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CAPIseid

Safety and Effectiveness of Capivasertib with Fulvestrant in Patients with Advanced Breast Cancer and Diabetes – a Multi-country Observational Study using Secondary Real-World Data

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	AstraZeneca AB, 15185 Södertälje, Sweden
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PASS INFORMATION

Title	CAPIseid: Safety and Effectiveness of Capivasertib with Fulvestrant in Patients with Advanced Breast Cancer and Diabetes – a Multi-country Observational Study using Secondary Real-World Data
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Marketing authorisation holder(s)	AstraZeneca AB 151 85 Södertälje Sweden
Joint PASS	No
Research question and objectives	The main objectives of this non-interventional study are to assess (i) the risk of acute complications of hyperglycaemia (including diabetic ketoacidosis) and (ii) time to first subsequent therapy (TFST) or death due to any cause in adult patients with advanced breast cancer and type 1 or type 2 diabetes receiving capivasertib + fulvestrant treatment. **Primary objectives:** **1a – Safety:** To estimate the safety of capivasertib + fulvestrant by assessment of the cumulative incidence (proportion) of acute complications of hyperglycaemia (composite), including diabetic

	ketoacidosis, in adults with diabetes mellitus and breast cancer. **1b – Effectiveness:** To estimate the effectiveness of capivasertib + fulvestrant by assessment of TFST in adults with diabetes mellitus and breast cancer. **Secondary objectives:** **2a – Effectiveness**: To estimate the effectiveness of capivasertib + fulvestrant by assessment of real-world overall survival (rwOS) in adults with diabetes mellitus and breast cancer. **2b – Effectiveness:** To estimate the effectiveness of capivasertib + fulvestrant by assessment of time to treatment discontinuation (TTD) in adults with diabetes mellitus and breast cancer. **Exploratory objectives:** **3 – Effectiveness:** To estimate the effectiveness of capivasertib + fulvestrant by assessment of real-world progression-free survival (rwPFS) in adults with diabetes mellitus and breast cancer. **4**. To assess the baseline characteristics associated with the risk of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant[1] **5.** To estimate the cumulative incidence (proportion) of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, **stratified into insulin-dependent diabetes and non-insulin-dependent diabetes**.

[1] Exploratory objective 4 aims to better characterise the study population to further contextualise safety outcome estimates obtained from this study.

	6. To estimate the effectiveness of capivasertib + fulvestrant by assessment of TFST in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, **stratified into insulin-dependent diabetes and non-insulin-dependent diabetes**. **7.** To estimate rwOS in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, **stratified into insulin-dependent diabetes and non-insulin-dependent diabetes**. **8.** To re-evaluate primary objectives (1a/b) in adults with diabetes mellitus and **known ER+/HER2- advanced breast cancer with ≥1 *PIK3CA/AKT1/PTEN* alteration**[2] receiving capivasertib + fulvestrant. **9.** To estimate the cumulative incidence (proportion) of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, and **having a baseline HbA1c level ≥ 8.0%**.[3] **10.** To estimate the safety of capivasertib + fulvestrant by assessment of the cumulative incidence (proportion) of **individual components of acute complications of hyperglycaemia** (i.e., diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome) in adults with diabetes mellitus and breast cancer.

[2] Patients must have information that confirms that they have ***ER+/HER2- advanced*** breast cancer with ***at least one PIK3CA/AKT1/PTEN alteration*** to be considered as "known". Patients with missing information on any of these breast cancer characteristics (i.e., staging [advanced] and biomarkers [ER+/HER2-, at least one *PIK3CA/AKT1/PTEN* alteration]) will be considered as "unknown" and will not be included in the exploratory objective 8 analyses. A July 2024 feasibility assessment indicated that *PIK3CA/AKT1/PTEN* alteration status is the characteristic most often unavailable in European data sources.

[3] Patients must have laboratory results confirming an HbA1c level ≥ 8.0% (based on last recorded HbA1c value in the 90 days prior to and including index date). Of the selected data sources, the required laboratory results are available in the Danish NPR registry and USA Optum Market Clarity.

	11. To describe the **anti-diabetic treatment patterns over follow-up** in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant.[4]
Country (-ies) of study	The initial list of countries to be included in this study are France, Germany, Denmark, and the United States. However, as capivasertib was only recently approved in the EU (European Commission Decision in June 18th, 2024), market launch and reimbursement decisions in European countries are ongoing, whereas capivasertib was approved on November 16th, 2023 in the United States. Therefore, in addition to this initial list of European countries, alternative countries in Europe will be considered if any of these initial countries become unsuitable based on market launch and reimbursement decisions.
Author(s)	PPD (AstraZeneca) PPD PPD (AstraZeneca) PPD PPD (Aetion Inc.) PPD PPD (Aetion Inc.) PPD PPD (Aetion Inc.) PPD

[4] Exploratory objective 11 aims to better understand the study population to further contextualise safety outcome estimates obtained in this study.

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2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AI	Aromatase inhibitor
AKT	Protein kinase B
AKT1	AKT serine-threonine kinase 1
ASD	Absolute standardised difference
ATE	Average treatment effect
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca
CDK4/6	Cyclin-dependent kinase 4/6
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DPP-4	Dipeptidyl peptidase 4
EMA	European Medicines Agency
EMR	Electronic medical record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ER+	Oestrogen receptor-positive
EU	European Union
EU PAS	European post-authorisation study
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide 1
GP	General practitioner
HbA1c	Glycated haemoglobin
HER2-	Human epidermal growth factor receptor 2-negative
HR	Hazard ratio
HR+	Hormone receptor-positive
ICD (-10)	International Classification of Diseases (Tenth Revision)
InGef	Institute for Applied Health Research Berlin
IPTW	Inverse probability of treatment weighting

Abbreviation or special term	Explanation
JAR	Joint Assessment Report
K-M	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	Mammalian target of rapamycin
NIS	Non-interventional study
NPR	National Patient Register
OS	Overall survival
PASS	Post-authorisation safety study
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity score
PTEN	Phosphatase and tensin homolog
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk Management Plan
rwOS	Real-world overall survival
rwPFS	Real-world progression-free survival
SAP	Statistical Analysis Plan
SD	Standard deviation
SGLT-2	Sodium-glucose cotransporter-2
SNDS	Système National Des Données De Santé
TFST	Time to first subsequent therapy
THIN	The Health Improvement Network
TTD	Time to treatment discontinuation
UK	United Kingdom
USA	United States of America

3. RESPONSIBLE PARTIES

3.1 AstraZeneca responsible parties

Name	Professional title	Role in study	Degree	Email address
PPD		Scientific/Study Lead	PPD	
		Scientific Oversight/Advisor		
		Outcomes Research		
		Regulatory		
		Medical		
		Clinical		
		Statistician		
		Patient Safety/Pharmacovigilance		
		Patient Safety/Pharmacovigilance		
		Patient Safety/Risk Management		
		Qualified Person Responsible For Pharmacovigilance		
		Project Management		

Name	Professional title	Role in study	Degree	Email address
PPD		Patient Safety	PPD	
		Senior Reviewer		

3.2 Other responsible parties

Other responsible parties from Aetion Inc.

Name	Professional title	Role in study	Degree	Email address
PPD		Study Lead	PPD	
		Science Lead		
		Epidemiology Expert		
		Lead Biostatistician		
		Data Lead		

Administrative changes of responsible persons will be documented in the study management system.

4. ABSTRACT

Title

CAPIseid: Safety and Effectiveness of Capivasertib with Fulvestrant in Patients with Advanced Breast Cancer and Diabetes – a Multi-country Observational Study using Secondary Real-World Data

Version: 2.0

Date: 02 June 2025

Authors (affiliation)

- PPD (AstraZeneca)
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- PPD (Aetion Inc.)
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- PPD (Aetion Inc.)

Rationale and background

Approximately 70% of advanced breast cancers are hormone receptor positive and do not have human epidermal growth factor receptor 2 overexpression (HER2-). Of these, 50% have tumours with a phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT) signalling pathway alteration, including *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha* (*PIK3CA*) or *AKT serine-threonine kinase 1 (AKT1)* activating mutations or *phosphatase and tensin homolog (PTEN)* loss. These alterations contribute to the promotion of breast cancer cell survival and proliferation, resistance to endocrine therapy, and disease progression. Capivasertib (TRUQAP™) is a first-in-class AKT inhibitor, in combination with fulvestrant (FASLODEX™), a selective oestrogen receptor degrader, for the treatment of adult patients with oestrogen receptor-positive (ER+), HER2- locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN* alterations following recurrence or progression on or after an endocrine-based regimen. Capivasertib was approved by the United States of America (USA) Food and Drug Administration (FDA) on November 16th, 2023 and in the European Union (EU) on June 18th, 2024.

The PI3K-AKT signalling pathway targeted by capivasertib has a pivotal role in glucose homeostasis and inhibitors of this pathway are associated with serious adverse hyperglycaemic events. In the CAPItello-291 trial, the incidence of grade ≥3 hyperglycaemic adverse events

was higher in patients receiving capivasertib + fulvestrant therapy (2.3%, 8/355) compared to patients receiving placebo + fulvestrant therapy (0.3%, 1/350). A concern is that patients with a history of diabetes mellitus (including those requiring insulin) may require intensified antidiabetic treatment to minimise their risk of complications of hyperglycaemia. This non-interventional study will address these knowledge gaps and improve understanding of the safety and effectiveness of capivasertib + fulvestrant in populations with breast cancer with diabetes.

Research question and objectives

The main objectives of this non-interventional study are to assess (i) the risk of acute complications of hyperglycaemia (including diabetic ketoacidosis) and (ii) time to first subsequent therapy (TFST) or death due to any cause in adult patients with advanced breast cancer and type 1 or type 2 diabetes receiving capivasertib + fulvestrant treatment.

Primary objectives:

1a. Safety: To estimate the safety of capivasertib + fulvestrant by assessment of the cumulative incidence (proportion) of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer.

1b. Effectiveness: To estimate the effectiveness of capivasertib + fulvestrant by assessment of TFST in adults with diabetes mellitus and breast cancer.

Secondary objectives:

2a. Effectiveness: To estimate the effectiveness of capivasertib + fulvestrant by assessment of real-world overall survival (rwOS) in adults with diabetes mellitus and breast cancer.

2b. Effectiveness: To estimate the effectiveness of capivasertib + fulvestrant by assessment of time to treatment discontinuation (TTD) in adults with diabetes mellitus and breast cancer.

Exploratory objectives:

3. Effectiveness: To estimate the effectiveness of capivasertib + fulvestrant by assessment of real-world progression-free survival (rwPFS) in adults with diabetes mellitus and breast cancer.

4. To assess the baseline characteristics associated with the risk of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant.

5. To estimate the cumulative incidence (proportion) of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, **stratified into insulin-dependent diabetes and non-insulin-dependent diabetes**.

6. To estimate the effectiveness of capivasertib + fulvestrant by assessment of TFST in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, **stratified into insulin-dependent diabetes and non-insulin-dependent diabetes**.

