European Union Risk Management Plan	
Drug Substance	Capivasertib
Version Number	2
Succession Number	2
Data lock point	30 April 2024
Date of final sign-off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR TRUQAP™ (CAPIVASERTIB)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Applicant's Deputy Qualified Person for Pharmacovigilance (QPPV), as delegated by the QPPV.

ADMINISTRATIVE INFORMATION

Rationale for submitting an updated RMP

This EU RMP (Version 2) has been updated to add a new important identified risk of "Diabetic ketoacidosis".

Summary of significant changes in this RMP

Part II, Module SV:	Post-marketing exposure data were added.
Part II, Module SVII:	A new important identified risk of "*Diabetic ketoacidosis*" was added, and the existing important potential risk of "C*omplications of hyperglycaemia*" was amended to "*Complications of hyperglycaemia (excluding diabetic ketoacidosis)*".
Part II, Module SVIII:	Updated to align with the changes to safety concerns in Part II, Module SVII, as outlined above.
Part V:	Details of the risk minimisation measures for the new important identified risk of "*Diabetic ketoacidosis*" were added.
Part VI:	Updated to align with the changes to safety concerns in Part II, Module SVII, as outlined above.
Part VII: Annex 4	Minor updates made to the targeted safety follow-up questionnaire titled "*Complications of hyperglycaemia data collection form*".

Other RMP versions under evaluation

Not applicable.

Details of currently approved RMP

Version number:	Version 2-Succession 2
Approved with procedure:	EMEA/H/C/006017/II/0001
Date of approval:	30 January 2025

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADR	adverse drug reaction
AE	adverse event
AI	Aromatase inhibitor
AKT	AKT serine/threonine kinase (protein)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BD	twice a day
CDK	cyclin-dependent kinase
CTCAE	Common Terminology Criteria for Adverse Events
EEA	European Economic Area
EU	European Union
ER	oestrogen receptor
HbA1c	haemoglobin A1c
HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HR	hormone receptor
IC_{50}	concentration for 50% inhibition
IHC	immunohistochemistry
ILD	interstitial lung disease
INN	International Non-proprietary name
mTOR	mammalian target of rapamycin
PI3K	phosphatidylinositol-3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (gene)
PK	pharmacokinetic
PL	Package Leaflet
PT	Preferred Term
PTEN	Phosphatase and Tensin Homolog
QTc(F)	QT interval corrected (by Fridericia's formula)
RMP	Risk Management Plan
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
TBC	to be confirmed
ULN	upper limit of normal
US	United States (of America)
WHO	World Health Organization

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Capivasertib
Pharmacotherapeutic group(s) (ATC Code)	L01EX27
Marketing Authorisation Applicant	AstraZeneca AB, 15185 Södertälje, Sweden
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	TRUQAP
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: AKT kinase inhibitor.
	Summary of mode of action: AKT is a pivotal node in the PI3K signalling cascade regulating multiple cellular processes including cellular survival, proliferation, cell cycle, metabolism, gene transcription and cell migration. AKT activation in tumours is a result of upstream activation from other signalling pathways, mutations of AKT, loss of PTEN function and mutations in the catalytic subunit of PI3K (PIK3CA).
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Summary of Product Characteristics
Indication(s) in the EEA	**Current:** • TRUQAP is indicated in combination with fulvestrant for the treatment of adult patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration following recurrence or progression on or after an endocrine-based regimen.
Dosage in the EEA	**Current:** The recommended dose of TRUQAP in combination with fulvestrant is 400 mg (two 200 mg tablets) taken orally twice daily, approximately 12 hours apart (total daily dose of 800 mg), with or without food, for 4 days followed by 3 days off treatment. Treatment with TRUQAP should continue until disease progression or unacceptable toxicity occurs. TRUQAP should be co-administered with fulvestrant. The recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter.
Pharmaceutical form(s) and strengths in the EEA	**Current:** Film-coated tablets for oral administration. Each tablet contains 160 mg or 200 mg of capivasertib plus excipients.

Table I-1 Product Overview

Will the product be subject to additional monitoring in the EU?	Yes

II. PART II: SAFETY SPECIFICATION

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

II.1.1 ER-positive/HER2-negative Advanced Breast Cancer

As there are limited epidemiological data in the literature for the HR (including ER)-positive/HER2-negative breast cancer population, general breast cancer information is provided herein, with HR-positive/HER2-negative breast cancer information included where available.

Incidence

Breast cancer is the most common cancer in women, accounting for 2.3 million new cases worldwide in 2020. Approximately 11.7% of all new cancers are female breast cancers, which has an annual incidence rate of 46.3 per 100000 worldwide. Australia/New Zealand, Europe, and North America have the highest incidence rate by region (Globocan [Global] 2020). In men, breast cancer is rare, with male breast cancers accounting for less than 1% of all diagnosed cases (Siegel et al 2021, Miao et al 2011).

According to data from the US SEER programme, it is estimated that in 2021, there were approximately 284200 new breast cancer cases in women and 2650 new cases in men in the US (American Cancer Society 2021).

In the EU, the number of cases of breast cancer in women and men in 2020 was 355457 and accounted for approximately 13.3% of all new cancer cases diagnosed (ECIS 2020).

HR-positive/HER2-negative breast cancer is the most frequent subtype of breast cancer, comprising approximately 70% of all breast cancers (Howlader et al 2014).

Prevalence

At the end of 2020, breast cancer was the most prevalent cancer worldwide, with an estimated 7.8 million women diagnosed with breast cancer within the previous 5 years (Globocan [Global] 2020).

In the EU, an estimated 2138117 women were living with breast cancer diagnosed in the last 5 years, providing a 5-year prevalence proportion of 552.23 per 100000 (Globocan [Europe] 2020).

In the US, 287850 cases of female breast cancer were expected to be diagnosed in 2022 (American Cancer Society 2022). The breast cancer subtype HR-positive/HER2-negative is the most common subtype in the US, with an age-adjusted rate of 87.4 new cases per 100000 women, based on 2015 to 2019 case data (SEER 2015 to 1019). In men in the US, an

estimated 2710 new cases of breast cancer were expected to be diagnosed in 2022 (American Cancer Society 2022).

For men, the lifetime risk of breast cancer is about 1 in 833 (American Cancer Society 2022).

Demographics of the population in the indication (age, gender, racial and/or ethnic origin) and risk factors for the disease

Breast cancer is mainly a disease in females, with less than 1% of cases occurring in males (Ottini et al 2010); however, population-based studies have indicated that the probability of being diagnosed with invasive cancer is marginally higher for men than for women, reflecting differences in life expectancy in addition to cancer risk (DeSantis et al 2019, Miao et al 2011).

Approximately 10.5% of breast cancers occur in women younger than 45 years (Mitri et al 2012). Worldwide, 48% of newly diagnosed breast cancer patients are 45 years to 64 years old. In Europe (47%) and in the US (53%), breast cancer is most frequently diagnosed among older women (55 years to 75 years of age) (Santa-Maria et al 2016). In the US, the median age at diagnosis is 62 years, with 50.0% of patients diagnosed at 55 years to 74 years according to the SEER programme. In both the EU and the US, breast cancer incidence is much higher among adults and increases with age, with the highest incidence rate among those 65 years and older (Santa-Maria et al 2016, Noone et al 2018). In men, a study of male breast cancer risk in Denmark, Finland, Geneva, Norway, Singapore, and Sweden indicated the average age at diagnosis was 69.6 years (Miao et al 2011).

