EU RMP	
Drug Substance	Saxagliptin/dapagliflozin FDC
Version Number	11
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EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for QTERN ™ (SAXAGLIPTIN AND DAPAGLIFLOZIN FIXED-DOSE COMBINATION)

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 SV
Post-marketing patient exposure data is updated.

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

Part II 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 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.

Details of currently approved RMP	**Version Number**: v 10 Succession 1 **Approved with procedure**: EMEA/H/C/004057/EMA/VR/0000254377 **Date of approval:** 24 April 2025

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
AE	Adverse event
ATC	Anatomical Therapeutic Chemical Classification
CHF	Congestive heart failure
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase 4
EEA	European economic area
EMA	European medicines agency
EPAR	European public assessment report
EU	European union
FDC	Fixed-dose combination
GLP-1	Glucagon-like peptide-1
GVP	Good pharmacovigilance practices
HbA1c	Glycosylated haemoglobin
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HIRD	Healthcare Integrated Research Database
HR	Hazard Ratio
IRR	Incidence rate ratio
NYHA	New York Heart Association
PASS	Post-authorisation safety study
PL	Package leaflet
PPV	Positive predictive value
PV	Pharmacovigilance
RR	Risk ratio
RMMs	Risk minimisation measures
RMP	Risk management plan
SGLT2	Sodium glucose cotransporter-2
SmPC	Summary of product characteristics
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus

Abbreviation/ Special term	**Definition/Explanation**
UTI	Urinary tract infection

1 PART I: PRODUCT OVERVIEW

Table 1-1 Product Overview

Active substance(s) (INN or common name)	Saxagliptin and dapagliflozin
Pharmacotherapeutic group(s) (ATC Code)	Combinations of oral blood glucose lowering drugs, Anatomical Therapeutic Chemical Classification (ATC) code: A10BD21
Marketing Authorisation Holder	AstraZeneca AB
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	QTERN
Marketing authorisation procedure	Centralised Procedure according to Article 3 (1) and Point 3 of Annex of Regulation EC/726/2004/EC

Brief description of the product	QTERN is a fixed-dose combination (FDC) product and contains 2 oral anti-hyperglycaemic agents used in the management of type 2 diabetes mellitus (T2DM): saxagliptin and dapagliflozin. Saxagliptin is a highly potent, selective, reversible, competitive, orally active inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme. DPP-4 potently converts the insulinotropic hormone glucagon-like peptide-1 (GLP-1) from active GLP-1(7-36) to inactive GLP-1(9-36). Inhibitors of DPP-4 thereby increase concentrations of endogenous, active (intact) GLP-1 and potentiate its endocrinological actions, augmenting prandial insulin secretion and improving the overall glycaemic profile in patients with T2DM. Dapagliflozin is a highly potent, selective, and reversible sodium glucose cotransporter-2 (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. 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 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

Table 1-1 Product Overview

	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. Saxagliptin/dapagliflozin FDC combines these agents with a complementary mechanism of action for significant reductions in glycosylated haemoglobin (HbA1c), allowing more patients to achieve their target glycaemic goals (< 7% HbA1c), with an established safety profile consistent with that seen for its mono-components.
Hyperlink to the Product Information	QTERN Summary of Product Characteristics
Indication(s) in the EEA	Current: QTERN, fixed dose combination of saxagliptin and dapagliflozin, is indicated in adults aged 18 years and older with T2DM: - to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of QTERN do not provide adequate glycaemic control, - when already being treated with the free combination of dapagliflozin and saxagliptin
	Proposed: Not applicable
Dosage in the EEA	**Current:** The recommended dose is one 5 mg saxagliptin/10 mg dapagliflozin tablet once daily.
	Proposed: Not applicable
Pharmaceutical forms and strengths	**Current:** 5 mg saxagliptin/10 mg dapagliflozin film-coated tablets
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

2.1.1 Indication: Type 2 diabetes mellitus

Part II, Module SI is not required for a fixed combination medicinal product – no new active substance in accordance with *Guideline on good pharmacovigilance practices (GVP), Part II, Module SI – Epidemiology of the indication and the target population* (EMA 2017) section V.C.1.1.

2.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

2.2.1 Summary of key safety findings from non-clinical data

QTERN is a fixed combination medicinal product which does not contain a new active substance.