7. To estimate rwOS in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, **stratified into insulin-dependent diabetes and non-insulin-dependent diabetes**.

8. To re-evaluate primary objectives (1a/b) in adults with diabetes mellitus and **known ER+/HER2- advanced breast cancer with ≥1 *PIK3CA/AKT1/PTEN* alteration**[5] receiving capivasertib + fulvestrant.

9. To estimate the cumulative incidence (proportion) of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, and **having a baseline HbA1c level ≥ 8.0%**.[6]

10. To estimate the safety of capivasertib + fulvestrant by assessment of the cumulative incidence (proportion) **of individual components of acute complications of hyperglycaemia** (i.e., diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome) in adults with diabetes mellitus and breast cancer.

11. To describe the **anti-diabetic treatment patterns over follow-up** in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant.

The exploratory objectives 4 and 11 are intended to better characterise and understand the study population to further contextualise safety outcome estimates obtained from this post-authorisation safety study (PASS).

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[5] Patients must have information that confirms that they have ***ER+/HER2- advanced*** breast cancer with ***at least one PIK3CA/AKT1/PTEN alteration*** to be considered as "known". Patients with missing information on any of these breast cancer characteristics (i.e., staging [advanced] and biomarkers [ER+/HER2-, at least one *PIK3CA/AKT1/PTEN* alteration]) will be considered as "unknown" and will not be included in the exploratory objective 8 analyses. A July 2024 feasibility assessment indicated that *PIK3CA/AKT1/PTEN* alteration status is the characteristic most often unavailable in European data sources.

[6] Patients must have laboratory results confirming an HbA1c level ≥ 8.0% (based on last recorded HbA1c value in the 90 days prior to and including index date). Of the selected data sources, the required laboratory results are available in the Danish NPR registry and USA Optum Market Clarity.

Study design

This non-interventional, longitudinal, capivasertib + fulvestrant new-user cohort study will use secondary data (administrative claims, electronic medical records [EMR] and/or registries) from multiple EU member states and the USA. The study will include two distinct cohorts: a safety cohort for assessing safety outcomes and an effectiveness cohort for evaluating effectiveness outcomes.

Study period

The study period will begin 12 months before the reimbursement decision date of each respective country for the European data sources and on November 16, 2022, for the USA data source (12 months prior to FDA marketing authorisation) to allow for a 12-month look-back period before the index date. No patients who received capivasertib + fulvestrant before their respective country's reimbursement decision date (Europe) or marketing authorisation date (USA) will be included in this study. The end of the study period will be the last possible date of follow-up when all patients still in the study are censored (i.e., end of all available data). These dates (the study start and study end dates) will differ by country as reimbursement decision dates will differ by country, and the length of data lag at the time of data extraction will also be different for each data source.

The accrual period is defined as the time within the study period during which patients can enter the cohort (i.e., from capivasertib + fulvestrant reimbursement decision date in each European country or marketing authorisation in the USA) and ends 30 days prior to the end of all available data for the safety outcomes and 365 days prior to the end of all available data for the effectiveness outcomes. The difference in the patient accrual period for the two cohorts is to allow for sufficient follow-up data to accrue to measure the outcomes of interest.

A given patient's index date will be determined by first identifying their earliest (by date) record of capivasertib use (prescription or dispensation) within the accrual period. Following this, the patients' records will be examined for any fulvestrant use within a ±28-day window of the initial capivasertib use. If a record of fulvestrant use is observed within this window, the index date is set as the earlier of the two medication dates.

Follow-up will begin on the index date and will continue until death, disenrolment/de-registering/emigration, or last available data.

Population

The study population will consist of all adults with diabetes mellitus and breast cancer in the selected secondary data sources who, during the accrual period, initiate treatment with capivasertib + fulvestrant (index date) and meet the following eligibility criteria.

Inclusion criteria

1. Female or male on index date
2. Age ≥18 years on index date
3. At least one diagnosis of breast cancer in the 365 days prior to and including the index date
4. At least one diagnosis of type 1 or 2 diabetes mellitus[7] in the 365 days prior to and including the index date
5. Continuous enrolment[8] in the 365 days prior to and including the index date
6. Previous endocrine treatment (involving an aromatase inhibitor, tamoxifen, or oral selective oestrogen receptor degrader) in the 365 days before the index date to one day prior to the index date

For exploratory objective 8 only: ER+/HER2- advanced (i.e., locally advanced [stage IIIB or IIIC] or metastatic [stage IV]) breast cancer with ≥1 *PIK3CA/AKT1/PTEN* alterations documented in the 365 days prior to and including the index date.

For exploratory objective 9 only: The last recorded HbA1c value is ≥8.0% in the 90 days prior to and including the index date.

Exclusion criteria[9]

1. Received more than two types of endocrine therapy, administered sequentially (not concurrently) in the 365 days before the index date to one day prior to the index date
2. Prior use of an AKT inhibitor (including capivasertib) in the 365 days before the index date to one day prior to the index date

[7] This does not include patients with pre-diabetes.
[8] Continuous enrolment is defined as time in which patients have uninterrupted membership or coverage in a health insurance plan or healthcare system, evidenced by no gap or missing data in their enrolment records within the data source for a period of at least 365 days prior to and including the index date. Enrolment in Optum Market Clarity will be defined using claims enrolment and not EMR activity. The absence of enrolment gaps guarantees complete data capture, reflecting patients' health and treatment patterns while preventing potential bias.
[9] At the time of the end of data collection in Q4 2029, all approved combinations of capivasertib with other treatments will be thoroughly evaluated to assess whether revisions to the exclusion criteria are warranted. Any changes will be reflected in a protocol amendment.

3. Prior use of a PI3K inhibitor (including alpelisib) in the 365 days prior to and including the index date

4. Prior use of a mammalian target of rapamycin (mTOR) inhibitor (including everolimus) in the 365 days prior to and including the index date

Subgroups based on insulin dependency will be considered for exploratory objectives 5 through 7.

Variables

Identification of the population

- Breast cancer
- Diabetes mellitus (type 1 or 2)

Exposure

- Treatment with capivasertib + fulvestrant

Outcomes

- Primary outcomes:
    - Safety: Acute complications of hyperglycaemia (composite), including diabetic ketoacidosis
    - Effectiveness: TFST
- Secondary outcomes:
    - rwOS
    - TTD
- Exploratory outcomes:
    - rwPFS
    - Time-to-acute complications of hyperglycaemia (composite), including diabetic ketoacidosis

- Acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, stratified by insulin-dependent diabetes and non-insulin-dependent diabetes
- TFST stratified by insulin-dependent diabetes and non-insulin-dependent diabetes
- rwOS stratified by insulin-dependent diabetes and non-insulin-dependent diabetes
- Primary safety outcome (acute complications of hyperglycaemia [composite], including diabetic ketoacidosis) and effectiveness outcome (TFST) in patients with ER+/HER2- advanced breast cancer with ≥1 *PIK3CA/AKT1/PTEN* alteration[10]
- Primary safety outcome (acute complications of hyperglycaemia [composite], including diabetic ketoacidosis) in patients with a recorded baseline HbA1c level ≥ 8.0%
- Individual components of the primary safety outcome: Diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome
- Anti-diabetic treatment patterns

Covariates

There may be differences in data availability in each of the selected data sources. Covariates will only be included in data sources where the information is captured and will be assessed at index date or during the look-back period.

- Age
- Sex
- Race
- Ethnicity
- Country of residence

[10] Patients must have information that confirms that they have ***ER+/HER2- advanced*** breast cancer with ***at least one PIK3CA/AKT1/PTEN alteration*** to be considered as "known". Patients with missing information on any of these breast cancer characteristics (i.e., staging [advanced] and biomarkers [ER+/HER2-, at least one *PIK3CA/AKT1/PTEN* alteration]) will be considered as "unknown" and will not be included in the exploratory objective 8 analyses. A July 2024 feasibility assessment indicated that *PIK3CA/AKT1/PTEN* alteration status is the characteristic most often unavailable in European data sources.

- Body mass index
- Socio-economic status
- Tobacco use
- Alcohol abuse
- Drug abuse
- Type of diabetes
- Postmenopausal status (for female patients only)
- Concurrent use of luteinizing hormone-releasing agonist
- Metastatic breast cancer diagnosis
- Site of metastases
- Time since advanced breast cancer diagnosis
- Time since initial diabetes diagnosis
- History of other cancers
- Previous CDK4/6i use
- Previous fulvestrant use
- Prior primary tumour surgery
- Number of prior anti-oestrogen therapies (i.e., fulvestrant, tamoxifen, anastrozole, letrozole, exemestane, or oral selective oestrogen receptor degrader therapies)
- Number of prior tamoxifen therapies
- Number of prior anastrozole therapies
- Number of prior letrozole therapies
- Number of prior exemestane therapies
- Number of prior oral selective oestrogen receptor degrader therapies

- Prior chemotherapy
- Concomitant use of other medications affecting blood glucose level, regardless of type
- Concurrent metformin use
- Concurrent use of other medications for comorbidities
- Comorbidity that interferes with blood glucose
- Recent healthcare use: frequency of hospitalisations within the past year
- Recent healthcare use: emergency department visits within the past year
- Recent healthcare use: outpatient physician visits within past year
- Recent healthcare use: primary care visits within the past year
- Calendar year of index date (2024, 2024, 2025, etc.)
- Baseline HbA1c level

Data sources

Considering that capivasertib + fulvestrant has only recently been approved by the European Medicines Agency (EMA) at the time of protocol development, it is currently uncertain which European countries will provide reimbursement, which will affect drug uptake and therefore the final selection of data sources.

The initial list of data sources provided in this protocol has been guided by a feasibility assessment conducted in July 2024 (3 months after the Committee for Medicinal Products for Human Use [CHMP] decision). During the feasibility assessment, a proxy was used to identify potential capture of capivasertib exposure in data sources. This proxy was "capture of drugs which target the PI3K-AKT signalling pathway, such as alpelisib (a PI3K inhibitor) and everolimus (an mTOR inhibitor)". In addition to the potential of a data source to capture capivasertib exposure, the following criteria were used for data source selection: (i) the availability of the data elements required to meet the study objectives, (ii) the potential sample size of relevant patients in the data source, (iii) the data source representativeness of the target population in each country, (iv) the possibility of linkage with cancer-specific data source(s), and (v) the possibility of linkage with, or integration of, laboratory data (specifically, HbA1c values). Based on the feasibility assessment, the data sources currently selected for use in this PASS are:

- The Système National Des Données De Santé (SNDS) in France
- The Institute for Applied Health Research Berlin (InGef) in Germany
- The National Patient Register (NPR) in Denmark
- The Optum Market Clarity® dataset in the USA

The assumptions used in the selection of the databases will be monitored during the conduct of the study, as capivasertib market launches and reimbursement decisions in the EU are ongoing. If necessary, the following contingency plans will be considered:

1. If the selected European data sources (SNDS, InGef, or NPR) are no longer fit for the study conduct, alternative European data sources (provided in Appendix C) will be considered for replacement.