According to SEER data, age-adjusted incidence of breast cancer is highest in White females (103 per 100000 population). Incidence of age-adjusted breast cancer in Black and Asian/Pacific Islander females is 98.6 and 81.3 per 100,000 population, respectively. Breast cancer risk is lower in Hispanic females, with an age-adjusted incidence rate of 77.7 per 100000 population (SEER 2020).

Risk factors for breast cancer include age, family history (including hereditary genetic mutations), obesity, radiation exposure, and benign breast disease. Additional risk factors specific to female HR-positive breast cancer include early menarche (before age 12) or late menopause (after age 55), nulliparous women or women who are over age 30 at their first birth, and combined postmenopausal hormone therapy use (Kluttig and Schmidt-Pokrzywniak 2009, Bilimoria et al 1995, Kelsey et al 1993, Althuis et al 2004, Yang et al 2011). Additional risk factors specific to male breast cancer include high oestrogen levels, and Klinefelter syndrome (American Cancer Society 2018).

The main existing treatment options

The preferred treatment for advanced HR-positive/HER2-negative breast cancer is sequential endocrine-based therapy in the majority of cases, except for patients with visceral crisis or

where there is concern about (or evidence of) endocrine resistance; for these patients' chemotherapy is normally prescribed.

The combination of endocrine therapy with a CDK4/6 inhibitor has shown substantial progression-free survival benefit and a significant increase in overall survival compared with endocrine therapy alone, and is now considered the first-line standard of care (Cardoso et al 2020). In terms of backbone endocrine therapy, for patients who did not relapse on an AI, or within 12 months of stopping adjuvant AI, a CDK4/6 inhibitor is generally administered in combination with an AI; while in patients who relapsed on adjuvant AI therapy, or within 12 months of stopping adjuvant AI, fulvestrant is advised as combination partner with a CDK4/6 inhibitor. In women, endocrine therapy with or without a CDK4/6 inhibitor is recommended for both post- and pre-menopausal patients where, in the latter setting, it is provided in conjunction with the suppression or ablation of ovarian function. In men, the treatment approach for advanced breast cancer is similar to that of women, with some particularities: tamoxifen is the preferred treatment in HR-positive metastatic disease; in addition, AIs should be used in combination with a luteinising-hormone releasing hormone agonist or surgical orchidectomy due to hypothalamic-pituitary negative feedback.

Targeted therapies approved for advanced HR-positive/HER2-negative breast cancer in combination with endocrine agents, typically used in second line, are:

- the mTOR inhibitor everolimus in combination with exemestane, approved for HR-positive/HER2-negative - breast cancer in postmenopausal women only, after treatment failure with letrozole or anastrozole (US) / after recurrence or progression following a non-steroidal aromatase inhibitor (EU).
- the PI3K inhibitor alpelisib in combination with fulvestrant, approved in men and postmenopausal women whose tumours have eligible PIK3CA mutations, after disease progression following an endocrine-based regimen (US) / endocrine therapy as monotherapy (EU).

The optimal sequence and integration of endocrine therapies are not fully established and are largely determined by which treatments were previously administered, the duration of response to those treatments, burden of disease, patient preference, and availability (Cardoso et al 2020). Tumours eventually develop endocrine therapy resistance, progress, and require different treatments. Subsequent treatment with endocrine monotherapy, including fulvestrant, remains an option in current international guidelines.

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

The majority of patients with breast cancer are diagnosed at an early stage (79% to 87% diagnosed at Stage I or II), while 13% to 21% of patients are diagnosed at Stage III or IV.

Between 6% and 7% of patients have metastases at diagnosis (Cancer Research UK 2022). Stage at diagnosis has been associated with a degree of deprivation, age, and ethnicity (Lyratzopoulos et al 2013, Public Health England 2020).

HR-positive/HER2-negative breast cancer has generally a better prognosis than other subtypes of breast cancer; however, its annual relapse rate continues 10 years after the first diagnosis. In addition, HR-positive breast cancer has a high incidence rate, and for this reason, is the most common cause of breast cancer-related deaths. Although HR-positive breast cancer first responds to endocrine treatment, 15% to 20% of tumours have primary endocrine resistance, and 30% to 40% develop resistance to endocrine treatment during the course of their disease (Lei et al 2019).

Breast cancer is the fifth leading cause of cancer mortality worldwide, with 685000 deaths (Globocan [Breast cancer] 2021). In Europe, the WHO reported in 2020 that breast cancer mortality was 141765, and the crude rate 15.3 per 100000 (WHO Cancer Today 2020).

Metastatic breast cancer remains an incurable disease, with an the estimated worldwide 5-year survival rate of 29% for women and 22% for men (WHO Cancer Today 2020). Based on data reported between 2015 and 2019 in the US, female patients with advanced HR positive/HER2-negative breast cancer had a 5-year survival rate of 31.9% (SEER 2015 to 1019).

Important comorbidities

A study of newly diagnosed female patients with stage I to III breast cancer reported that the 5 most prevalent comorbidities were: hypertension (32.8%), arthritis (32.8%), thyroid problem (22.4%), hypercholesterolaemia (12.7%), and diabetes (12.0%). Comorbidities, specifically hypertension, arthritis, and diabetes, were associated with poorer quality of life in multiple domains among breast cancer survivors (Fu et al 2015).

In a study published in 2019, the most prevalent baseline comorbidities in female breast cancer patients (all stages) were cardiovascular conditions (39.0%), followed by pain/pain inflammation (34.8%) (Ng et al 2019).

II.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of Key Findings from Non-Clinical Data

Key safety findings from non-clinical studies and their relevance to human usage are described below.

Toxicity

- **Key issues identified from acute or repeat-dose toxicity studies:**

  Insulin signalling

  Increased levels of blood glucose and insulin were seen in both rats and dogs. Accompanying findings included the presence of increased levels of plasma fructosamine (rats), glycosylated haemoglobin (rats and dogs), glycogen accumulation in the liver (rats and dogs), liver hypertrophy (rats), hypertrophy/hyperplasia or vacuolation of the pancreatic islet cells (rats and dogs) and glucosuria (rats and dogs). The pathological findings in the liver and pancreas were not noted at the end of the recovery period in the dog, indicating reversibility. In the rat, findings were still present at the end of the recovery period, but at a lower severity, indicating partial recovery.

  Relevance to human use: The observed effects on glucose and insulin in animal models and associated findings are considered related to the pharmacological activity of TRUQAP, and increased blood glucose (hyperglycaemia) is one of the most common on-target adverse effects of PI3K/AKT inhibitors (Liu et al 2022). These non-clinical findings are therefore relevant to human use, and hyperglycaemia has been classified as an ADR for TRUQAP (see Section II.7.1.1 for further details).

  Renal function

  TRUQAP caused changes in several renal parameters. Polyuria was noted in the 1-month and 6-month rat studies and was associated with increased water consumption and accompanied by glucosuria and proteinuria. Proteinuria is suggestive of altered renal tubular function (possibly due to increased glucose). There were no kidney histopathology findings in the 1-month rat study; however, in the 6-month rat study there was decreased tubular epithelial cell size associated with nuclear crowding noted in the kidneys which correlated with reduced kidney weight and size. In a rat renal study TRUQAP increased the fractional excretion of sodium, chloride, potassium, and phosphate; and caused a slight increase in phosphate and a slight decrease in potassium plasma concentrations. Although the mechanism for these changes is not clear, AKT is known to play a role in proximal tubular glucose and phosphate transport (Kempe et al 2010).

