: breast cancer, bladder cancer and prostate cancer (important potential risks). There is robust evidence from multiple data sources with over 580,000 person-years of overall exposure demonstrating no increased risk of breast cancer, bladder cancer and prostate cancer. These findings are consistent across different populations, study designs, and analytical approaches.

A summary of the rationale for the removal of these risks are presented below.

II.7.2.2.1 BREAST CANCER

The risk of breast cancer, previously categorised as an important potential risk is removed from the list of safety concerns.

The Cancer PASS, encompassing 130,358 person-years of dapagliflozin exposure across four international databases (CPRD, PHARMO, HIRD, Medicare), demonstrated that the propensity score–adjusted incidence rate of female breast cancer, in the overall cohorts, was comparable amongst dapagliflozin new users and comparator antidiabetic drug new users.

The pooled adjusted incidence rate ratio (IRR) of 1.01 across all databases show that dapagliflozin users had the same risk of female breast cancer as patients taking other diabetes medications, with no meaningful difference between treatment groups. Validated algorithms

correctly identified breast cancer cases (positive predictive value [PPV] 81.5-99.0% of the time) and additional analyses confirmed that any potential errors in cancer diagnosis would not have masked an increased cancer risk with dapagliflozin.

These findings, corroborated by balanced results from the DECLARE cardiovascular outcomes trial where 17160 patients were randomised and analysed (dapagliflozin 36 [0.4%] vs placebo 35 [0.4%] cases) and the supportive meta-analyses (Spiazzi et al 2023) of 76 randomized controlled trials with SGLT2i that reported no increased risk of breast cancer with dapagliflozin (RR, 0.98; 95% CI, 0.66-1.47 from 23 dapagliflozin studies), provided robust evidence to support the removal of the safety concern. The review of the postmarketing data also does not indicate breast cancer as a safety signal for dapagliflozin

All post-approval commitments are completed; there are no planned clinical measures, additional risk minimisation measures or further additional pharmacovigilance activities for this risk. Based on the results from Cancer PASS and DECLARE study, breast cancer is removed as an important potential risk from the EU RMP and will be monitored through routine pharmacovigilance activities.

II.7.2.2.2 Bladder Cancer

The risk of bladder cancer, previously categorised as an important potential risk is removed from the list of safety concerns.

The Cancer PASS, encompassing 286,950 person-years of dapagliflozin exposure across four international databases (CPRD, PHARMO, HIRD, Medicare), demonstrated that dapagliflozin is not associated with increased bladder cancer risk.

The pooled adjusted IRR below 1.0 across all databases indicate that dapagliflozin users had lower bladder cancer risk compared to other diabetes treatments. Validated algorithms correctly identified bladder cancer cases (PPV 88.2-97.8% of the time) and additional analyses confirmed that any potential errors in cancer diagnosis would not have masked an increased cancer risk with dapagliflozin.

These findings, corroborated by balanced results from the DECLARE trial (dapagliflozin 26 [0.3%] vs placebo 45 [0.5%] cases), and the supportive meta-analyses (Spiazzi et al 2023) of 76 randomized controlled trials with SGLT2i that reported no increased risk of bladder cancer with dapagliflozin (RR 0.63; 95% CI: 0.42-0.95 from 23 dapagliflozin studies) provided robust evidence to support the removal of the safety concern . The review of the post-marketing data does not indicate bladder cancer as a safety signal for dapagliflozin.

All post-approval commitments are completed; there are no planned clinical measures, additional risk minimisation measures or further additional pharmacovigilance activities for

this risk. Based on the results from Cancer PASS and DECLARE study, bladder cancer is removed as an important potential risk from the EU RMP and will be monitored through routine pharmacovigilance activities.

II.7.2.2.3 PROSTATE CANCER

The risk of prostate cancer, previously categorised as an important potential risk is removed from the list of safety concerns.

The Cancer PASS (165,308 person-years) demonstrated that dapagliflozin is not associated with increased risk of the male composite cancer endpoint (prostate, colon/rectum, lung, stomach, NHL, melanoma). The adjusted IRR of below 1.0 across all databases with associated 95% CIs crossing 1.0 indicated that dapagliflozin users had no increased risk of male composite cancer compared to other diabetes treatments, with almost 50% of the composite outcome composed of prostate cancer.