2. Study timelines could be extended, after consideration/discussions with the EMA, to allow for sufficient patient count accrual over time in the selected European data source(s).

Study size

Based on patient count estimations from the feasibility assessment, by the end of the study period, SNDS will have between 856-1,712 eligible patients, InGef will have between 396-791 eligible patients, NPR will have between 83-166 eligible patients, and Optum Market Clarity will have between 1,249-2,497 eligible patients, depending on drug uptake and other assumptions (testing rates and test failure rates) applied during feasibility assessment.

A sample size of 150 patients in each country will enable estimation of the primary safety outcome with a precision of 4.1% (assuming incidence of acute complications of hyperglycaemia of 5.9%, providing an estimated 95% confidence interval [CI]: 2.7%, 11.0%) and estimation of the primary effectiveness outcome (TFST as a proxy of progression-free survival [PFS]) with a precision of ~1.7 months (using the observed clinical trial PFS of 7.3 months, providing an estimated 95% CI: 5.7, 9.2 months). This precision for the PFS is close to the level of precision (1.8 months) in the 95% CI for median PFS observed in the capivasertib + fulvestrant AKT-altered subgroup of CAPItello-291 (95% CI: 5.5, 9.0).

A minimum sample size of 150 patients is achievable under even the worst-case assumptions (minimum expected counts) for three of the four data sources (SNDS, InGef, and Optum Market Clarity). NPR will provide a sample size of approximately 150 patients if the assumptions are close to the best-case scenario (in which the projected sample size from NPR is 166). However, the depth of data from NPR, which potentially includes the ability to capture biomarker

information (i.e., ER status, HER2 status, and *PIK3CA/AKT1/PTEN* alteration status) through the Pathology Registry as well as laboratory results in the EU, is a major rationale for inclusion of this data source in the study. Optum Market Clarity will provide the largest sample size and will capture laboratory results and biomarker information in a subset of patients; hence, the selection of this non-European data source.

It is therefore anticipated that at least three of the data sources will provide sufficient size to meet the precision estimates observed as specified above, with the NPR data source meeting that precision when the assumptions lead to a best-case scenario for patient numbers.

Data analysis

Given the study objectives, analyses will be descriptive, except for exploratory objective 4, which assesses risk factors for acute complications of hyperglycaemia. Subgroups will be explored descriptively with no confirmatory statistical testing, except for exploratory objectives 5 to 7 which may assess the marginal effect of having insulin-dependent diabetes on acute complications of hyperglycaemia, TFST, and rwOS, respectively (if deemed feasible). All analyses will be conducted separately by country and data source.

Categorical variables will be presented as counts (n) and proportions (%) with 95% CI where relevant. Continuous variables will be presented as means with standard deviation and as medians with interquartile range, where appropriate. The primary and secondary planned analyses are:

Primary analysis

- Acute complications of hyperglycaemia (composite), including diabetic ketoacidosis: Descriptive summary of follow-up time; total number of events and number of events per patient; and cumulative incidence (proportion of patients experiencing the event). These results will be reported among patients in the safety cohort.

- TFST: Summarised using Kaplan-Meier (K-M) plot, and median K-M survival estimates with 95% CI among patients in the effectiveness cohort.

Secondary analysis

- rwOS: Summarised using K-M plot, and K-M survival estimate of rwOS at 1 year will be presented with 95% CI among patients in the effectiveness cohort.

- TTD: Summarised using K-M plot, and median K-M survival estimates with 95% CI among patients in the effectiveness cohort.

Milestones

Milestone	Planned date
Registration in the HMA-EMA Catalogue of real-world data studies	Q4 2025 (study will be registered after PRAC approval of protocol – anticipated to be in 2025)
Start of data collection	Q4 2026[a]
Interim report	Q3 2027
End of data collection	Q4 2029
Final report of study results	Q3 2030

[a] Start of data collection for this secondary database study is defined as date for first data extraction as per definition in Module VIII of GVP.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Registration in the HMA-EMA Catalogue of real-world data studies	Q4 2025 (study will be registered after PRAC approval of protocol – anticipated to be in 2025)
Start of data collection	Q4 2026[a]
Interim report	Q3 2027
End of data collection	Q4 2029
Final report of study results	Q3 2030

[a] Start of data collection for this secondary database study is defined as date for first data extraction as per definition in Module VIII of GVP.

7. RATIONALE AND BACKGROUND

7.1 Background

Approximately 70% of advanced breast cancers are hormone receptor positive (HR+)—the tumours express oestrogen and/or progesterone receptors—and do not have human epidermal growth factor receptor 2 overexpression (HER2-) (1). In these patients, current guidelines recommend endocrine-based therapy, often aromatase inhibitors (AI) or fulvestrant, as first-line treatment in combination with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, based on their effect on progression-free and overall survival compared to endocrine therapy alone (2,3). After progression on first-line systemic therapy, there are a number of options from which to choose second-line therapy and beyond (Figure 1), with chemotherapy reserved for patients with significant symptoms from large tumour burden, known as visceral crisis (2).

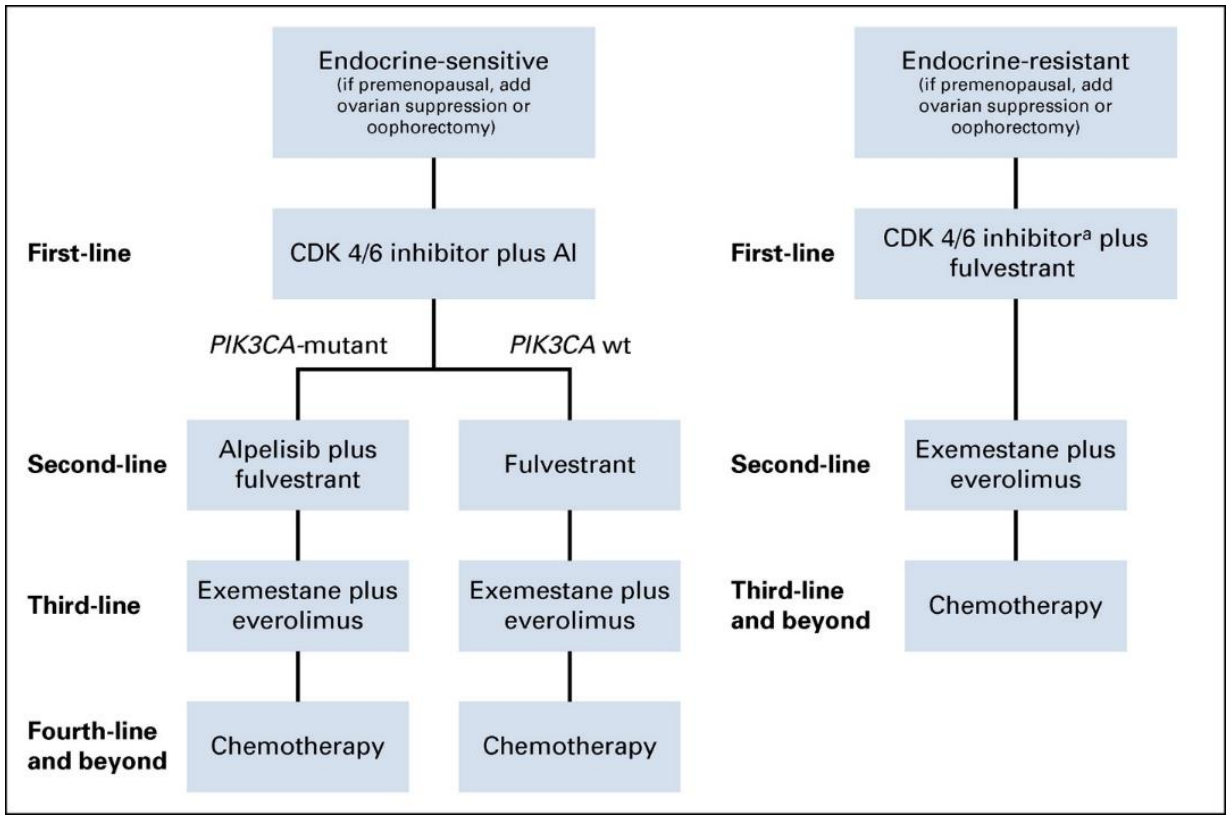

Figure 1 Proposed sequencing of treatment for advanced HR+/HER2- breast cancer

Figure retrieved from McAndrew et al. (2)

Abbreviations: AI, aromatase inhibitor; CDK, cyclin-dependent kinase; wt, wild type.

Note: Endocrine-sensitive disease includes de novo metastatic disease or patients who recurred more than a year after completing adjuvant endocrine treatment, whereas endocrine-resistant would include those patients who recurred while receiving or within 1 year of completing adjuvant endocrine treatment or progressing while receiving endocrine treatment for advanced disease.

[a] If *PIK3CA*-mutant, can consider alpelisib, but toxicity profile would favour a CDK4/6 inhibitor doublet.

Of patients with HR+/HER2- advanced breast cancer, 50% have tumours with a phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT) signalling pathway alteration, including *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha* (*PIK3CA)* or *AKT serine-threonine kinase 1 (AKT1)* mutations or *phosphatase and tensin homolog (PTEN)* loss (1). These alterations lead to the overactivation of the PI3K-AKT signalling pathway, contributing to the promotion of breast cancer cell survival and proliferation, resistance to endocrine therapy, and disease progression (4,5). AKT is the key node of the PI3K-AKT pathway (1). Inhibitors of the pathway, alpelisib (PI3K α-selective inhibitor) and everolimus (mammalian target of rapamycin [mTOR] inhibitor), are approved for the treatment of HR+/HER2- advanced breast cancer (Figure 1).

On November 16th, 2023, AstraZeneca (AZ) received approval from the United States of America (USA) Food and Drug Administration (FDA) for capivasertib (TRUQAP™), a first-in-class AKT inhibitor, in combination with fulvestrant (FASLODEX™), a selective oestrogen receptor degrader, for treatment of adults with HR+/HER2- locally advanced or metastatic breast cancer with one or more *PIK3CA*/*AKT1*/*PTEN* alterations, "following progression on at least one endocrine-based treatment regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy" (6,7). Capivasertib is orally administered using an intermittent dosing schedule of four days at 400 mg twice daily followed by three days off (8). Following the adoption of a positive opinion by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use for capivasertib on April 25th, 2024, AZ received the European Commission Decision on June 18th, 2024, granting the European Union (EU) Marketing Authorisation for a similar indication, albeit with added specification of oestrogen receptor-positive (ER+)/HER2- breast cancer given the mode of action of fulvestrant (9).