Relevance to human use: The inhibition of renal tubular transporter proteins can lead to increases in blood creatinine (without any corresponding renal function impairment) and as increases in blood creatinine have been observed in patients in the TRUQAP clinical development programme, blood creatinine increased is included as an ADR in the TRUQAP SmPC.

Other AEs related to the markers of renal function were also reported in the TRUQAP clinical development programme; however, these were considered due to an inhibition of renal transporters (MATE1, MATE2K, and OCT2) and dehydration, and not due to a direct effect of TRUQAP on the kidneys.

- **Reproductive/developmental toxicity:**

  TRUQAP had an adverse effect on embryonic survival and early postnatal growth when administered to pregnant and lactating rats. AKT knockout mice demonstrated defects in both foetal and postnatal growth, which persisted into adulthood (Cho et al 2001).

  Exposure to TRUQAP was confirmed in suckling rat pups, which may indicate the potential for excretion of TRUQAP in milk.

  TRUQAP caused degenerative changes in the testes in both rats and dogs with associated findings in the epididymides and a reduction in organ weight. The pathology findings in the male reproductive tract were still present after 4 weeks off dose, however this is not unexpected as these tissues usually require more than 28 days to demonstrate evidence of recovery (due to the normal length of the spermatogenic cycle). Based on the nature of the changes observed, full recovery is expected.

  There was no effect on male fertility in the rat 6-month study.

  Relevance to human use: These reproductive and development toxicity findings were expected based on the pharmacological action of this compound and indicate that TRUQAP may cause foetal harm in women of childbearing potential. The SmPC recommends that all patients receiving TRUQAP should use effective contraception during treatment (and for a set duration post-treatment discontinuation), and that TRUQAP should not be used during pregnancy or breast-feeding. Use in this population is therefore not anticipated and, consequently, reproductive/development toxicity does not constitute a safety concern for TRUQAP.

- **Genotoxicity:**

  TRUQAP is not an in vitro genotoxin although it increased the incidence of micronucleated immature erythrocytes in the bone marrow of rats. As the majority of micronuclei contained a kinetochore signal, it can be concluded that TRUQAP has an

aneugenic thresholded mode of action. Furthermore, TRUQAP did not induce increases in DNA damage in the liver of rats in the Comet assay.

Relevance to human use: TRUQAP is indicated only for use in the advanced cancer setting, and consequently the theoretical risk for the development of secondary malignancies is unlikely to impact the benefit-risk assessment in this patient population. No safety concern has therefore been identified for inclusion in this RMP.

- **Carcinogenicity:**

  Carcinogenicity studies are in progress to support the potential clinical development of TRUQAP in populations other than those referenced in International Council for Harmonisation S9 guidelines.

  Relevance to human use: Not applicable.

Safety pharmacology

- **Cardiovascular system, including potential effect on the QT interval:**

  TRUQAP inhibits the hERG channel, with an IC50 of 73.0 μmol/L, via an underlying mechanism that may be due to increases in plasma glucose and insulin levels (Marfella et al 2001, van Noord et al 2010). Data from an isolated rabbit heart model suggest that TRUQAP may be classified as low risk in terms of triggering QT associated arrhythmia or Torsades de Pointes. In the dog telemetry study, heart rate was decreased for up to 8 hours following a single dose of TRUQAP. At higher TRUQAP doses, there were peak decreases in systolic and diastolic blood pressure recovering within 4 hours, plus a sustained prolongation of QT interval corrected for heart rate using an individual linear regression formula and increase in integrated measure of left ventricular contractility, along with elevation of both glucose and insulin levels; these are known to play an important role in QT, potentially contributing to the changes observed.

  Increases in cardiac contractility were observed in the dog telemetry and dog 1-month toxicity studies; the mechanism underlying these observations is unknown. Decreases in blood pressure have also been noted in dogs, rats, and guineapigs, consistent with the vaso-relaxant activity of TRUQAP identified in a rat aorta study and the increase in coronary flow seen in the isolated rat and rabbit heart studies.

  Relevance to human use: These findings were primarily observed in animals exposed to higher levels of TRUQAP than the clinically therapeutic dose of 400 mg twice daily, 4 days on 3 days off. Therefore, TRUQAP is not predicted to pose a clinically significant safety risk for QTc prolongation or other cardiac toxicities, and no safety signal for these events has been identified in TRUQAP clinical studies.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

TRUQAP is only indicated for use in combination with fulvestrant. The pivotal dataset in support of this combination treatment was derived from Study D3615C00001 (CAPItello-291), in which patients received weekly oral TRUQAP 400 mg (twice daily: 4 days on, 3 days off) and fulvestrant (at the approved dose regimen [500 mg intramuscular injections on Day 1 of Weeks 1 and 3 of Cycle 1, and then on Day 1, Week 1 of each cycle thereafter]). Study treatment was continued until disease progression unless there was evidence of unacceptable toxicity, or if the patient requested to stop the study treatment.

Exposure to TRUQAP in combination with fulvestrant in the pivotal CAPItello-291 study by number of cycles, age group, sex, and race is presented in Table II-1, Table II-2, and Table II-3, respectively.

Table II-1 Duration of Exposure to TRUQAP plus Fulvestrant (CAPItello-291 Study) (N = 355)

Duration of exposure	Number of patients (%)	Patient-years exposure
≥ 1 month	312 (87.9)	209.0
≥ 2 months	258 (72.7)	201.6
≥ 3 months	231 (65.1)	195.9
≥ 4 months	195 (54.9)	185.2
≥ 5 months	186 (52.4)	181.8
≥ 6 months	165 (46.5)	172.2
≥ 12 months	80 (22.5)	108.9
≥ 18 months	23 (6.5)	40.4
≥ 24 months	2 (0.6)	4.3

Table II-2 Exposure to TRUQAP plus Fulvestrant by Age Group and Gender (CAPItello-291 Study) (N = 355)

Age group (years)	Male		Female	
	Number of patients (%)	Patient-years exposure	Number of patients (%)	Patient-years exposure
< 65	3 (0.8)	0.6	237 (66.8)	142.4
65 to 74	0	0	91 (25.6)	56.2
≥ 75	0	0	24 (6.8)	11.8

Table II-3 Exposure to TRUQAP plus Fulvestrant by Race (CAPItello-291 Study) (N = 355)

Race	Number of patients (%)	Patient-years exposure
White	201 (56.6)	110.6
Asian	95 (26.8)	73.0
American Indian or Alaska Native	2 (0.6)	0.6
Black or African American	4 (1.1)	1.5
Native Hawaiian or Other Pacific Islander	1 (0.3)	0.8
Other [a]	52 (14.6)	24.5

[a] Race data for France, Hungary, Belgium, Australia are not allowed to be collected.

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

II.4.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

- ***Paediatric and adolescent patients (< 18 years in the US and EU, < 20 years in Japan)***
  - Reason for exclusion: This population was excluded from TRUQAP clinical studies based on the general principle that paediatric patients are not exposed to the investigational product where the benefit-risk profile for the intended adult population has not yet been established.
  - Is it considered to be included as missing information: No
  - Rationale: Breast cancer is a disease of adults, with only exceptional occurrence in the paediatric population (Kennedy and Boughey 2013). Consequently, use in paediatric and adolescent patients is not indicated or anticipated for the target indication, and therefore this population is not relevant for inclusion as missing information.