DECLARE trial results were concordant, showing similar prostate cancer rates between groups (dapagliflozin 73 [1.4%] vs placebo 63 [1.2%] cases). Cumulative review of Cancer PASS, DECLARE data, and AstraZeneca's global safety database do not support an association between prostate cancer and dapagliflozin.

All post-approval commitments are completed; there are no planned clinical measures, additional risk minimisation measures or further additional pharmacovigilance activities for this risk. Based on a comprehensive evidence review, prostate cancer is removed as an important potential risk from the EU RMP and will be monitored through routine pharmacovigilance activities.

II.7.3 Details of important identified risks, important potential risks and missing information

II.7.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk: Diabetic Ketoacidosis including events with atypical presentation

The T1DM indication was approved in EU on 20 March 2019 (EURMP v16) and removed in 2021. The removal of the T1DM indication in EU was not due to any safety or efficacy concerns. In clinical studies, DKA occurred more frequently in T1DM patients than in T2DM patients, and was included as a common ADR in the SmPC for the T1DM indication. DKA was previously included in the EU-RMP as an important identified risk for the T1DM indication (as well as for the T2DM indication) and aRMM were implemented for T1DM. These aRMM are now removed. The potential for off-label use of FORXIGA for the treatment of T1DM patients cannot be excluded since the product was previously approved in this indication. Guidance is provided in the SmPC (section 4.4).

General information on DKA is included in the SmPC (section 4.4), e.g. regarding cases with atypical presentation (with only moderately increased blood glucose values) and guidance regarding treatment when DKA is suspected.

Potential mechanisms: Unknown.

Evidence source(s) and strength of evidence:

There have been postmarketing reports of ketoacidosis, including DKA, in patients with T2DM taking dapagliflozin or other SGLT2 inhibitors.

In the DECLARE CV outcomes study, events adjudicated as DKA were rare overall. There were more patients with events of adjudicated DKA in the dapagliflozin group compared with the placebo group. In the DAPA-HF, DAPA-CKD and DELIVER studies events of DKA were rare in the T2DM population, and there were no events of ketoacidosis reported in the non-diabetic population.

In clinical studies with T1DM, there was a higher number of diabetic ketoacidosis (DKA) in the dapagliflozin-treated patients compared to placebo.

Characterisation of the risk: SGLT2 inhibitors reduce blood glucose independent of insulin and may result in diabetic patients presenting with DKA and near-normal glucose values.

In the T2DM ST placebo-controlled pool, the search for potential events of ketoacidosis identified 4 events (0.07%) in subjects treated with dapagliflozin versus none in the placebo group. Of these events, there was 1 SAE of DKA, 1 non-serious AE of metabolic acidosis, and 2 non-serious AEs of ketonuria. In addition, 1 SAE of metabolic acidosis occurred in a subject after discontinuation of study drug as per protocol (20 days after last dose of study drug). From postmarketing use, there are cases reported with near-normal glucose values.

In the DECLARE CV outcomes study, there were more patients with events of adjudicated DKA in the dapagliflozin group compared with the placebo group: 27 (0.3%) and 12 (0.1%), respectively. The DKA events were evenly distributed over the study period. Precipitating factors for DKA were as expected in a T2DM population. The most common contributing factors were similar between treatment groups (e.g., illness/severe illness, infection, changed or missed insulin dose or underdose of insulin, and poor intake of food and/or drink). The most common signs and symptoms were similar between treatment groups, e.g., abdominal pain, confusion, fatigue, fever sign, frequent urination, thirst, fruity scented breath, loss of consciousness, nausea, malaise, vomiting, shortness of breath, weakness. Most patients in the dapagliflozin group had concomitant insulin treatment at the time of the DKA event (22 of 27 patients), and all patients in the placebo group. Three patients in the dapagliflozin group with DKA had T1DM, and none in the placebo group.