7.2 Rationale

The PI3K-AKT signalling pathway targeted by capivasertib has a pivotal role in glucose homeostasis and inhibitors of this pathway (including alpelisib, a PI3K inhibitor, and everolimus, a mTOR inhibitor) are associated with serious adverse hyperglycaemic events (1, 10-12). In the CAPItello-291 trial, the incidence of hyperglycaemic adverse events (which included the preferred terms "hyperglycaemia" and "blood glucose increased") of Common Terminology Criteria for Adverse Events (CTCAE; v5.0) grade ≥3 was higher in patients receiving capivasertib + fulvestrant therapy (2.3%, 8/355) compared to patients receiving placebo + fulvestrant therapy (0.3%, 1/350) in the overall study population. CCI [redacted] Hyperglycaemic emergencies and severe

complications (e.g., diabetic ketoacidosis) were uncommon in the capivasertib + fulvestrant group [redacted]. Individuals with type 1 diabetes, type 2 diabetes requiring insulin treatment, or those with uncontrolled diabetes (defined as HbA1c ≥8.0% at baseline) were excluded from the CAPItello-291 clinical trial (1).

As per the Summary of Product Characteristics (13), a concern is that patients with a history of diabetes mellitus (including those requiring insulin)—who have an elevated baseline risk of hyperglycaemia and associated complications—"may require intensified anti-diabetic treatment and should be closely monitored" while on treatment involving capivasertib + fulvestrant to minimise their risk of complications of hyperglycaemia. The EU label for capivasertib does not list type 1 diabetes or type 2 diabetes requiring insulin treatment as a contraindication. Therefore, the absence of safety data in patients with type 1 and type 2 diabetes (requiring insulin treatment, or HbA1c ≥ 8.0%) is considered in the EU Risk Management Plan ([RMP]; V2 S2) as missing information, which requires further in-depth characterisation (14). In particular, complications of hyperglycaemia (excluding diabetic ketoacidosis) are considered an important potential risk, while diabetic ketoacidosis is considered an important identified risk that warrants further study (14).

The proposed non-interventional study (NIS) will address these knowledge gaps and improve understanding of the safety (i.e., acute complications of hyperglycaemia, including diabetic ketoacidosis as per the RMP) and effectiveness (including overall survival [OS]) of capivasertib + fulvestrant in adult patients with ER+/HER2- breast cancer and diabetes mellitus, (including those with insulin-dependent diabetes or uncontrolled diabetes [defined as a baseline HbA1c ≥ 8.0%], as these patients were excluded from the pivotal CAPItello-291 study). This gap is particularly relevant as a key safety concern for capivasertib is complications of hyperglycaemia (such as diabetic ketoacidosis) for which the baseline risk is elevated in diabetic patients

8. RESEARCH QUESTION AND OBJECTIVES

8.1 Research question

The main objectives of this NIS are to assess (i) the risk of acute complications of hyperglycaemia (including diabetic ketoacidosis) and (ii) the time to first subsequent therapy or death (TFST) in adult patients with advanced breast cancer and type 1 or type 2 diabetes receiving capivasertib + fulvestrant treatment. [redacted]

The primary safety outcome addresses the *Important Identified Risk* of diabetic ketoacidosis summarised in Table II-5 and *Important Potential Risk* of complications of hyperglycaemia (excluding diabetic ketoacidosis) summarised in Table II-6 of the EU RMP V2 S2 (14) CCI [redacted].

The selection of TFST as the primary effectiveness outcome is based on the consideration that TFST is the most reliable measure of effectiveness in situations where tumour measurement or OS are not available or are incomplete such as real-world datasets. In a systematic review that included 21 clinical trials where TFST and progression-free survival ([PFS]; assessed by investigators and/or central review boards) were measured in solid tumours in the advanced/metastatic setting, TFST showed a strong correlation (degree of correlation [R] ≥ 0.85) with both investigator determined PFS and central review board determined PFS (15).

Additional effectiveness outcomes—real-world overall survival, time to treatment discontinuation, and real-world progression-free survival—have been included as secondary or exploratory outcomes to further characterise effectiveness of capivasertib + fulvestrant use in adult patients with advanced breast cancer and diabetes. Descriptive anti-diabetic treatment patterns will be explored to help contextualise findings of the primary safety outcome.

8.2 Primary objectives

1a. Safety: To estimate the safety of capivasertib + fulvestrant by assessment of the cumulative incidence (proportion) of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer.

1b. Effectiveness: To estimate the effectiveness of capivasertib + fulvestrant by assessment of TFST in adults with diabetes mellitus and breast cancer.

8.3 Secondary objectives

2a. Effectiveness: To estimate the effectiveness of capivasertib + fulvestrant by assessment of real-world overall survival (rwOS) in adults with diabetes mellitus and breast cancer.

2b. Effectiveness: To estimate the effectiveness of capivasertib + fulvestrant by assessment of time to treatment discontinuation (TTD) in adults with diabetes mellitus and breast cancer.

8.4 Exploratory objectives

3. **Effectiveness**: To estimate the effectiveness of capivasertib + fulvestrant by assessment of real-world progression-free survival (rwPFS) in adults with diabetes mellitus and breast cancer**.**

4. To assess the baseline characteristics associated with the risk of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant.

5. To estimate the cumulative incidence (proportion) of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, **stratified into insulin-dependent diabetes and non-insulin-dependent diabetes**.

6. To estimate the effectiveness of capivasertib + fulvestrant by assessment of TFST in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, **stratified into insulin-dependent diabetes and non-insulin-dependent diabetes**.

7. To estimate rwOS in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, **stratified into insulin-dependent diabetes and non-insulin-dependent diabetes**.

8. To re-evaluate primary objectives (1a/b) in adults with diabetes mellitus and **known ER+/HER2- advanced breast cancer with ≥1 *PIK3CA/AKT1/PTEN* alteration**[11] receiving capivasertib + fulvestrant.

9. To estimate the cumulative incidence (proportion) of acute complications of hyperglycaemia (composite), including diabetic ketoacidosis, in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant, and **having a baseline HbA1c level ≥ 8.0%**.[12]

10. To estimate the safety of capivasertib + fulvestrant by assessment of the **cumulative incidence (proportion) of individual components of acute complications of**

[11] Patients must have information that confirms that they have ***ER+/HER2- advanced*** breast cancer with ***at least one PIK3CA/AKT1/PTEN alteration*** to be considered as "known". Patients with missing information on any of these breast cancer characteristics (i.e., staging [advanced] and biomarkers [ER+/HER2-, at least one *PIK3CA/AKT1/PTEN* alteration]) will be considered as "unknown" and will not be included in the exploratory objective 8 analyses. A July 2024 feasibility assessment indicated that *PIK3CA/AKT1/PTEN* alteration status is the characteristic most often unavailable in European data sources.

[12] Patients must have laboratory results confirming an HbA1c level ≥ 8.0% (based on last recorded HbA1c value in the 90 days prior to and including index date). Of the selected data sources, the required laboratory results are available in the Danish National Patient Register (NPR), and USA Optum Market Clarity®.

hyperglycaemia (i.e., diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome), in adults with diabetes mellitus and breast cancer.

11. To describe the **anti-diabetic treatment patterns over follow-up** in adults with diabetes mellitus and breast cancer receiving capivasertib + fulvestrant.

The exploratory objectives 4 and 11 are intended to better characterise and understand the study population to further contextualise safety outcome estimates obtained from this PASS.

9. RESEARCH METHODS

9.1 Study design

This non-interventional, longitudinal, capivasertib + fulvestrant new-user cohort study will use secondary data (administrative claims, electronic medical records [EMR] and/or registries) from multiple EU member states and the USA. Details on the selected data sources are located in section 9.4.

The primary population of interest will include adult patients with breast cancer and diabetes who initiate capivasertib + fulvestrant after receiving treatment with an AI, tamoxifen, or selective oestrogen receptor degrader. The study will include two distinct cohorts:

- A safety cohort for assessing the cumulative incidence (proportion) of acute complications of hyperglycaemia (primary objective 1a and exploratory objectives 5, 8a, 9, and 10), risk factors for acute complications of hyperglycaemia (exploratory objective 4), and anti-diabetic treatment patterns (exploratory objective 11)

- An effectiveness cohort for assessing TFST, rwOS, TTD, and rwPFS (primary objective 1b, secondary objectives 2a and 2b, and exploratory objectives 3, 6, 7, and 8b)

For exploratory objectives 5 through 7, both the safety cohort and the effectiveness cohort will be categorised by insulin dependency status. For exploratory objective 8, a subset of patients in both cohorts who have known ER+/HER2- advanced breast cancer with ≥ 1 *PIK3CA/AKT1/PTEN* alteration(s) will be assessed for primary safety and effectiveness outcomes. For exploratory objective 9, a subset of the safety cohort with a recorded HbA1c level ≥ 8.0% will be assessed for the primary safety outcome.

The study design, including the assessment windows for entry criteria, look-back period, and outcomes, are presented in Figure 2. Eligibility criteria and assessment periods are defined in section 9.2.

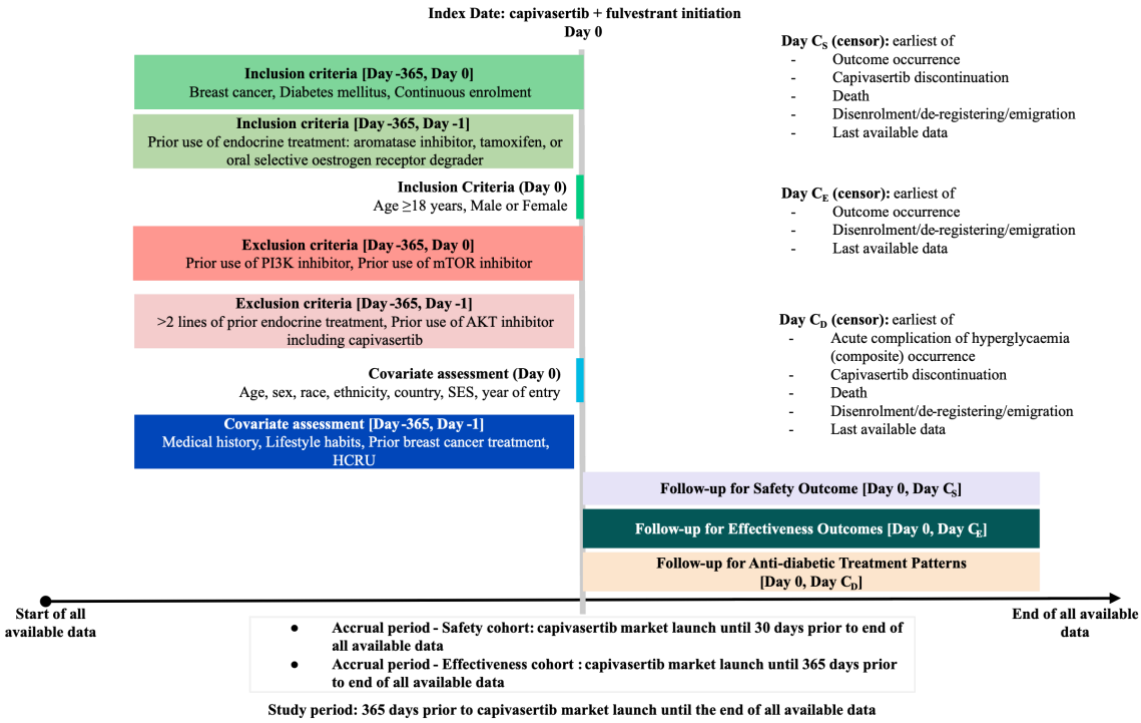

Figure 2 Study design diagram

Note: The index date (Day 0) will be determined by identifying the first record of capivasertib. If fulvestrant use is observed within a ±28-day window of the initial capivasertib use, the index date is the earliest of the two medication start dates. Refer to section 9.2.2.3 for further details.