- ***Patients with an Eastern Cooperative Oncology Group performance status of ≥ 2***
  - Reason for exclusion: Patients with poor performance status are generally excluded from clinical studies to ensure they are well enough to attend the trial site and comply with study procedures, and to ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: There is no scientific rationale to suspect that the safety profile of TRUQAP treatment in patients with a performance status of ≥ 2 would differ from that of the general target patient population. Consequently, this criterion is not relevant for inclusion as missing information.

- ***Pregnant and/or breastfeeding women***
  - Reason for exclusion: In non-clinical studies, TRUQAP had an adverse effect on rat embryonic survival and early postnatal growth. Exposure to TRUQAP was also confirmed in suckling pups. Women who were pregnant or breastfeeding were therefore excluded from TRUQAP clinical studies to avoid potential harm to the unborn foetus or breastfed infant.
  - Is it considered to be included as missing information: No
  - Rationale: The SmPC recommends that all patients receiving TRUQAP should use effective contraception during treatment (and for a set duration post-treatment discontinuation), and that that TRUQAP should not be used during pregnancy or

breastfeeding. Use in this population is therefore not anticipated and is consequently not relevant for inclusion as missing information.

- ***Patients with spinal cord compression, symptomatic brain metastases, or leptomeningeal disease***
  - Reason for exclusion: Patients with these conditions have significantly worse prognoses and a reduced life expectancy and are therefore generally excluded from clinical studies to avoid factors that may confound the understanding and interpretation of safety and efficacy data. Of note, patients with stable brain metastases were not excluded from clinical studies.
  - Is it considered to be included as missing information: No
  - Rationale: There is no evidence of a different safety profile in patients with stable brain metastases from the TRUQAP clinical studies to date. Furthermore, there is no scientific rationale to suspect that the safety profile of patients with symptomatic brain metastases, leptomeningeal disease, or spinal cord compression would be different to that of the general target patient population, and further investigation of this patient population is not feasible due to their poor prognosis. Consequently, this criterion is not relevant for inclusion as missing information.

- ***Patients with a past medical history or concurrent clinically active ILD or radiation pneumonitis***
  - Reason for exclusion: Patients with a past history of ILD / pneumonitis were excluded from TRUQAP clinical studies in order to eliminate confounding factors that may compromise the ability to characterise the safety profile of TRUQAP and ensure interpretability of safety data.
  - Is it considered to be included as missing information: No
  - Rationale: There is no scientific rationale to suggest that the safety profile of TRUQAP treatment in patients with a past medical history or concurrent clinically active ILD or radiation pneumonitis would differ from that of the general target patient population. Further characterisation of safety in this population is therefore not warranted, and consequently, this criterion is not relevant for inclusion as missing information.

- ***Patients with clinically important abnormalities in cardiac rhythm or any factors that increase the risk of QTc prolongation or arrhythmic events***
  - Reason for exclusion: TRUQAP was active at the hERG-encoded potassium channel, with an IC_{50} of 73.0 µmol/L. Data from an isolated rabbit heart model suggest that the risk of QT-associated arrhythmia or Torsades de Pointes is low. Nevertheless, in order to protect the safety of patients, those with clinically important abnormalities in cardiac rhythm (eg, complete left bundle branch block, third degree heart block, or QTcF > 470 msec) or any factors that increase the risk of QTc prolongation or arrhythmic events (eg, heart failure, congenital long QT syndrome, etc) were excluded from TRUQAP clinical studies.
  - Is it considered to be included as missing information: Yes

- ***Patients with decreased cardiac ejection fraction***
  - Reason for exclusion: Patients with abnormal cardiac function are generally excluded from clinical studies to avoid factors that may confound the understanding and interpretation of safety data. Consequently, patients with decreased left ventricular ejection fraction (ie, < 50%) were excluded from TRUQAP clinical studies.
  - Is it considered to be included as missing information: No
  - Rationale: No safety signal for decreases in cardiac ejection fraction or associated sequalae has been identified from the patient populations enrolled into TRUQAP clinical studies, and consequently clinical data do not support an association between TRUQAP and effects on cardiac contractility. Therefore, a different safety profile in patients with decreased cardiac ejection fraction to that characterised for the general target patient population is not anticipated and consequently, this criterion is not relevant for inclusion as missing information.

- ***Patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment, or HbA1c ≥ 8.0%***
  - Reason for exclusion: In non-clinical studies, increased levels of glucose and insulin were seen in both rats and dogs, which is considered related to the pharmacological activity of TRUQAP. Patients with clinically significant abnormalities of glucose metabolism (defined as diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment or a HbA1c ≥ 8.0% [63.9 mmol/mol]) were therefore excluded from TRUQAP clinical studies in the interests of patient safety.
  - Is it considered to be included as missing information: Yes

- ***Patients with a creatinine > 1.5 × ULN concurrent with creatinine clearance < 50 ml/min***

  - Reason for exclusion: Patients with varying degrees of pre-existing impaired renal function are generally excluded from clinical studies to avoid factors that may confound the understanding and interpretation of safety data. Consequently, patients with a creatinine > 1.5 × ULN concurrent with creatinine clearance < 50 ml/min were excluded from TRUQAP clinical studies.
  - Is it considered to be included as missing information: No
  - Rationale: Since the initiation of the TRUQAP clinical development programme, data from a population PK analysis have indicated that no dose adjustments are required for patients with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment. Therefore, given the availability of these data (which do not raise any safety concerns), these patient populations are not considered relevant for inclusion as missing information.

    No data are available for patients with severe renal impairment (creatinine clearance < 30 ml/min); however, Section 4.2 (*Posology and method of administration – Special populations*) of the SmPC states that TRUQAP is not recommended for use in these patients. Administration of TRUQAP in this patient population is therefore not anticipated. Consequently, use in patients with severe renal impairment is not classified as an area of missing information.

- ***Patients with a total bilirubin of > 1.5 × ULN and an AST / ALT > 2.5 × ULN (or > 5 × ULN in the presence of liver metastases)***

  - Reason for exclusion: Patients with pre-existing hepatic impairment are generally excluded from clinical studies to avoid factors that may confound the understanding and interpretation of safety data. Additionally, TRUQAP is primarily metabolised by CYP3A4 and UGT2B7 enzymes, and in rats, plasma liver enzyme levels were increased in 1-month and 6-month toxicology studies. Consequently, patients with a total bilirubin of > 1.5 × ULN and an AST / ALT > 2.5 × ULN (or > 5 × ULN in the presence of liver metastases) were excluded from TRUQAP clinical studies.
  - Is it considered to be included as missing information: No
  - Rationale: Since the initiation of the TRUQAP clinical development programme, data from a population PK analysis have indicated that no dose adjustments are required for patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1 × ULN to ≤ 1.5 × ULN). Patients with moderate hepatic impairment (bilirubin > 1.5 × ULN to ≤ 3 × ULN) should only receive TRUQAP if the benefit outweighs the risk (and these patients should be monitored closely for signs of

toxicity). Therefore, given the availability of these data, these patient populations are not considered relevant for inclusion as missing information.

No data are available for patients with severe hepatic impairment (bilirubin > 3 × ULN); however, Section 4.2 (*Posology and method of administration - Special populations*) of the SmPC states that TRUQAP in not recommended for use in these patients. Administration of TRUQAP in this patient population is therefore not anticipated. Consequently, use patients with severe hepatic impairment is not classified as an area of missing information.