In the T1DM placebo-controlled Phase III pool, subjects were advised to monitor blood ketones in case of suspected symptoms of DKA and seek medical advice/attention if their self-measured blood ketone reading was ≥ 0.6 mmol/L. In the pooled 52-week data, events adjudicated as DKA were reported in 20 (3.5%) subjects in the dapagliflozin 5 mg group and 6 (1.1%) subjects in the placebo group. DKA events occurred evenly distributed over the clinical trial period. Inadequate insulin doses (missed insulin dose or insulin pump failure) were the most common precipitating factors. Seven of the 20 events of DKA in the dapagliflozin 10 mg group occurred in patients with blood glucose in the euglycemic range (< 14 mmol/l or 250 mg/dl). Subjects with DKA events responded to conventional treatment for DKA.

From postmarketing sources, the most frequently reported events by Preferred Term (PT) were Diabetic ketoacidosis, Ketoacidosis, Ketonuria, Urine ketone body present, Metabolic acidosis and Euglycaemic diabetic ketoacidosis. Isolated cases had a fatal outcome. The majority of these contained limited relevant information and the remaining contained different confounding factors.

AstraZeneca has conducted a retrospective epidemiology study looking at the incidence of DKA among patients with T2DM in the US (D1690R00013). Among patients with T2DM initiating a new medication or medication class, DKA events were rare: 310 events were identified in over 200000 person-years of exposure to ADs. Overall the DKA rate per 1000 PY was 1.4 (95% CI 1.2-1.6). The rates were similar when age-standardised to the European diabetes population and when limited to episodes where there was no prior diagnosis of DKA.

Risk factors and risk groups: Risk factors include post-operative episodes affecting insulin requirement/deficiency; dehydration and restricted oral glucose intake due to dieting (especially low carbohydrate diet); loss of appetite due to, eg, gastrointestinal infection, depression, or malaise; severe infections or other severe medical conditions such as myocardial infarction and stroke; and pancreatic insufficiencies due pancreatitis, cancer, or alcohol abuse.

Preventability: Awareness about the symptoms of ketoacidosis. Rare cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

Guidance is provided in the SmPC (see Section V.1).

Impact on the benefit-risk balance of the product: Diabetic ketoacidosis is an acute, major, and potentially life-threatening event. The condition is a complex metabolic state generally characterised by hyperglycaemia, ketoacidosis, and ketonuria and is believed to be caused by an absolute lack of insulin.

Public health impact: As the impact is only to the treated population, there is no public health impact.

Important Potential Risks:

There are no important potential risks for dapagliflozin

II.7.3.2 Presentation of missing information

Use in patients with NYHA class IV

Evidence source: Use in patients with NYHA class IV is missing information as there is insufficient evidence to determine if the safety profile in this population is different to that of the general target population.

The studies DAPA-HF, DETERMINE-preserved, DETERMINE-reduced and DELIVER included in total 11824 patients. Of these, 3168 patients were in NYHA class III and 62 patients were in NYHA class IV. Although the results from subgroup analysis by NYHA class were similar between treatment groups across NYHA classes with regard to serious adverse events, events suggestive of volume depletion, renal events and fractures, and consistent with the overall population, the limited number of patients means there is insufficient evidence to conclude that the safety profile of this population is different to that of the general target population receiving dapagliflozin.

The SmPC Section 4.4 includes a statement that experience in clinical studies with dapagliflozin in NYHA class IV is limited.

Population in need of further characterisation: Routine pharmacovigilance alone is appropriate as further characterisation through additional pharmacovigilance activities are neither feasible or warranted.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Table II-19 Summary of Safety Concerns

Important identified risks	Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	None
Missing information	Use in patients with NYHA class IV

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for safety concerns

See Annex 4 for AE follow-up questionnaire for spontaneous reports of diabetic ketoacidosis.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