In addition to what is known for the individual components, in support of saxagliptin/dapagliflozin FDC, a 3-month repeated-dose oral combination toxicity study with saxagliptin and dapagliflozin was conducted in rats (DN12107). In this study, dapagliflozin at 0.4 mg/kg/day and saxagliptin at 2 mg/kg/day were administered individually and as a combination. No toxicologic or toxicokinetic interactions were observed at area under the concentration-time curve (AUC) exposures 7 times those at the maximum recommended human dose (MRHD) for both compounds. When dosed in combination, saxagliptin did not alter mean dapagliflozin systemic exposures and dapagliflozin did not substantially alter mean saxagliptin systemic exposure or the exposure of its metabolite. Dapagliflozin- and saxagliptin-related effects were wholly consistent with findings observed in previous studies and consisted of non-adverse effects, most of which were generally attributed to the intended pharmacology. Additional non-clinical in vitro pharmacokinetic (PK) assessments have shown that neither saxagliptin nor its metabolite altered the metabolism of dapagliflozin by inhibiting uridine diphosphate glucuronosyltransferase (UGT) 1A9 (DN930059456).

In conclusion, there are no new nonclinical findings that preclude the safe administration of saxagliptin in combination with dapagliflozin at daily doses of up to 5 mg and 10 mg, respectively.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

2.3.1 Summary of clinical trial exposure

Estimates of overall cumulative subject exposure are provided in Table 2-1, based on actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials.

Table 2-1 Estimated cumulative subject exposure from clinical trials

Treatment	**Number of subjects (N = 5156[#])**
Saxagliptin/Dapagliflozin	2431
Comparator/ Placebo	2767
Blinded	0
Overall	5156[#]

Cumulative numbers from initiation of the first clinical trials up to 14 July 2024. Data from completed studies: CV181-168, CV181-169, CV181-191, CV181-341, D1689C00012(CV181-363), CV181-364, D168BC00001(CV181-369), D1683C00005, D1689C00014, MB102-129, D1689C00013(CV181-365),D168AC00001, D168AC00002, D1683C00008 and ongoing study: D1683C00013.

[#]Summary includes data from cross-over study CV181-191 where subjects received both Drug and Comparator/Placebo. For this reason, the sum of the treatment group totals exceeds the total number of patients in all trials.

Cumulative summary tabulations of exposure by age/sex and by racial group are presented in Table 2-2 and Table 2-3, respectively.

Table 2-2 Estimated cumulative subject exposure to saxagliptin and dapagliflozin from completed and ongoing clinical trials by age and sex

Age range (years)	**Number of subjects**		
	Male	**Female**	**Total**
<18 Years	0	0	0
18 – 64 Years	1074	963	2037
>= 65 Years	222	172	394
Total	**1296**	**1135**	**2431**

Cumulative numbers from initiation of the first clinical trials up to 14 July 2024. Data from completed studies: CV181-168, CV181-169, CV181-191, CV181-341, D1689C00012(CV181-363), CV181-364, D168BC00001(CV181-369), D1683C00005, D1689C00014, MB102-129, D1689C00013(CV181-365), D168AC00001, D168AC00002, D1683C00008 and ongoing study D1683C00013.

Table 2-3 Estimated cumulative subject exposure to saxagliptin and dapagliflozin from completed and ongoing clinical trials by racial group

Racial group	Number of subjects
Caucasian	1782
Black	249
Asian	288
Other	112
Unknown	0
Total	**2431**

Data from completed and ongoing clinical trials as of 14 July 2024. Data from completed Studies: CV181-168, CV181-169, CV181-191, CV181-341, D1689C00012(CV181-363), CV181-364, D168BC00001(CV181-369), D1683C00005, D1689C00014, MB102-129, D1689C00013(CV181-365), D168AC00001, D168AC00002, D1683C00008 and ongoing study D1683C00013.

Information on the clinical development programmes for the individual mono-components is provided in their respective EU RMPs.

2.4 MODULE SIV: Populations not studied in clinical trials

2.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Part II, Module SIV is not required for a fixed combination medicinal product – no new active substance in accordance with *Guideline on GVP, Part II, Module SIV – Populations not studied in clinical trials* (EMA 2017) section V.C.1.1.

Exclusion criteria applied to the clinical studies in the QTERN clinical development programme were based on previous criteria in clinical studies for the individual mono-components.