- ***Patients with severe or uncontrolled systemic diseases (eg, Hepatitis B or C infection), or with known HIV or immunodeficiency syndrome***
  - Reason for exclusion: Patients severe or uncontrolled systemic diseases, or with known HIV or immunodeficiency syndrome, are generally excluded from clinical studies due to the potential for drug-drug interactions with relevant concomitant medications, and to ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: There is no scientific rationale to suspect that the safety profile in patients with severe or uncontrolled systemic diseases, or with known HIV or immunodeficiency syndrome will differ to that which has been characterised in the general target patient population. Provided the guidance on the use of concomitant medications in Section 4.5 (*Interaction with other medicinal products and other forms of interaction*) of the TRUQAP SmPC is followed, there is no clinical reason why these patients should not receive TRUQAP treatment. Consequently, this criterion is not relevant for inclusion as missing information.

- ***Use of potent inhibitors or inducers of CYP3A4 or drugs that are sensitive to CYP3A4 inhibition***
  - Reason for exclusion: TRUQAP is primarily metabolised by CYP3A4 and UGT2B7 enzymes, and in vitro experiments indicate that TRUQAP is a time-dependent and reversible inhibitor of CYP3A4. Co-administration of compounds that inhibit these enzymes may increase exposure to TRUQAP and hence potentially affect toxicity, while inducers may decrease the exposure to TRUQAP and may potentially affect efficacy. Furthermore, the exposure and toxicity of drugs that are sensitive to CYP3A inhibition may be increased by TRUQAP. The concomitant use of such compounds was therefore an exclusion criterion in TRUQAP clinical studies to avoid interactions, in order to ensure optimal assessment of the efficacy and safety profile of TRUQAP.
  - Is it considered to be included as missing information: No

- Rationale: Section 4.5 (*Interaction with other medicinal products and other forms of interaction*) of the SmPC states that the concomitant use of strong CYP3A4 inducers is not recommended, and guidance is provided in respect of dose adjustments for strong CYP3A inhibitors and drugs that are sensitive to CYP3A4 inhibition. Considering this guidance, usage in this population is anticipated to be low and controlled, and therefore this population is not considered to be relevant for inclusion as missing information.

II.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.

II.4.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table II-4 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure TRUQAP + fulvestrant (CAPItello-291 study; N = 355)
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with hepatic impairment:	
Moderate hepatic impairment [a]	1 participant
Severe hepatic impairment [a]	0 participants
Patients with renal impairment [b]	
Moderate renal impairment [b]	46 participants
Severe renal impairment [b]	0 participants
Patients with cardiac impairment (including QTc prolongation, heart failure, uncontrolled hypotension, left ventricular ejection fraction decreased, or cardiac arrhythmia)	Not included in the clinical development programme
Immunocompromised patients	Not included in the clinical development programme
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Patients with relevant different ethnic origin:	
American Indian or Alaska Native	2 participants
Asian	95 participants
Black or African American	4 participants
Native Hawaiian or Other Pacific Islander	1 participant
White	201 participants
Other	52 participants
Subpopulations carrying relevant genetic polymorphisms	No data available

[a] The definitions for hepatic impairment are as follows: moderate hepatic impairment = bilirubin > 1.5 × ULN to ≤ 3 × ULN and any AST; and severe hepatic impairment = bilirubin > 3 × ULN and any AST.

[b] The definitions for renal impairment are as follows: moderate renal impairment: creatinine clearance 31 to 50 ml/min, and severe renal impairment: creatinine clearance < 30 ml/min.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II.5.1 Method Used to Calculate Exposure

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

The sales volume is provided as the number of tablets (200 mg and 160 mg) distributed. For the sales of the 200 mg tablets, the estimated post-marketing patient exposure data for the reporting period is an approximation based on the assumption that each patient took the recommended dose of four 200 mg tablets of TRUQAP a day (400 mg BD dose) for 4 days a week followed by 3 days off treatment. Therefore, a patient-year worth of exposure is calculated by multiplying 16 tablets of 200 mg (total dose per week) by 52 weeks (one year). For the 160 mg tablets, the estimated post-marketing patient exposure data for the reporting period is an approximation based on the assumption that each patient took the reduced dose of four 160 mg tablets of TRUQAP a day (320 mg BD dose) for 4 days a week followed by 3 days off treatment. Therefore, a patient-year worth of exposure is calculated by multiplying 16 tablets of 160 mg per day (total dose per week) by 52 weeks (one year).

Based on the above, the total number of tablets a year is 832 tablets (16 tablets a week multiplied by 52 weeks). Therefore, to present exposure in patient-years, the total number of tablets distributed (200 mg and 160 mg) is thus divided by 832.

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

II.5.2 Exposure

The cumulative global post-marketing patient exposure to TRUQAP (tablets [200 mg and 160 mg]) since launch to 30 April 2024 has been estimated to be approximately 318.9 patient-years for 200 mg and 49.9 patient-years for 160 mg tablets.

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

Potential for misuse for illegal purposes

Based on the clinical setting of use, mode of action, physiological and pharmacological activity, and lack of stimulant and addictive properties, TRUQAP is unlikely to have any potential for abuse.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of Safety Concerns in the Initial RMP Submission

II.7.1.1 Risk Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The reasons for not including a risk in the list of safety concerns in the initial EU RMP (Version 1) are presented below:

- *Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):*
  - Decreased appetite, dry skin, dysgeusia, dyspepsia, fatigue, hyperglycaemia, mucosal inflammation, nausea, stomatitis, urinary tract infection, and vomiting.
- *Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:*
  - Anaemia, blood creatinine increased, and glycosylated haemoglobin increased.
- *Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice):*
  - Diarrhoea, and skin toxicity (including dermatitis, dermatitis exfoliative generalised, drug eruption, erythema multiforme, pruritus, rash, and toxic skin eruption).
- *Known risks that do not impact the risk-benefit profile:*
  - Hypersensitivity.

II.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The following topics were classified as safety concerns for TRUQAP in the initial EU RMP (Version 1):

Important identified risk

There are no important identified risks.

Important potential risk

- **Complications of Hyperglycaemia**
  - *Risk-benefit impact:* There is the potential for hyperglycaemia to result in complications. Whilst such events have rarely been observed in the TRUQAP clinical development programme, complications of hyperglycaemia can be life-threatening, and require early detection, careful monitoring, and timely medical intervention.

Missing Information

- **Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%)**
  - *Risk-benefit impact:* Only limited data are available in patients with clinically significant abnormalities of glucose metabolism (defined as diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment or a HbA1c ≥ 8.0% [63.9 mmol/mol]) as these patients were excluded from the pivotal study. Uncertainty therefore remains as to whether the safety profile of TRUQAP in this population may differ to that of the broader target population in the post-marketing setting, and consequently further data are required to aid characterisation.

- **Use in patients with clinically important abnormalities in cardiac rhythm (eg, QT prolongation)**
  - *Risk-benefit impact*: Whilst no safety signal for QT prolongation or associated sequalae has been observed from a review of data from the TRUQAP clinical development programme, it is acknowledged that patients with clinically important abnormalities in cardiac rhythm were excluded from the pivotal CAPItello-291 study. Consequently, and in recognition that there are no restrictions on TRUQAP use in this population in the post-marketing setting, additional safety data are required to further characterise abnormalities in cardiac rhythm.