No additional pharmacovigilance activities are ongoing or planned at this point in time.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies are ongoing or planned at this point in time.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Table V-1 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Diabetic Ketoacidosis including events with atypical presentation	Routine risk communication: SmPC sections 4.4, 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Symptoms of DKA included, and direction to assess patients immediately, regardless of blood glucose level, if these symptoms occur. Information included that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected. (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. (SmPC section 4.4). Information that FORXIGA should not be used for patients with T1DM (SmPC section 4.4). Information on how to detect symptoms of DKA and instructions to seek medical attention (PL section 2, 4).
Important potential risks	
None	
Missing information	
Use in patients with NYHA class IV	Routine risk communication: SmPC section 4.4

PL Package leaflet; SmPC Summary of product characteristics

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V:1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Diabetic Ketoacidosis including events with atypical presentation	Routine risk minimisations measures: SmPC sections 4.4, 4.8 PL section 4 Information includes that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered (SmPC section 4.4). Information that FORXIGA should not be used for patients with T1DM (SmPC section 4.4).	Routine PV: AE follow-up forms for spontaneous reports
Important potential risks		
None		
Missing information		
Use in patients with NYHA class IV	Routine risk minimisation measures: SmPC section 4.4	None

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR FORXIGA/EDISTRIDE (DAPAGLIFLOZIN)

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

FORXIGA/EDISTRIDE'S Summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how FORXIGA/EDISTRIDE should be used.

This summary of the RMP for FORXIGA/EDISTRIDE 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 FORXIGA/EDISTRIDE'S RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

FORXIGA/EDISTRIDE is authorised for treatment of type 2 diabetes mellitus in adults and children aged 10 years and above as an adjunct to diet and exercise, for treatment of symptomatic chronic heart failure in adults and for treatment of chronic kidney disease in adults (see SmPC for the full indications). It contains dapagliflozin as the active substance and it is given orally.

Further information about the evaluation of FORXIGA/EDISTRIDE'S benefits can be found in FORXIGA/EDISTRIDE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

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

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

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of FORXIGA/EDISTRIDE, together with measures to minimise such risks and the proposed studies for learning more about FORXIGA/EDISTRIDE's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute the routine risk minimisation measures.

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

If important information that may affect the safe use of FORXIGA/EDISTRIDE is not yet available, it is listed under 'missing information' below.

VI.2.1 List of important risks and missing information

Important risks of FORXIGA/EDISTRIDE are risks that need special risk management activities to further investigate or minimise 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 FORXIGA/EDISTRIDE. 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 (e.g., on the long term use of the medicine).

Table VI-1 List of Important Risks and Missing Information

Important identified risks	Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	None
Missing information	Use in patients with NYHA class IV

Table VI-2 Important Identified Risk – Diabetic Ketoacidosis Including Events with Atypical Presentation

Evidence for linking the risk to the medicine	Postmarketing experience with use of SGLT2 inhibitors, including dapagliflozin. In clinical studies with T1DM, there was a higher number of diabetic ketoacidosis (DKA) in the dapagliflozin-treated patients compared to placebo. DKA was also reported in the T2DM DECLARE study with rare frequency.
Risk factors and risk groups	Postoperative episodes affecting insulin requirement/deficiency; dehydration and restricted oral glucose intake due to dieting (especially low carbohydrate diet); loss of appetite due to, eg, gastrointestinal infection, depression, or malaise; severe infections or other severe medical conditions such as myocardial infarction and stroke; and pancreatic insufficiencies due pancreatitis, cancer, or alcohol abuse.
Risk minimisation measures	Routine risk minimisations measures: SmPC sections 4.4, 4.8 PL sections 2, 4 Information includes that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. (SmPC section 4.4).

Table VI-3 Missing Information – Use in Patients with NYHA Class IV

Risk minimisation measures	Routine risk minimisation measures: SmPC Section: 4.4

VI.2.2 Post-authorisation development plan

VI.2.2.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of FORXIGA.

VI.2.2.2 Other studies in post-authorisation development plan

There are no studies required for FORXIGA.