2.4.2 Limitations to detect adverse reactions in clinical trial development programmes

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

2.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Populations typically under-represented in clinical trial development programmes were not included in clinical trials with the saxagliptin/dapagliflozin combination. These include pregnant/breast-feeding women, patients with hepatic impairment (e.g., significant hepatic

disease), patients with moderate to severe renal impairment, patients with cardiovascular impairment (e.g., cardiovascular disease within 3 months of screening/enrolment visit, severe congestive heart failure [CHF], unstable or acute CHF), and patients with immunocompromised conditions.

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented is estimated based on QTERN's monthly actual ex-factory sales volume from each local marketing company. These data represent all QTERN formulation delivered to various distribution channels (for example wholesalers, pharmacies etc) worldwide.

The sales volume is provided as the number of tablets distributed. The estimated post-marketing patient exposure data for the reporting period is an approximation based on the assumption that each patient took one tablet of 5 mg saxagliptin/10 mg dapagliflozin or 5 mg saxagliptin /5 mg dapagliflozin a day. Therefore, a patient-year worth of exposure is calculated by dividing number of tablets per day by 365 days (total number of tablets per patient year).

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to 5 mg saxagliptin/10 mg dapagliflozin or 5 mg saxagliptin /5 mg dapagliflozin a day. More detailed patient-level data (e.g., gender, ethnicity, age category, off-label use, specific populations etc) are not available.

2.5.2 Exposure

Cumulative global post-marketing patient exposure for QTERN from launch to 30 June 2025 has been estimated to be approximately 724931 patient-years.

Cumulative exposure is summarised by region in the table below.

Table 2-4 QTERN cumulative exposure in patient years by region

Region [a]	Estimated exposure (patient-years)	
	5 mg saxagliptin/10 mg dapagliflozin	5 mg saxagliptin/5 mg dapagliflozin
Europe	178794	0
Rest of world	545438	699
Total	**724232**	**699**

[a] Cumulative exposure as of 30 June 2025, reference: QTERN PBRER (reporting period 15 July 2024 to 14 July 2025)

2.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Part II, Module SVI is not required for a fixed combination medicinal product – no new active substance (4.b.) in accordance with *Guideline on GVP, Part II, Module SVI – Additional EU requirements for the safety specification* (EMA 2017) section V.C.1.1.

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of safety concerns in the initial RMP submission

Not applicable.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns for QTERN. AstraZeneca has revised safety concerns to align with the mono-component dapagliflozin EU RMP.

Missing information specific to the dapagliflozin monocomponent indications, i.e., 'Use in patients with New York Heart Association (NYHA) class IV' and 'Long term safety in the paediatric population (aged 10 years and above)' do not apply for the QTERN's approved indication. Missing information specific to saxagliptin monocomponent 'Use in pregnancy and breastfeeding' do not apply for QTERN.

2.7.2.1 Reclassification of important identified risks

Not applicable

2.7.2.2 Reclassification of important potential risks

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.

2.7.2.2.1 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 (Clinical Practice Research Datalink [CPRD], PHARMO, Healthcare Integrated Research Database [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 SGLT2 inhibitors that reported no increased risk of breast cancer with dapagliflozin (Risk ratio (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 post marketing 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.

2.7.2.2.2 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 SGLT2 inhibitors 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.

2.7.2.2.3 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.

The 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.

2.7.3 Details of important identified risks, important potential risks and missing information

2.7.3.1 Presentation of important identified risks and important potential risks

Safety data available for co-administration of saxagliptin and dapagliflozin are consistent with observations on saxagliptin and dapagliflozin as individual treatments; thus, it is appropriate to base the safety profile of the saxagliptin/dapagliflozin FDC on both the experience with the

combined use of saxagliptin and dapagliflozin and on the safety profiles of the individual component products.

There are no unique important identified risks or important potential risks for the saxagliptin/dapagliflozin FDC.

2.7.3.2 Presentation of missing information

There is no missing information unique to the saxagliptin/dapagliflozin FDC.

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the safety concerns

Important identified and potential risks and missing information based on the individual monocomponents are listed in Table 2-5.

Table 2-5 Summary of safety concerns

Important identified risks	Diabetic ketoacidosis [DKA] including events with atypical presentation (dapagliflozin component)
Important potential risks	Pancreatic cancer (saxagliptin component)
Missing Information	None

3 PART III: PHARMACOVIGILANCE PLAN

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for safety concerns:

See Annex 4 for AE follow-up questionnaires for the safety concerns: Pancreatic cancer and DKA including events with atypical presentation.