9.2 Setting

9.2.1 Study population

Capivasertib is currently approved by the EMA and FDA, in combination with fulvestrant, for adults with locally advanced or metastatic ER+/HER2- breast cancer with one or more *PIK3CA*/*AKT1*/*PTEN* alterations, following recurrence or progression on or after an endocrine-based regimen. This study specifically aims to focus on patients with these cancer characteristics who also have diabetes mellitus.

In a feasibility assessment conducted in July 2024 (see Appendix A) results indicated that while most European administrative health databases (i.e., claims data and EMR) lack data on cancer staging and biomarker status (i.e. ER status, HER2 status, *PIK3CA/AKT1/PTEN* alteration status), they collect comprehensive information on specific cancer treatments, diabetes management, and acute complications of hyperglycaemia in large, representative populations. Conversely, disease-specific data sources like cancer registries gather comprehensive information on cancer characteristics (e.g., staging and biomarker status), but often lack crucial

details about acute complications of hyperglycaemia, specific cancer treatments, and/or diabetes management.

The use of proxy data or algorithms to mitigate the limitations with administrative health data to delineate cancer staging has been unsuccessful. Two algorithms which identify cancer staging in locally advanced or metastatic breast cancer were identified. The first, developed by Yuen et al. (16) used hospital discharge data from Emilia Romagna region (Italy) linked to cancer registry data. This algorithm demonstrated limited accuracy, with a sensitivity of 0.6% and a positive predictive value (PPV) of 46.2% for identifying stage III breast cancers, and a sensitivity of 22.5% and a PPV of 15.9% for stage IV breast cancers. The second algorithm, developed by Smith et al. (17), used covariates from the USA Medicare claims-based data to predict cancer stage. While it achieved higher sensitivity values of 83% and 81%, and PPVs of 24% and 98% for stage III and stage IV breast cancer respectively, it requires a granularity of information which is not available in the data sources (see section 9.4) such as date of the incident breast cancer diagnosis, axillary lymph node involvement, or axillary lymph node dissection.

Consequently, study eligibility criteria were relaxed to remove the specification for cancer staging (locally advanced or metastatic) and biomarker status (ER+, HER2-, *PIK3CA*/*AKT*/*PTEN* alteration) with the assumption capivasertib + fulvestrant will be mostly used in the patient population as per the drug's label. Relaxing these eligibility criteria will ensure that safety and effectiveness data on patients treated with capivasertib + fulvestrant can be obtained for patients in Europe. However, this may result in some patients who do not have documented *PIK3CA/AKT/PTEN* alterations being included in the study cohorts. To mitigate this limitation, two items have been incorporated into this study:

1. The addition of an exploratory objective (exploratory objective 8), in which results will be reported among patients who are known to have ER+/HER2- advanced breast cancer, with at least one *PIK3CA*/*AKT1*/*PTEN* alteration.

2. The addition of Optum Market Clarity, a large USA-based data source that includes breast cancer staging information and laboratory results (e.g., ER, HER2, and *PIK3CA/AKT1/PTEN* values and HbA1c laboratory values). Additional information on Optum Market Clarity can be found in section 9.4.

The study population will consist of adults with diabetes mellitus and breast cancer in the selected secondary data source(s) who, during the accrual period (see section 9.2.2), initiate treatment with capivasertib + fulvestrant and meet the following eligibility criteria. These criteria were informed, in part, by CAPItello-291 trial eligibility criteria, the EMA-approved indication, and the Feasibility Assessment Report (see Appendix A).

9.2.1.1 Inclusion criteria

Patients who initiate combination treatment of capivasertib + fulvestrant therapy within the accrual period will be included in the safety and effectiveness cohorts if they meet all the following inclusion criteria:

1. Female or male on index date
2. Age ≥18 years on index date
3. At least one diagnosis of breast cancer in the 365 days prior to and including the index date
4. At least one diagnosis of type 1 or 2 diabetes mellitus[13] in the 365 days prior to and including the index date
5. Continuous enrolment[14] in the 365 days prior to and including the index date
6. Previous endocrine treatment (involving an AI, tamoxifen, or oral selective oestrogen receptor degrader) in the 365 days before the index date to one day prior to the index date

9.2.1.2 Exclusion criteria[15]

Patients who meet any of the following criteria will be excluded from the safety and effectiveness cohorts:

1. Received more than two types of endocrine treatments, administered sequentially (not concurrently) in the 365 days before the index date to one day prior to the index date
2. Prior use of AKT inhibitor (including capivasertib) in the 365 days before the index date to one day prior to the index date

[13] This does not include patients with pre-diabetes.
[14] Continuous enrolment is defined as time in which patients have uninterrupted membership or coverage in a health insurance plan or healthcare system, evidenced by no gap or missing data in their enrolment records within the data source for a period of at least 365 days prior to and including the index date. Enrolment in Optum Market Clarity will be defined using claims enrolment and not EMR activity. The absence of enrolment gaps guarantees complete data capture, reflecting patients' health and treatment patterns while preventing potential bias (18).
[15] At the time of the end of data collection in Q4 2029, all approved combinations of capivasertib with other treatments will be thoroughly evaluated to assess whether revisions to the exclusion criteria are warranted. Any changes will be reflected in a protocol amendment.

3. Prior use of PI3K inhibitor (including alpelisib) in the 365 days prior to and including the index date

4. Prior use of mTOR inhibitor (including everolimus) in the 365 days prior to and including the index date

9.2.1.3 Exploratory objective 8: eligibility criteria

Patients will be included in the analyses for exploratory objective 8 if they meet the same inclusion and exclusion criteria as the safety and effectiveness cohorts, in addition to the following inclusion criterion:

1. ER+/HER2- advanced (locally advanced [stage IIIB or IIIC] or metastatic [stage IV]) breast cancer with ≥1 *PIK3CA/AKT1/PTEN* alterations documented in the 365 days prior to and including the index date.

This inclusion criterion will be assessed in data source(s) where biomarker and cancer staging data are available (Danish NPR and Optum Market Clarity).

9.2.1.4 Exploratory objective 9: eligibility criteria

Patients will be included in the analyses for exploratory objective 9 if they meet the same inclusion and exclusion criteria as the safety cohort, in addition to the following inclusion criterion:

1. The last recorded HbA1c value is ≥8.0% in the 90 days prior to and including index date

This inclusion criterion will be assessed in data source(s) where laboratory results are available (Danish NPR and Optum Market Clarity).

9.2.1.5 Subgroups

Patients who meet the same inclusion and exclusion criteria as the safety and effectiveness cohorts will be categorised into the following subgroups of insulin dependency status for exploratory objectives 5 through 7. See section 9.3.3.3 for further details on the exploratory outcome definitions and details on the following subgroups:

- Insulin dependency status (19,20):
    - Insulin-dependent diabetes: at least four prescriptions of insulin documented in the outpatient setting from 365 days before the index date up to and including the index date

- Non-insulin-dependent diabetes: less than four prescriptions of insulin documented in the outpatient setting from 365 days before the index date up to and including the index date

9.2.2 Study time frame

9.2.2.1 Study period

The study period will begin 12 months before the reimbursement decision date of each respective country for the European data sources and on November 16, 2022, for the USA data source (12 months prior to FDA marketing authorisation) to allow for a 12-month look-back period before the index date. No patients who received capivasertib + fulvestrant before their respective country's reimbursement decision date (Europe) or marketing authorisation date (USA) will be included in this study. The end of the study period will be the last possible date of follow-up when all patients still in the study are censored. These dates will differ by country as reimbursement decision dates will differ by country, and the length of data lag at the time of data extraction will also be different for each data source.

9.2.2.2 Accrual period

The accrual period is defined as the time within the study period during which patients can enter the cohort (i.e., from capivasertib + fulvestrant reimbursement decision date in each European country or marketing authorisation in the USA) and ends 30 days prior to the end of all available data for the safety cohort and 365 days prior to the end of all available data for the effectiveness cohort. The difference in the patient accrual period for the two cohorts is to allow for sufficient follow-up data to accrue to measure the outcomes of interest.

The actual end date for the accrual period for the safety and effectiveness cohorts will differ by country and data source as specified in Table 1 below.

Table 1 End of accrual period for safety and effectiveness cohorts by data source

Data source name (Country)	SNDS (France)	InGef (Germany)	NPR (Denmark)	Optum Market Clarity (USA)
Type of data source	Insurance claims	Insurance claims	EMRs	EMRs and insurance claims
Data lag	9 months	9 months	2 months	6 months
End of accrual period for safety cohort	Q4 2028	Q4 2028	Q2 2029	Q1 2029
End of accrual period for effectiveness cohort	Q4 2027	Q4 2027	Q2 2028	Q1 2028

Data source abbreviations: SNDS, Système National Des Données De Santé; InGef, Institute for Applied Health Research Berlin; NPR, National Patient Register

9.2.2.3 Index date

A given patient's index date will be determined by first identifying their earliest (by date) record of capivasertib use (prescription or dispensation) within the accrual period. Following this, the patient's medical records will be examined for any fulvestrant use within a ±28-day window of the initial capivasertib use. If a record of fulvestrant use is observed within this window, the index date is set as the earlier of the two medication dates (Figure 3).

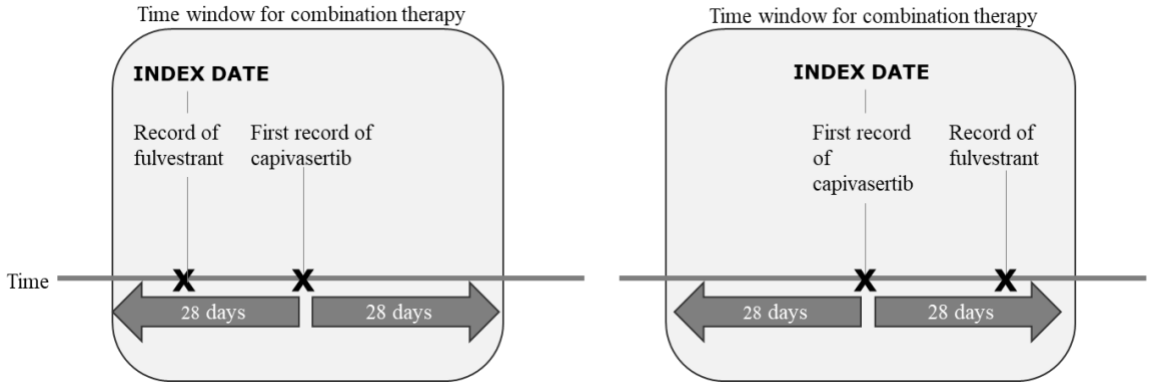

Figure 3 Illustration for determining the index date in capivasertib and fulvestrant combination therapy

Note: Index date is set based on the earlier date of the two medications when both are within the specified time window for combination therapy.