VII. PART VII: ANNEXES

ANNEX 4: Specific adverse drug reaction follow-up forms

- Questionnaire (dapagliflozin) – Diabetic ketoacidosis

ANNEX 6: Details of proposed additional risk minimisation activities

Not applicable

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Request for Additional Information in response to event or symptoms of diabetic ketoacidosis

Case ID #_____
Manufacturer Date of Receipt _____

Reporter Information		
Reporter Name:	**Reporter address:**	**Telephone #:** **Fax#:** **Email:**

Please note that information already provided in the original event report does not need to be repeated in this form!

Patient Details							
Initials:	**Sex:** ☐ Male ☐ Female	**Weight:**	☐ lb	☐ kg	**Height:**	☐ in	☐ cm
Date of Birth *(DD/MM/YY)* **or Age:**		**Ethnic Origin:**			**Race:**		

Type of diabetes					
Not applicable ☐ (non-diabetic)	T1DM ☐	T2DM ☐	LADA ☐	Ketosis prone ☐	Other:

Duration of diabetes				
< 1 Year ☐	1-3 Year ☐	3-5 Year ☐	5-10 Year ☐	>10 Year ☐

Adverse Event Details				
Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*	**Outcome**	
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died
Diagnostic criteria and clinical diagnosis of the event(s):				
Was the patient hospitalized for the event(s)? ☐ Yes ☐ No **Was treatment provided?** ☐ Yes ☐ No			*If 'Yes' to any of the questions to the left, please provide a brief statement of clinical course, relevant treatment and any complications from the event(s):*	

Dapagliflozin therapy			
Indication:	**Daily dosage:**	**Start Date** *(DD/MM/YY):*	**Stop Date** *(DD/MM/YY):*
Was dapagliflozin stopped due to the event(s)?		☐ Yes, permanently ☐ Yes, temporarily	☐ No ☐ N/A

If yes, did the event(s) improve after stopping dapagliflozin?	☐ Yes, permanently ☐ Yes, temporarily	☐ No	☐ N/A
Was dapagliflozin re-introduced?	☐ Yes, permanently ☐ Yes, temporarily	☐ No	☐ N/A
If yes, did the event(s) recur after reintroduction?	☐ Yes, permanently ☐ Yes, temporarily	☐ No	☐ N/A
Does the reporter consider there to be a causal relationship between dapagliflozin and the adverse event(s)?		☐ Yes	☐ No
Please explain:			

Antidiabetic medications (include treatments up to 3 months in advance of the reported event)

Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was this a suspect medication?
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

Please comment on any known missed or changed doses in addition to what is listed above:

Other relevant concomitant medications
Exclude drugs used to treat the event

Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was this a suspect medication?
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

Relevant medical history, concurrent diseases or other contributing factors		Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	If yes, please provide details
Previous episodes of ketoacidosis	☐ Yes ☐ No			
Carbohydrate reduced diet/Reduced caloric intake	☐ Yes ☐ No			
Surgery	☐ Yes ☐ No			
Infection	☐ Yes ☐ No			
Alcohol intake	☐ Yes ☐ No			
Recent Cardiovascular Episode	☐ Yes ☐ No			
Missed insulin dose	☐ Yes ☐ No			
Insulin pump failure	☐ Yes ☐ No			
Pancreatic disorder	☐ Yes ☐ No			

Relevant medical history, concurrent diseases or other contributing factors		Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	If yes, please provide details
Dehydration	☐ Yes ☐ No			
Increased exercise	☐ Yes ☐ No			
Other, please specify:	☐ Yes ☐ No			
	☐ Yes ☐ No			
	☐ Yes ☐ No			

Laboratory Test	Peak Value	Unit	Sample date *(DD/MM/YY)*	Reference Values (…….to ……)	Follow-up value If available	Follow-up Date *(DD/MM/YY)*
Blood/Plasma Glucose						
Blood pH						
PCO_2						
Serum Bicarbonate						
Serum Potassium (K)						
Serum Sodium (Na)						
Blood/Serum Ketones						
Urine Ketones						
c-Peptide						
Lactate						
Betahydroxybutyrate						
eGFR						
Creatinine						
Other, please specify :						

Date and Signature

Date: _____

Signature (Reporting Physician): _____

Contact Information

Please return completed form to:

Fax:

E-mail:

Mail:

Thank you for completing this form.