Other forms of routine pharmacovigilance activities:

There are no other forms of routine pharmacovigilance activities.

3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no planned additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of RMMs specifically for QTERN.

There are no planned additional pharmacovigilance activities from the individual mono-components saxagliptin and dapagliflozin.

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing or planned additional pharmacovigilance studies or activities for QTERN.

There are no ongoing and planned additional pharmacovigilance activities from the individual mono-components saxagliptin and dapagliflozin.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable. There are no post-authorisation efficacy studies, planned or ongoing, for QTERN.

5 PART V: RISK MINIMISATION MEASURES

5.1 ROUTINE RISK MINIMISATION MEASURES

Table 5-1 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 (dapagliflozin component)	Routine risk communication: Summary of product characteristics (SmPC) sections 4.4 and 4.8. PL sections 2 and 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 QTERN should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected. (SmPC section 4.4, PL sections 2 and 4). Before initiating QTERN, factors in the patient history that may predispose to ketoacidosis should be considered. (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	
Pancreatic cancer (saxagliptin component)	None
Missing information	
None	

DKA Diabetic Ketoacidosis; SmPC Summary of product characteristics

5.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V Table 5-1 are sufficient to manage the safety concerns of the medicinal product.

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Diabetic ketoacidosis including events with atypical presentation (dapagliflozin component)	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. QTERN should be discontinued if DKA is suspected or diagnosed (SmPC section 4.4). PL sections 2 and 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for DKA including events with atypical presentation. No additional pharmacovigilance activities.
Important potential risks		
Pancreatic cancer (saxagliptin component)	No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for spontaneous reports. No additional pharmacovigilance activities.
Missing information		
None		

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR QTERN (SAXAGLIPTIN/DAPAGLIFLOZIN FDC)

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

QTERN's summary of product characteristics (SmPC) *for EU RMP* and its package leaflet give essential information to healthcare professionals and patients on how QTERN should be used.

This summary of the RMP for QTERN 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 QTERN's RMP.

6.1 THE MEDICINE AND WHAT IT IS USED FOR

QTERN is authorised in adults aged 18 years and older with type 2 diabetes mellitus (see SmPC for the full indication). It contains saxagliptin and dapagliflozin as the active substances and it is given by oral route of administration.

Further information about the evaluation of QTERN's benefits can be found in QTERN's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/qtern.

6.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of QTERN, together with measures to minimise such risks and the proposed studies for learning more about QTERN'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/PI> 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 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 routine risk minimisation measures.

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

6.2.1 List of important risks and missing information

Important risks of QTERN 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 QTERN. 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 6-1 List of important risks and missing information

Important identified risks	Diabetic ketoacidosis including events with atypical presentation (dapagliflozin component)
Important potential risks	Pancreatic cancer (saxagliptin component)
Missing Information	None

6.2.2 Summary of important risks

Table 6-2 Important identified risk – Diabetic ketoacidosis including events with atypical presentation

Evidence for linking the risk to the medicine	Post-marketing experience with use of SGLT2 inhibitors, including dapagliflozin. DKA including events with atypical presentation is an important identified risk for dapagliflozin.
Risk factors and risk groups	Risk factors such as 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 e.g., 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 minimisation measures: SmPC sections 4.4 and 4.8. SmPC section 4.4 where it is stated that QTERN should be discontinued if DKA is suspected or diagnosed. PL sections 2 and 4.

Table 6-3 Important potential risk – Pancreatic cancer

Evidence for linking the risk to the medicine	The potential risk of pancreatic cancer has been discussed in published literature and evaluated by health authorities for the class as well as for other incretin-based antidiabetics (GLP- 1 analogues). Pancreatic cancer is an important potential risk for saxagliptin.
Risk factors and risk groups	There is an increase in risk of pancreatic cancer among patients with T2DM. Age, gender, race, cigarette smoking, obesity, diabetes, chronic pancreatitis, cirrhosis of the liver, occupational exposure, family history, and infections of the stomach with the ulcer causing bacteria *Helicobacter pylori* are other known risk factors.
Risk minimisation measures	No risk minimisation measures

6.2.3 Post-authorisation development plan

There are no ongoing or planned additional pharmacovigilance studies or activities for QTERN.

6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligations of QTERN.

6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for QTERN.