II.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

The following changes to the list of safety concerns have been made in this EU RMP:

- **"Diabetic ketoacidosis" is a new important identified risk**
  - *Changes in the level of scientific evidence for the causal association or risk-benefit impact*: There is a plausible mechanism of action for how TRUQAP may lead to hyperglycaemia, and occurrences of diabetic ketoacidosis have been reported in the TRUQAP clinical development programme and subsequently during post-marketing use. In addition, it was determined upon further evaluation that some spontaneous reports of hyperglycaemia met the laboratory diagnostic criteria for diabetic ketoacidosis. Whilst the majority of patients recovered from diabetic ketoacidosis, cases with a fatal outcome were also reported. Upon review of data from all sources, it was observed that diabetic ketoacidosis can occur at any time during TRUQAP treatment; however, some cases developed in less than 10 days. Consequently, a reasonable possibility of a causal relationship between TRUQAP and diabetic ketoacidosis has been confirmed, and whilst diabetic ketoacidosis has been uncommonly observed in the TRUQAP clinical development programme, it may result in a fatal outcome, and may therefore impact the benefit-risk balance of TRUQAP.
- **The existing important potential risk of "Complications of hyperglycaemia" has been updated to "Complications of hyperglycaemia (excluding diabetic ketoacidosis)"**
  - *Reasons for the amendment of the existing safety concern*: The important potential risk of "Complications of hyperglycaemia" initially included diabetic ketoacidosis. However, as diabetic ketoacidosis (including ketoacidosis) is now considered causally related to TRUQAP and has been added to the RMP as an important identified risk (as described above), this event has subsequently been excluded from this important potential risk.

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

Potential mechanisms

Hyperglycaemia is an on-target effect of PI3K inhibition (Liu et al 2022), and therefore the effects of TRUQAP on glucose and insulin metabolism is considered related to the pharmacological activity of the compound. Whilst TRUQAP-induced hyperglycaemia is considered to be mainly due to decrease in glucose uptake and increase in gluconeogenesis/reduced glycogen synthesis, it may also lead to relative insulin deficiency, and severe hyperglycaemia with relative insulin deficiency may subsequently lead to diabetic ketoacidosis.

Evidence source(s) and strength of evidence

There is a plausible mechanism of action for how TRUQAP may lead to hyperglycaemia, and uncommon occurrences of diabetic ketoacidosis associated with severe hyperglycaemia have been reported in the TRUQAP clinical development programme, and subsequently during post-marketing use.

Characterisation of the risk

This risk is characterised utilising data from the pivotal CAPItello-291 study in Table II-5.

Furthermore, from a review of all available data (including post-marketing sources), it was noted that diabetic ketoacidosis can occur at any time during TRUQAP treatment, and in some cases, developed in less than 10 days. Cases of diabetic ketoacidosis with a fatal outcome were also reported.

Risk factors and risk groups

No specific risk factors for the development of diabetic ketoacidosis in TRUQAP-treated patients has been identified. However, in a setting of additional comorbidities and treatments (eg, dehydration, malnourishment, infection/sepsis, and concurrent chemotherapy/steroid use) the risk of hyperglycaemia progressing to diabetic ketoacidosis may be greater.

Preventability

As described in the TRUQAP SmPC and PL, healthcare professionals should undertake regular fasting glucose and HbA1c level monitoring (with particular emphasis on additional monitoring in the first 8 weeks of treatment with TRUQAP) and timely assessment of any signs and symptoms indicative of hyperglycaemia. Patients should also be informed to immediately contact their healthcare professional should any symptoms of hyperglycaemia and/or diabetic ketoacidosis occur.

TRUQAP treatment should be interrupted immediately in patients where diabetic ketoacidosis is suspected, and permanently discontinued if diabetic ketoacidosis is confirmed.

Impact on the risk-benefit balance of the product

If not recognised or managed appropriately, diabetic ketoacidosis can be life-threatening, or result in a fatal outcome.

Public health impact

There is no potential public health impact beyond that within the treated population.

Table II-5 Important Identified Risk: Diabetic Ketoacidosis

Indication *(pivotal dataset)*	Treatment group	Number of patients (%)						
		Frequency and severity		Serious	Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade ≥ 3		Resolved	Not resolved	Resulted in death	
ER-positive/HER2-negative breast cancer *(CAPItello-291 study)*	**Diabetic ketoacidosis (PT)**							
	TRUQAP + fulvestrant (N = 355)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	1 (0.3)
	Placebo + fulvestrant (N = 350)	0	0	0	0	0	0	0

It is noted that diabetic ketoacidosis is characterised by a cluster of relevant PTs, of which only the events in this table have been observed in the pivotal study.

Important Potential Risk: Complications of Hyperglycaemia (Excluding Diabetic Ketoacidosis)

Potential mechanisms

Hyperglycaemia is an on-target effect of PI3K inhibition, and therefore its occurrence in TRUQAP-treated patients is considered related to the pharmacological activity of the compound (Liu et al 2022). If left untreated, or in patients with risk factors for poor blood sugar control (eg, those with medical history of type 1 or 2 diabetes, pre-diabetes, concurrent infections, or those receiving concomitant systemic corticosteroids), hyperglycaemia can potentially lead to complications.

Evidence source(s) and strength of evidence

Rare occurrences of complications due to hyperglycaemia have been reported in the TRUQAP clinical development programme.

Characterisation of the risk

This risk is characterised in Table II-6.

Risk factors and risk groups

No specific risk factors for the development of complications of hyperglycaemia in TRUQAP-treated patients have been identified. However, patients with risk factors for poor blood sugar control (as defined above) may be at greater risk of experiencing hyperglycaemia leading to associated complications.

Preventability

As described in the TRUQAP SmPC and PL, prior to the start of TRUQAP treatment, patients should be informed to immediately contact their healthcare professional should symptoms of hyperglycaemia or associated complications occur. Regular fasting glucose and HbA1c level monitoring (with particular emphasis on additional monitoring in the first 8 weeks of treatment with TRUQAP) and the timely assessment of any signs and symptoms indicative of complications of hyperglycaemia should also be undertaken.

Based on the severity of hyperglycaemia, TRUQAP dosing may be interrupted, reduced, or discontinued, and provision of appropriate medical intervention (in accordance with local practice) should help to prevent complications.

Impact on the risk-benefit balance of the product

Poorly controlled hyperglycaemia can lead to complications, which may be life-threatening. This may also disproportionately impact morbidity and quality of life in the target patient population.

Public health impact

There is no potential public health impact beyond that within the treated population.

Table II-6 Important Potential Risk: Complications of Hyperglycaemia (Excluding Diabetic Ketoacidosis)

Indication *(pivotal dataset)*	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade ≥ 3	Serious	Resolved	Not resolved	Resulted in death	
ER-positive/ HER2-negative breast cancer *(CAPItello-291 study)*	**Diabetic metabolic decompensation (PT)**							
	TRUQAP + fulvestrant (N = 355)	2 (0.6)	1 (0.3)	1 (0.3)	2 (0.6)	0	0	0
	Placebo + fulvestrant (N = 350)	0	0	0	0	0	0	0

The important potential risk of 'complications of hyperglycaemia' is characterised by a cluster of relevant PTs, of which only the events in this table have been observed in the pivotal study.

II.7.3.2 Presentation of Missing Information

Missing Information: Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%)

Evidence source

Only limited data are available in patients with clinically significant abnormalities of glucose metabolism (defined as diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment or a HbA1c ≥ 8.0% [63.9 mmol/mol]) as these patients were excluded from the pivotal study.

Population in need of further characterisation

Patients with ER-positive/HER2-negative breast cancer who have type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%).