9.2.2.4 Look-back period

For both cohorts, the look-back period is set as 12 months prior to the index date. This timeframe is critical for confirming patients' eligibility (see sections 9.2.1.1 and 9.2.1.2).

9.2.2.5 Follow-up period

Follow-up will begin on the index date and will continue until death, disenrolment/de-registering/emigration, or last available data. Outcome-specific censoring criteria will be applied during analysis and are summarised in Table 2 (refer to section 9.3.3 for outcome definitions).

Table 2 Outcome-specific follow-up periods

Outcome[a]	Follow-up period	Definition
Acute complications of hyperglycaemia (composite)	Safety follow-up period	From the index date until the earliest of: outcome occurrence, capivasertib discontinuation (defined in section 9.3.2), death, disenrolment/de-registering/emigration, or last available data.

Outcome[a]	Follow-up period	Definition
TFST, rwOS, TTD, rwPFS	Effectiveness follow-up period	From the index date until the earliest of: outcome occurrence, disenrolment/de-registering/emigration, or last available data. Patients who have not experienced the event prior to the end of the follow-up period will be censored on the date of last available data.
Anti-diabetic treatment patterns	Treatment patterns follow-up period	From the index date until the earliest of: acute complication of hyperglycaemia (composite; defined in section 9.3.3), capivasertib discontinuation (defined in section 9.3.2), death, disenrolment/de-registering/emigration, or last available data.

a. Refer to section 9.3.3 for outcome definitions

9.3 Variables

9.3.1 Identification of the study population

Diagnoses of breast cancer and diabetes (type 1 or 2) will be needed for the identification of the study population, as follows:

Breast cancer will be identified using International Classification of Diseases (ICD) diagnosis codes or other relevant codes used in the specific data sources. These codes will be further developed in the Statistical Analysis Plan (SAP) to align with the classifications used by each data source and will be mapped to the ICD-10 code C50.x (21).

Diabetes diagnoses will be identified using an algorithm developed by Sharma et al. and validated in an EMR in the United Kingdom (UK) – the Health Improvement Network (THIN) data source (22).

This algorithm was selected based on a systematic review of algorithms used to identify diabetes type in administrative databases, conducted by Sajjadi et al. (23). The rationale for selecting this algorithm out of the several other algorithms described in the systematic review, was based on the following considerations:

- Validated in an adult population as opposed to paediatric only

- Availability of the required data elements in administrative health databases selected for this study (e.g., excluding algorithms which use self-reported diabetes, as this data is not available in the selected data sources for this study)

- High performance (i.e., higher sensitivity, specificity, and positive and negative predictive values) as the Sharma et al. algorithm has sensitivity, specificity, positive predictive value and negative predictive value of 100% compared to a reference standard of chart review by clinicians, which was the highest of all the other considered algorithms (22)

- Validation in a European population, to enhance the transportability of results

The Sharma et al. algorithm uses a combination of diagnostic codes and anti-diabetic medication to identify patients with type 1 or type 2 diabetes in a two-step process (22). The first step identifies all patients with either a diagnostic code, prescription code, or procedural code indicative of any type of diabetes, whereby the following exclusion criteria are then applied:

- Have no diabetes records except for metformin prescriptions (may possibly indicate cases of polycystic ovary syndrome and metabolic disease)
- Have only a single record of diabetes (either only one diagnosis code or one anti-diabetic prescription)
- Lack a diagnostic record for diabetes
- Have diagnostic codes for other diabetes mellitus subtypes only (e.g., gestational diabetes)

The cohort identified from the application of the first step above will then be further refined in step 2 of the algorithm to differentiate patients with type 1 diabetes versus type 2 diabetes using five variables in a descending level of importance as follows:

- Diagnostic code type assigned (e.g., E10.x for type 1 diabetes, and E11.x for type 2 diabetes)

- Cumulative days of noninsulin prescriptions (e.g., Anatomical Therapeutic Chemical [ATC] codes for alpha-glucosidase inhibitors [A10BF], biguanides like metformin [A10BA], combinations of oral blood glucose-lowering drugs [A10BD], DPP-4 inhibitors [A10BH], GLP-1 agonists [A10BJ], meglitinides [A10BX], SGLT-2 inhibitors [A10BK], sulfonylureas [A10BB], and thiazolidinediones [A10BG])

- Number of insulin prescriptions issued (insulins and analogues for injection [A10AB–A10AE] as insulin is needed for type 1 diabetes for survival once the disease has fully set in, however, it is less commonly needed for type 2 disease unless in more advanced stages of the disease

- Incident or prevalent case of diabetes mellitus
- Age at first record of diabetes mellitus

The full criteria for classification of patients are provided in Sharma et al. (22) and summarised below. Unspecific diagnostic codes refer to when both type 1 and type 2 diabetes mellitus codes were used in the same patient's record or when no type-specific code was used to record a patient's diabetes mellitus diagnosis. The patients classified with uncertainty are highlighted with an asterisk in the following paragraphs.

Patients with type 1 diabetes mellitus are patients who meet one of the following criteria:

- A diagnostic code of type 1 diabetes mellitus only, a prescription for insulin only.
- A diagnostic code of type 1 diabetes mellitus only, a prescription for insulin, and <6 months cumulatively of other anti-diabetic agents.
- A type 2 diabetes mellitus code only or unspecific diagnostic codes, a prescription for insulin only, and an incident case of diabetes mellitus or diagnosed with diabetes mellitus at <35 years of age.
- Unspecific diagnostic codes, a prescription for insulin and <6 months cumulatively of other anti-diabetic agents, and an incident case of diabetes mellitus or diagnosed with diabetes mellitus at <35 years of age.*

Patients with type 2 diabetes mellitus are patients who meet one of the following criteria:

- A diagnostic code for type 2 diabetes mellitus only and any quantity of prescription for other anti-diabetic agents with or without insulin.
- A diagnostic code for diabetes mellitus of any type and prescriptions for ≥6 months cumulatively of other anti-diabetic agents with or without insulin.
- A diagnostic code for diabetes mellitus of any type and any quantity of prescription for other anti-diabetic agents with no insulin prescription.
- A diagnostic code for type 2 diabetes mellitus or unspecific diagnostic codes and no prescribed treatment.
- A diagnostic code for type 1 diabetes mellitus only and no prescribed treatment.*

- A diagnosis of types 2 diabetes mellitus only or unspecific diagnostic codes, prescribed insulin only, but were a prevalent case and diagnosed with diabetes mellitus at ≥35 years of age.*

- Unspecific diagnostic codes, prescribed insulin with <6 months cumulatively of other anti-diabetic agents, a prevalent case, and diagnosed with diabetes mellitus at ≥35 years of age.*

The number of patients classified with uncertainty (*) based on the algorithm will be provided; however, these patients will be excluded from any analysis necessitating diabetes mellitus type as a covariate (including exploratory objectives 5-8) to minimise misclassification bias.

Note that the Sharma et al. algorithm (22) was developed using data from the UK using Read codes, drug codes, and Additional Health Data codes. These codes will be mapped to ICD-10 codes and other relevant codes specific to the data sources selected for the study. The adapted codes for the selected data sources will be outlined in the SAP. Additional algorithms as provided in Sajjadi et al. (23) which are based on ICD-10 codes will also be explored. The final algorithm to be used will be detailed in the SAP.

9.3.2 Exposure

The primary exposure of interest is treatment with capivasertib in combination with fulvestrant.

- **Posology of treatments:** the recommended dosing regimen for capivasertib according to the EMA's Summary of Product Characteristics (13) is 400 mg (two 200 mg tablets taken orally) twice daily, approximately 12 hours apart (total daily dose of 800 mg), for 4 days followed by 3 days off treatment (see Figure 4). For fulvestrant, the recommended dose is 500 mg administered intramuscularly on days 1, 15, and 29 for the first cycle, and once monthly (i.e., one dose every 28 days) thereafter.

Day	1	2	3	4	5*	6*	7*
Morning	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg			
Evening	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg			

* No dosing on day 5, 6 and 7.

Figure 4 Capivasertib dosing schedule for each week

Note: EU and USA dosing recommendations are similar (6, 13).

Treatment with capivasertib may be interrupted to manage adverse reactions and dose reduction can be considered as described in Table 3 below (13).

Table 3 Capivasertib dose reduction

Capivasertib dose reduction	Dose and schedule	Number and strength of tablets
First dose reduction	320 mg twice daily for 4 days followed by 3 days off treatment	Two 160 mg tablets twice daily
Second dose reduction	200 mg twice daily for 4 days followed by 3 days off treatment	One 200 mg tablet twice daily

- **Initiating treatment with capivasertib in combination with fulvestrant is defined as** having at least one prescription/dispensation of each medication—capivasertib and fulvestrant—issued within a ±28-day window of each other (Figure 3). Any additional anti-cancer therapy added to the capivasertib and fulvestrant combination does not align with the current approved indication for breast cancer at the time of protocol development and is not considered within the defined treatment exposure for this study. The following additional anti-cancer therapies will be considered in defining exposure for this study and will be further detailed in the SAP, as variations are expected between data sources given geographical differences (24,25):

    - Chemotherapy (e.g., doxorubicin, epirubicin, paclitaxel, docetaxel, 5-fluorouracil, capecitabine, cyclophosphamide, ixabepilone, eribulin, cisplatin, carboplatin, vinorelbine, gemcitabine)

    - Hormone therapy different from fulvestrant (e.g., tamoxifen, anastrozole, letrozole, exemestane)

    - Targeted therapy (e.g., abemaciclib, alpelisib, atezolizumab, denosumab, everolimus, neratinib, olaparib, palbociclib, pembrolizumab, pertuzumab, ribociclib, sacituzumab, talazoparib, trastuzumab, tucatinib)

- **Supply period:** The duration of a prescription will be defined using the dispensed days' supply. The number of days covered by the medication will be calculated based on the number of tablets prescribed/dispensed and the dosing instructions or dosing recommendation. For example, a single prescription fill for capivasertib of 64 tablets (200 mg each) would provide 4 weeks' (or 28 days') of supply, assuming the doses are taken as prescribed (patient takes 4 pills [800 mg] per day for 4 days per week).

- **Wash-out period (clearance window)**: A clearance window of 2 days will be used. This period is derived from 5 times the half-life (8.3 hours) of capivasertib, which is equal to 41.5 hours (or approximately 2 days).

- **Grace period**: A gap of 28 days between the end of the last prescription of capivasertib and the start of the subsequent one will be applied to account for possible delays in prescription refill, dose holds, or dose reductions. The duration of 28 days was selected as it aligns with one full treatment cycle duration, including fulvestrant monthly co-administration and capivasertib days off (for the fourth week).