There are no studies required for the mono-components, Saxagliptin and Dapagliflozin.

7 PART VII: ANNEXES

ANNEX 4: Specific adverse drug reaction follow-up forms

- QTERN (saxagliptin/dapagliflozin FDC) – Questionnaire for Pancreatic Cancer
- QTERN (saxagliptin/dapagliflozin FDC) – Questionnaire for Diabetic Ketoacidosis

AZ case ID:

Pancreatic Cancer Adverse Event Report Questionnaire

PLEASE PROVIDE THE INFORMATION BELOW FOR THE REPORTED ADVERSE EVENT(S):

Patient's date of birth or age: Gender:

Please provide suspect product(s) [those product(s) that are suspected to be associated with one or more adverse events]:

Daily dose of the suspect product(s) and regimen:

Route of administration:

Indication(s) for which the suspect product(s) was (were) prescribed:

Starting and stop dates of treatment/ treatment

duration: Lot/Batch number(s) and Expiration date(s)

Provide any other suspect medications, not listed above, that may have contributed to the occurrence of the adverse event (s), including indication for which they were prescribed and treatment dates:

Please provide details of adverse event(s):

Start date if known:

Time lag if adverse event(s) occurred after cessation of treatment with the suspect product(s):

Please describe the malignancy:

Anatomical location:
Histological type:
TNM classification:
Grade:
Second/ secondary**:**
Other, specify:

Signs and symptoms in chronological order:

Diagnostic tests (provide test names, dates, results and normal ranges – provide pre-treatment results if available):

CT/ MRI/ ultrasound:

Histopathology:

Cytology:

Genetic testing:

CD marker evaluation:

Other, specify:

Please provide prior screening tests results if appropriate (e.g., mammogram, Pap test, colonoscopy):

Final diagnosis:

Is this a new diagnosis (acute event) or a relapse/disease progression of a pre-existing condition? Was there a precipitating factor for exacerbation?

Did the event require hospitalization? If yes, specify which

event: Treatment of adverse event(s):

Adverse event(s) stop date and outcome (information on recovery and sequelae, if any):

For fatal outcome, please provide cause of death and a comment on its possible relationship to the suspect product(s):

Did the adverse event(s) abate after use stopped or dose reduced (if applicable)?

Did the adverse event(s) reappear after re-introduction of the suspect product(s) (if applicable)? Please provide causal relationship assessment between the suspect product(s) and adverse

event(s):

Please list any concomitant medications:
Medication name, daily dose/regimen, indication; start/stop date and time or duration

Are there any other etiological factors: relevant medical and/or drug history (please mark with an
"X" all that apply):

Exposure to environmental factors, specify:
Smoking Diet,
specify: Chronic
alcohol use
Chemicals exposure [asbestos, benzenes, nickel, etc.]:
Radiation exposure [sun rays, x-rays, radioactive
elements]:
Infection (e.g., Papilloma, Cytomegalovirus, Schistosoma, hepatitis, HIV/AIDS):
Medication-induced [e.g., hormone replacement therapy (HRT), diethylstilbestrol (DES)]:
Immunosuppression, specify:
Chemotherapy:
Related co-morbidities, specify:
Family history, specify:
Other, specify:

Additional questions:

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

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:**		

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):*	

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

Was Saxagliptin/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 Saxagliptin/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 diabetic ketoacidosis	☐ Yes ☐ No			
Carbohydrate reduced diet	☐ 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**
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			
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						
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.

ANNEX 6: Details of proposed additional risk minimisation activities

Not Applicable

LIST OF REFERENCES

DN12107
Dapagliflozin (BMS-512148) and Saxagliptin (BMS-477118): A three-month oral combination toxicity study in rats (Study No. DN12107). Bristol-Myers Squibb Company, 2013, Document Control No. 930071746.

DN930059456
Dapagliflozin (BMS-512148): Evaluation of the potential for saxagliptin (BMS-477118) and its major metabolite, BMS-510849, to inhibit UGT1A9 in human liver microsome incubations using dapagliflozin or propofol as substrates. Bristol-Myers Squibb Company; 2012. Document Control No. 930059456.

Spiazzi et al 2023
Spiazzi BF, Naibo RA, Wayerbacher LF, Piccoli GF, Farenzena LP, Londero TM, et al. Sodium-glucose cotransporter-2 inhibitors and cancer outcomes: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2023;198:110621.