Missing Information: Use in patients with clinically important abnormalities in cardiac rhythm (eg, QT prolongation)

Evidence source

Whilst no safety signal for QT prolongation or associated sequalae has been observed from a review of data from the TRUQAP clinical development programme, it is acknowledged that patients with clinically important abnormalities in cardiac rhythm were excluded from the pivotal CAPItello-291 study.

Population in need of further characterisation

Patients with ER-positive/HER2-negative breast cancer who have clinically important abnormalities in cardiac rhythm (eg, QT prolongation).

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the Safety Concerns

The safety concerns for TRUQAP are summarised in Table II-7.

Table II-7 Summary of Safety Concerns

Important identified risks	• Diabetic ketoacidosis
Important potential risks	• Complications of hyperglycaemia (excluding diabetic ketoacidosis)
Missing information	• Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%) • Use in patients with clinically important abnormalities in cardiac rhythm (eg, QT prolongation)

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are as follows:

- **Specific adverse reaction follow-up questionnaires:** A targeted follow-up safety questionnaire is in place to enable comprehensive data collection for the important identified risk of "*Diabetic ketoacidosis*" and the important potential risk of "*Complications of hyperglycaemia (excluding diabetic ketoacidosis)*" in a standardised way across regions and prescribers. The information received will facilitate ongoing surveillance activities in the post-marketing setting, and will enable more complete collection of data, thereby optimising risk evaluation.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

- **Study short name and title**: A database study of the safety and effectiveness of TRUQAP (capivasertib) + fulvestrant in patients with advanced breast cancer and type 1 or type 2 diabetes
  - ***Rationale and study objectives***: The rationale for this study is to address the lack of efficacy and safety data for patients with insulin-dependent or uncontrolled diabetes (assessed as a baseline HbA1c ≥ 8.0%), given the exclusion of these patients from the pivotal CAPItello-291 study. This gap is particularly relevant as a key safety concern for TRUQAP is complications of hyperglycaemia (such as diabetic ketoacidosis), for which the baseline risk is elevated in diabetic patients.

    The primary objective of this non-interventional post-authorisation study is to assess the effectiveness and safety of TRUQAP + fulvestrant in patients with advanced breast cancer and diabetes (type 1 or type 2; insulin- or non-insulin-dependent) who have received prior endocrine treatment.
  - ***Study design***: The proposed study will apply a non-interventional, longitudinal, population-based, cohort design to secondary data derived from multiple large data sources that are representative of EU member states. Data sources in the US may also be included if required to attain the desired sample size. The accrual period for patients will begin as of the regulatory marketing approval date for TRUQAP in the country where the potential participant resides.
  - ***Study population***: The target study population is adult patients with type 1 or type 2 diabetes, including those with insulin-dependent diabetes who initiate treatment for advanced breast cancer. Patients will be selected using a combination of diagnosis codes for advanced breast cancer, prescription medications, and, if necessary, other diagnoses or procedures that are indicative of advanced breast cancer. Necessary

inclusion and exclusion criteria will be applied to ensure that the study population is representative of TRUQAP + fulvestrant users.

- ***Milestones*:**
  - *Submission of feasibility report*: Jul 2024
  - *Protocol submission*: Oct 2024
  - *Interim report completion*: Q3 2027
  - *Final study report completion*: Q3 2030

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

A summary of additional pharmacovigilance activities is provided in Table III-1.

Table III-1 Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
A database study of the safety and effectiveness of TRUQAP (capivasertib) + fulvestrant in patients with advanced breast cancer and type 1 or type 2 diabetes Planned	To assess the effectiveness and safety of TRUQAP + fulvestrant in patients with advanced breast cancer and diabetes (type 1 or type 2; insulin- or non-insulin-dependent) who have received prior endocrine treatment	• Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%)	Submission of feasibility report	Jul 2024
			Protocol submission	Oct 2024
			Interim report completion	Q3 2027
			Final study report completion	Q3 2030

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

Not applicable.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

A summary of routine risk minimisation measures per safety concern are provided in Table V-1.

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

Safety concern	Routine risk minimisation activities
Important Identified Risk	
Diabetic ketoacidosis	**Routine risk communication:** • SmPC Section 4.8 • PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4: – Treatment modification guidelines, including withholding dose, or discontinuing TRUQAP treatment – Detailed glucose monitoring guidance – Monitoring for signs and symptoms • PL Section 2: – How to detect early signs and symptoms **Other routine risk minimisation measures beyond the Product Information:** • Prescription-only medicine
Important Potential Risk	
Complications of hyperglycaemia (excluding diabetic ketoacidosis)	**Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4: – Monitoring for signs and symptoms • PL Section 2: – How to detect early signs and symptoms **Other routine risk minimisation measures beyond the Product Information:** • Prescription-only medicine
Missing Information	
Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%)	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4: – Close monitoring and potential intensification of existing anti-diabetic treatment

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

Safety concern	Routine risk minimisation activities
Use in patients with clinically important abnormalities in cardiac rhythm (eg, QT prolongation)	None.

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable - routine risk minimisation measures (as described in Section II.7.3.1) are sufficient to manage the safety concerns of TRUQAP.

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 Risk		
Diabetic ketoacidosis	**Routine risk minimisation measures:** • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 • Prescription-only medicine **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up questionnaire **Additional pharmacovigilance activities:** • None
Important Potential Risk		
Complications of hyperglycaemia (excluding diabetic ketoacidosis)	**Routine risk minimisation measures:** • SmPC Section 4.4 • PL Section 2 • Prescription-only medicine. **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up questionnaire **Additional pharmacovigilance activities:** • None

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%)	**Routine risk minimisation measures:** • SmPC Section 4.4 • PL Section 2 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • A database study of the safety and effectiveness of TRUQAP (capivasertib) + fulvestrant in patients with advanced breast cancer and type 1 or type 2 diabetes
Use in patients with clinically important abnormalities in cardiac rhythm (eg, QT prolongation)	None.	None.

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR TRUQAP (CAPIVASERTIB)

Summary of risk management plan for TRUQAP (capivasertib)

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

TRUQAP's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how TRUQAP should be used.

This summary of the RMP for TRUQAP 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 the TRUQAP RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

TRUQAP is authorised in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration following recurrence or progression on or after an endocrine-based regimen. It contains capivasertib as the active substance and it is given as two 200 mg tablets taken orally twice daily.

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

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

Important risks of TRUQAP, together with measures to minimise such risks and the proposed studies for learning more about the risks of TRUQAP, 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 PL 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 to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to 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, including Periodic Safety Update Report (PSUR) 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 TRUQAP is not yet available, it is listed under *missing information* below.

VI.2.1 List of Important Risks and Missing Information

Important risks of TRUQAP 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 TRUQAP. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table VI-1 List of Important Risks and Missing Information

Important identified risks	• Diabetic ketoacidosis
Important potential risks	• Complications of hyperglycaemia (excluding diabetic ketoacidosis)
Missing Information	• Safety in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%) • Use in patients with clinically important abnormalities in cardiac rhythm (eg, QT prolongation)

VI.2.2 Summary of Important Risks

Table VI-2 Important Identified Risk: Diabetic Ketoacidosis

Evidence for linking the risk to the medicine	There is a plausible mechanism of action for how TRUQAP may lead to hyperglycaemia, and uncommon occurrences of diabetic ketoacidosis associated with severe hyperglycaemia have been reported in the TRUQAP clinical development programme, and subsequently during post-marketing use.
Risk factors and risk groups	No specific risk factors for the development of diabetic ketoacidosis in TRUQAP-treated patients has been identified. However, in a setting of additional comorbidities and treatments (eg, dehydration, malnourishment, infection/sepsis, and concurrent chemotherapy/steroid use) the risk of hyperglycaemia progressing to diabetic ketoacidosis may be greater.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections 4.4 and 4.8 • PL Section 2 and 4 • Prescription-only medicine **Additional risk minimisation measures:** • No additional risk minimisation measures.