- **Treatment discontinuation** will be anchored on capivasertib use and will be calculated from the capivasertib + fulvestrant treatment start date (i.e., index date) plus the supply period plus the wash-out period plus the grace period, except for the following scenarios that will also be classified as treatment discontinuation (see Figure 5):

  - **Discontinuation without replacement:** If capivasertib is discontinued without replacement, and fulvestrant is continued as monotherapy, patient will be considered to have a treatment discontinuation after the capivasertib supply period + wash-out period + grace period (see Figure 5).

  - **Add-on:** If an additional systemic anti-cancer therapy (i.e., chemotherapy, hormone therapy different from fulvestrant, or targeted therapy) is added on to the capivasertib + fulvestrant combination (i.e. the capivasertib supply period overlaps with add-on therapy, or there is a concomitant prescription of capivasertib and add-on therapy), patients will be considered to have a treatment discontinuation on the start date of the add-on therapy (see Figure 5).

  - **Switch:** If capivasertib is stopped and replaced with another systemic anti-cancer therapy (i.e., chemotherapy, hormone therapy different from fulvestrant or targeted therapy), patient will be considered to have a treatment discontinuation at the time of other systemic anti-cancer therapy start date or wash-out period + grace period, whichever date comes first (see Figure 5).

  - **Fulvestrant discontinuation:** If fulvestrant is discontinued without replacement (i.e. a gap >28 days is observed between last fulvestrant injection and capivasertib subsequent prescription), and capivasertib is continued as monotherapy, patient will be considered to have a treatment discontinuation after the capivasertib supply period + wash-out period + grace period.

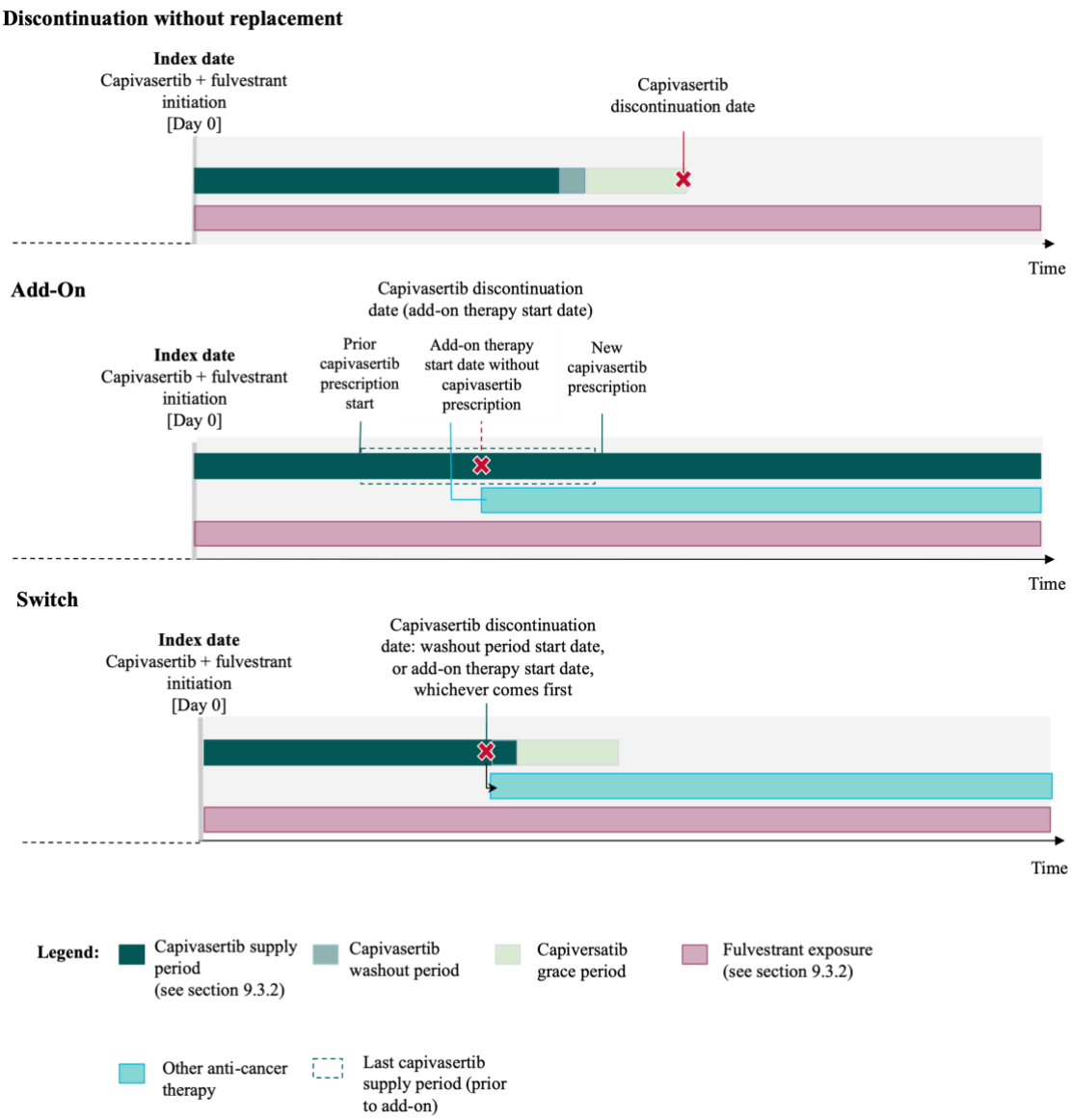

Figure 5 Potential capivasertib treatment discontinuation scenarios

Note: The above scenarios are illustrative only, additional scenarios will be detailed in the SAP.

- **Censoring at the end of follow-up**: If the observation period ends while the treatment is ongoing, this will be treated as a censoring event rather than a discontinuation. It indicates that the treatment was neither actively discontinued nor altered up to the end of the follow-up.

- **Data source availability**: Capivasertib and fulvestrant use will be determined using records of issued prescriptions or dispensed prescriptions from community pharmacies, and/or insurance claims (for simplicity, prescription is used for the rest of the document), depending on the data available in each data source. Relevant treatment codes will be

developed in the SAP. These codes will be mapped from the following ATC codes: L01EX27 (capivasertib) and L02BA03 (fulvestrant) (26).

9.3.3 Outcomes

9.3.3.1 Primary outcomes

Objective 1a Primary safety outcome: Acute complications of hyperglycaemia (composite, including diabetic ketoacidosis)

Acute complications of hyperglycaemia (composite, including diabetic ketoacidosis) are defined as any inpatient hospitalisation encounter (using either primary or secondary admission diagnosis codes) with diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome (including hyperosmolar hyperglycaemic state, hyperglycaemic coma, or hyperosmolar coma) recorded in routine care (using the ICD-10 codes provided in Table 4) between the index date and up to 30 days after the last capivasertib dose (based on the supply period defined in section 9.3.2) during follow-up. The rationale for including primary and secondary admission codes is based on a lack of consistency in coding for acute complications of hyperglycaemia, such as diabetic ketoacidosis. In some scenarios a primary admission code is used, and in some others a secondary admission code is used (27,28).

A sample list of codes is provided in Table 4. These codes will be mapped to relevant coding systems for the selected data sources and finalised in the SAP. These conditions were based on ICD-10 mapping of acute complications of hyperglycaemia Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, available literature and clinical input (27,28).

Table 4 Diagnosis codes for acute complications of hyperglycaemia

Type of hyperglycaemic event	Conditions	ICD-10 Codes
Acute complications of hyperglycaemia	Diabetic ketoacidosis	E10.1, E11.1, E13.1, E14.1
	Hyperosmolar hyperglycaemic syndrome, defined as any of the following: • Hyperosmolar hyperglycaemic state • Hyperglycaemic coma • Hyperosmolar coma	E11.0, E13.0, E14.0

The first occurrence of any of the acute complication of hyperglycaemia component events (i.e., diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome) on or after the index date will

be considered an event of interest. Censoring criteria for this outcome are listed in section 9.2.2.5.

For patients with multiple inpatient hospitalisation admission records for acute complications of hyperglycaemia, a gap of 7 days between hospital discharge and a new admission record for an acute complication of hyperglycaemia, will be used to define a recurrent event. The 7-day window aligns with previous research on recommended follow-up times, the median time between discharge and the first visit to primary care, and the median length of stay for diabetic ketoacidosis (29,30).

Objective 1b Primary effectiveness outcome: TFST

TFST is defined as time from the index date until the start date of the first subsequent anti-cancer therapy after discontinuation of capivasertib (as defined in section 9.3.2) or death due to any cause. All events will be included, regardless of progression status. Censoring criteria for this outcome are listed in section 9.2.2.5.

9.3.3.2 Secondary outcomes

The secondary outcomes of interest are derived from the secondary objectives (see section 8.3).

Secondary objective 2a: rwOS

rwOS is defined as time from index date until the date of death due to any cause. All deaths will be included, regardless of whether the patient discontinues capivasertib or receives another anti-cancer therapy. Patients without a documented death will be censored at the date of their last confirmed activity, which is defined as either the date of the patient's last known healthcare contact or the end of the study period if there is evidence of follow-up beyond that date. Other censoring criteria for this outcome are listed in section 9.2.2.5.

Secondary objective 2b: TTD

TTD is defined as time from the index date until discontinuation of capivasertib treatment (as defined in section 9.3.2) for any reason, including disease progression, toxicity, and death due to any cause. All events will be included, regardless of progression status. Censoring criteria for this outcome are listed in section 9.2.2.5.

9.3.3.3 Exploratory outcomes

Exploratory objective 3: rwPFS

rwPFS is defined as time from the index date until progression or death due to any cause. All events will be included, regardless of whether the patient discontinues capivasertib therapy or

receives another anti-cancer therapy. Censoring criteria for this outcome are listed in section 9.2.2.5.

Several algorithms have been identified for detecting recurrence in women with stage 0-III breast cancer (31-35) but only one algorithm by Nordstrom et al. (36) refers to progression of the disease as opposed to recurrence, although it is also limited to women with stage I-III cancer, excluding those with stage IV. Given that progression data is inconsistently recorded in administrative health databases and there is limited literature on algorithms for defining progression in advanced (stage IIIB, IIIC, or IV) breast cancer, an algorithm has been developed to determine this outcome. The structure of the algorithm is outlined below in Figure 6. It is adapted from the algorithms by Xu et al. (35), Holloway et al. (33) and Nordstrom et al. (36). An event of progression will be identified if at least one of the criteria outlined in Figure 6 occurs, none of which must be present at index date. The date of the progression event will be the date of the occurrence of the first criterion identified. While this algorithm could be validated if any of the selected data sources contains sufficient information for a validation study, current feasibility assessments indicate that none of the data sources selected in this study would enable a validation analysis. Even with the addition of the USA-based Optum Market Clarity data, there is insufficient information to perform a validation analysis. Despite the linkage between claims data and EMR in Optum Market Clarity, based on a recent feasibility study, real-world progression is captured in <10% of patients with breast cancer and diabetes through natural language processing (see section 9.4 for further details on data sources). Thus, this information cannot be reliably used to inform a validation analysis which requires comprehensive data on real-world progression in EMR (to serve as the gold standard).