Table VI-3 Important Potential Risk: Complications of Hyperglycaemia (Excluding Diabetic Ketoacidosis)

Evidence for linking the risk to the medicine	Rare occurrences of complications due to hyperglycaemia have been reported in the TRUQAP clinical development programme.
Risk factors and risk groups	No specific risk factors for the development of complications of hyperglycaemia in TRUQAP-treated patients have been identified. However, patients with risk factors for poor blood sugar control (eg, those with a medical history of type 1 or 2 diabetes, pre-diabetes, concurrent infections, or those receiving concomitant systemic corticosteroids) may be at greater risk of experiencing hyperglycaemia leading to associated complications.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.4 • PL Section 2 • Prescription-only medicine **Additional risk minimisation measures:** • No additional risk minimisation measures.

Table VI-4 Missing Information: Safety in Patients with Type 1 and Type 2 Diabetes (Requiring Insulin Treatment, or HbA1c ≥ 8.0%)

Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.4 • PL Section 2 **Additional risk minimisation measures:** • No additional risk minimisation measures.

Table VI-4 Missing Information: Safety in Patients with Type 1 and Type 2 Diabetes (Requiring Insulin Treatment, or HbA1c ≥ 8.0%)

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • A database study of the safety and effectiveness of TRUQAP (capivasertib) + fulvestrant in patients with advanced breast cancer and type 1 or type 2 diabetes

Table VI-5 Missing Information: Use in Patients with Clinically Important Abnormalities in Cardiac Rhythm (eg, QT Prolongation)

Risk minimisation measures	**Routine risk minimisation measures:** • No routine risk minimisation measures. **Additional risk minimisation measures:** • No additional risk minimisation measures.

VI.2.3 Post-Authorisation Development Plan

VI.2.3.1 Studies Which are Conditions of the Marketing Authorisation

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

VI.2.3.2 Other Studies in Post-Authorisation Development Plan

Other studies in the post-authorisation development plan are as follows:

- **A database study of the safety and effectiveness of TRUQAP plus fulvestrant in advanced breast cancer patients with type 1 or type 2 diabetes**
  - *Purpose of the study*: The rationale for this study is to address the lack of efficacy and safety data for patients with insulin-dependent or uncontrolled diabetes (assessed as a baseline HbA1c ≥ 8.0%), given the exclusion of these patients from the pivotal CAPItello-291 study. This gap is particularly relevant as a key safety concern for TRUQAP is complications of hyperglycaemia (such as diabetic ketoacidosis), for which the baseline risk is elevated in diabetic patients.

    The primary objective of this non-interventional post-authorisation study is to assess the effectiveness and safety of TRUQAP + fulvestrant in patients with advanced breast cancer and diabetes (type 1 or type 2; insulin- or non-insulin-dependent) who have received prior endocrine treatment.

VII. PART VII: ANNEXES

Annex 4 Specific Adverse Drug Reaction Follow-Up Forms

Annex 4: Specific Adverse Drug Reaction Follow-Up Forms

The following questionnaire will be used to collect further information on relevant safety concerns:

- Complications of Hyperglycaemia Data Collection Form

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Complications of Hyperglycaemia Data Collection Form
Case ID #_____ AZ Date of Receipt _____

Reporter Information		
Reporter Name:	**Reporter address:**	**Telephone #:** **e-mail:**

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

Patient Details							
Initials:	**Gender at Birth:** ☐ Male ☐ Female	**Weight:**	☐ lb	☐ kg	**Height:**	☐ in	☐ cm
Age:		**Ethnic Origin:**			**Race:**		

History: Type of diabetes					
Not applicable □ (non-diabetic)	T1DM □ T2DM □	Pre-diabetes □ Ketosis prone □	LADA* □	History of gestational diabetes □	Other (please specify):

Duration of diabetes since time to diagnosis				
< 1 Year ☐	1-3 Year ☐	3-5 Year ☐	5-10 Year ☐	>10 Year ☐

Test results prior to start of treatment with TRUQAP (capivasertib)				
Fasting glucose/Date:	Value:	HbA1C/ Date:	Value:	Not applicable ☐

*Latent autoimmune diabetes in adults

Adverse Event Details				
Adverse Event(s)	**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*	**Outcome**	
			☐ Recovered/resolved ☐ Recovering/resolving ☐ Not recovered/Not resolved	☐ Recovered with sequelae ☐ Patient died
			☐ Recovered/resolved ☐ Recovering/resolving ☐ Not recovered/Not resolved	☐ Recovered with sequelae ☐ Patient died

Was the patient hospitalised for the event(s)?	***Please provide a brief statement of clinical course including signs and symptoms, diagnostic criteria, clinical diagnosis and any complications from the event(s):***
☐ Yes ☐ No	
Was treatment provided?	
☐ Yes ☐ No **If yes, please specify:**	
Was Diabetologist /Endocrinologist consulted? ☐ Yes ☐ No	***If yes, please provide relevant consultation notes/documentations:***

Capivasertib therapy			
Indication:	**Dosing schedule:** **mg ___ Times a day ___** **Days on ___ Days off ___**	**Start Date** *(DD/MM/YY):*	**Stop Date** *(DD/MM/YY):*
Does the reporter consider there to be a causal relationship between capivasertib and the adverse event(s)?		☐ Yes	☐ No

Anti-diabetic medications (include treatments up to 3 months in advance of the reported event, as well as medications to treat AE)						
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
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

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			
Hyperosmolar Hyperglycaemic State (HHS)	☐ Yes ☐ No			
Reduced caloric/carbohydrate intake	☐ Yes ☐ No			
Surgery	☐ Yes ☐ No			
Infection	☐ Yes ☐ No			
Excessive alcohol intake	☐ Yes ☐ No			
Recent Cardio/Cerebro/Vascular Episode	☐ Yes ☐ No			
Missed insulin dose	☐ Yes ☐ No			
Dehydration	☐ Yes ☐ No			
High dose corticosteroids	☐ Yes ☐ No			
Other, please specify:	☐ Yes ☐ No			
	☐ Yes ☐ No			
	☐ Yes ☐ No			

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Complications of Hyperglycaemia Data Collection Form

Case ID #_____ AZ Date of Receipt _____

Laboratory Test	Baseline Value	Peak Value	Unit	Sample date *(DD/MM/YY)*	Reference Values (…….to ……)	Follow-up value If available	Follow-up Date *(DD/MM/YY)*
Blood/Plasma Fasting Glucose							
Blood/Plasma Random Glucose							
HbA1C							
Serum Osmolality							
Anion Gap							
Arterial/ Blood pH							
PCO_2							
Serum Bicarbonate							
Serum Potassium (K)							
Serum Sodium (Na)							
Blood/Serum Ketones							
Urine Ketones							
c-Peptide							
Lactate							
Betahydroxybutyrate							
eGFR							
Serum Creatinine							
Urea							
Other, please specify:							

Any additional comments:

Date and Signature

Date: _____

Signature (Reporting Physician): _____

Contact Information

Please return completed form to:

E-mail:

Thank you for completing this form.