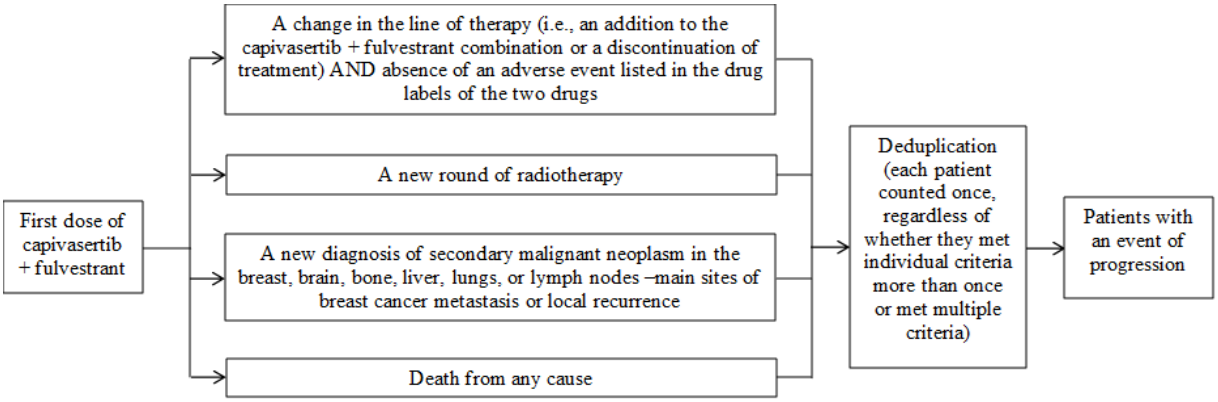

Figure 6 Algorithm for identification of progression in administrative health databases

Exploratory objective 4: Risk factors associated with acute complications of hyperglycaemia (composite, including diabetic ketoacidosis)

For exploratory objective 4, the outcome for this objective is the same as the primary safety outcome. Albeit this objective is to evaluate the baseline risk factors associated with acute complications of hyperglycaemia (composite, including diabetic ketoacidosis). Known and

potential baseline risk factors for acute complications of hyperglycaemia, selected through literature and clinical expert review, are listed in Appendix B.

Exploratory objectives 5, 6 and 7: Outcomes stratified by insulin dependency

The outcomes for exploratory objectives 5, 6, and 7 are the same as the outcomes for objectives 1a (acute complications of hyperglycaemia), 1b (TFST) and 2a (rwOS), albeit **stratified by insulin-dependent diabetes and non-insulin-dependent diabetes,** respectively.

The definition of insulin-dependent and non-insulin-dependent diabetes will be ascertained via prescriptions. There are currently no definitions available in the literature for insulin dependency. However, there are examples of algorithms that distinguish between type 1 and type 2 diabetes mellitus (including the algorithm previously detailed in section 9.3.1), which could help guide an approach for insulin dependency. Bruno et al. (37) define type 1 diabetes mellitus as "*at least two prescriptions of insulin over 12 months and continuous insulin-treatment in the following year*". Since the stratifications need to be present at the index date, this definition has been adapted to the following in this study: a patient will be considered to be insulin dependent if they have received at least four prescriptions of insulin in a non-hospital setting during the look-back period. This criterion applies only to insulin therapy initiated or managed in outpatient or non-hospital settings, reflecting the ongoing need for insulin administration. At least two prescription fills of insulin will identify early persistent users (38), while at least four prescription fills will ensure dependency over a year, as refills typically cover a 30- to 90-day supply (19,20), i.e., 4-12 fills a year. This definition helps ensure the accuracy of insulin dependency by accounting for potential errors in coding or unusual circumstances that may affect prescription records like temporary need for insulin due to medical procedures or acute illnesses. Insulin codes will be developed in the SAP to align with the classifications used by each data source and will be mapped from the ATC codes in group A10A Insulins and Analogues (from A10 Drugs Used in Diabetes).

Exploratory objective 8: Outcomes among adults with known characteristics of breast cancer

In exploratory objective 8, the primary outcomes (acute complications of hyperglycaemia and TFST) will be assessed among **locally advanced or metastatic breast cancer patients with ER+/HER2- status and ≥1 *PIK3CA/AKT1/PTEN* alterations** (depending on data availability). Patients must have information that confirms that they have ER+/HER2-, locally advanced or metastatic breast cancer with at least one *PIK3CA/AKT1/PTEN* alteration. A July 2024 feasibility assessment indicated that *PIK3CA/AKT1/PTEN* alteration status is the characteristic most often unavailable in European data sources. This objective aims to explore the primary outcomes in the indicated population as per EMA's Summary of Product Characteristics (13), given broader eligibility criteria are being utilised to select the study population (see section 9.2.1 for eligibility criteria). This objective will only be carried out if

the necessary data elements are available from at least one data source (which is currently proposed to be in the Danish National Patient Register (NPR) with linkage to the Pathology Registry and the Cancer Registry and potentially in the Optum Market Clarity data in the USA).

Exploratory objective 9: Acute complications of hyperglycaemia (composite, including diabetic ketoacidosis) among adults having a baseline HbA1c level ≥ 8.0%

In exploratory objective 9, the primary safety outcome, acute complications of hyperglycaemia (composite, including diabetic ketoacidosis) defined in Table 4 will be assessed **among patients with a recorded baseline HbA1c level ≥ 8.0%** (based on most recent result within 90 days prior to and including index date) in the safety cohort. This analysis will be carried out in the selected data sources with available laboratory results data (e.g., Danish NPR and Optum Market Clarity).

Exploratory objective 10: Acute complications of hyperglycaemia components

In exploratory objective 10, the components of acute complications of hyperglycaemia, diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome (defined in Table 4), will be assessed separately among the safety cohort across the safety follow-up period (as defined in section 9.2.2.5).

Exploratory objective 11: Anti-diabetic treatment patterns

In exploratory objective 11, anti-diabetic treatment patterns will be assessed in the safety cohort across the treatment patterns follow-up period (as defined in section 9.2.2.5). Anti-diabetic treatment drug classes are defined as: alpha-glucosidase inhibitors (ATC code A10BF), biguanides (ATC code A10BA), DPP-4 inhibitors (ATC code A10BH), GLP-1 agonists (ATC code A10BJ), insulins and analogues for injection (ATC code A10AB–A10AE), meglitinides (ATC code A10BX), SGLT-2 inhibitors (ATC code A10BK), sulfonylureas (ATC code A10BB), and thiazolidinediones (ATC code A10BG).

Anti-diabetic treatment episodes will be defined by any treatment duration (i.e., at least one prescription for an oral or injectable anti-diabetic of any duration) and require a 90-day grace period, aligned with commonly observed gaps in anti-diabetic persistence studies (39), without extension beyond the grace period. In case of overlapping prescriptions for the same anti-diabetic drug class, it will be assumed that the durations of episodes are additive (i.e. the supply days of the second overlapping episode will be shifted forward). Overlap of treatment episodes of different anti-diabetic drug classes will be considered combination therapies (drugs with ATC codes A10BD* will be considered combination therapies).

Anti-diabetic drug discontinuation will be defined as occurring if a patient:

- Does not use the treatment after a 90-day grace period (i.e. defined as having a gap exceeding 90 days) between the end of a prescription (based on its start date and duration) and the start of the next prescription, or if no additional prescription occurs.

- For drug combinations, the discontinuation of one drug class will be accounted for only in the analysis by class (refer to section 9.7.5.8 for further details).

9.3.4 Covariates

All covariates will be assessed either on index date or in the 12-month look-back period for study patients as outlined in Table 5. Operational definitions, along with relevant assessment periods for each covariate, will be detailed in the SAP. These may vary depending on the data source. It is important to note that not all data sources will capture all the covariates listed below.

Baseline characteristics, along with specific known or potential baseline risk factors or confounders for one or more outcomes of interest, were selected through a literature review process and clinical expert input (endocrinologists and oncology safety physicians). These are provided in Table 5. The relationships between the covariates and the exposure, as well as with the outcomes of interest, as identified through the literature review (summarized in Appendix B) and clinical expert input, are depicted in directed acyclic graphs Appendix B using the SPACE – Structured Preapproval and Postapproval Comparative study design framework (40).

Table 5 List of Covariates

Variable	Definition
Age at index date	Continuous and dichotomised: 18-64, 65+ years
Sex	Binary: male, female
Race (if available)	Categorical: categories to be defined according to availability of data (e.g., White, Black, Asian, Other, Unknown)
Ethnicity (if available)	Categorical: categories to be defined according to availability of data (e.g., Hispanic, Non-Hispanic, Unknown)
Country of residence	Categorical: each country will form a category
Body mass index (if available)	Binary: <30, ≥30 kg/m^2
Socio-economic status (if available)	Categorical: low, medium, high, unknown
Tobacco use (if available)	Categorical: yes, no, unknown

Variable	Definition
Alcohol abuse (if available)	Categorical: yes, no, unknown
Drug abuse (if available)	Categorical: yes, no, unknown
Type of diabetes[a]	Binary: type 1, type 2
Postmenopausal status (for female patients only)[b]	Categorical: yes, no, unknown
Concurrent use of luteinizing hormone-releasing agonist[c]	Categorical: yes, no, unknown
Metastatic breast cancer diagnosis	Categorical: yes, no, unknown
Site of metastases	Categorical: breast, brain, bone, liver, lungs, lymph nodes, other
Time since advanced breast cancer diagnosis (if available)	Continuous
Time since initial diabetes diagnosis (if available)	Continuous
History of other cancers	Categorical: yes, no, unknown
Previous CDK4/6i (abemaciclib, palbociclib, or ribociclib) use (if available)	Categorical: yes, no, unknown
Previous fulvestrant use[d]	Categorical: yes, no, unknown
Prior primary tumour surgery (e.g., mastectomy, lumpectomy)	Categorical: yes, no, unknown
Number of prior anti-oestrogen therapies[e]	Discrete: n of therapies
Number of prior tamoxifen therapies[d]	Discrete: n of therapies
Number of prior anastrozole therapies[d]	Discrete: n of therapies
Number of prior letrozole therapies[d]	Discrete: n of therapies
Number of prior exemestane therapies[d]	Discrete: n of therapies
Number of prior oral selective oestrogen receptor degrader therapies[d]	Discrete: n of therapies
Prior chemotherapy (paclitaxel, docetaxel, doxorubicin, epirubicin, cisplatin, carboplatin).	Binary: yes, no
Concomitant use of other medications affecting blood glucose level, regardless of type (systemic corticosteroids, statins, quinolones, thiazides and thiazide-like diuretics, beta blockers, atypical antipsychotics, protease inhibitors, calcineurin inhibitors, DPP4-inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonists, and sulfonylureas)	Binary: yes, no Categorical: categories by type
Concurrent metformin use	Binary: yes, no
Concurrent use of other medications for comorbidities	Binary: yes, no
Comorbidity that interferes with blood glucose levels: presence of at least one relevant condition (e.g., Cushing	Binary: yes, no

Variable	Definition
syndrome, acromegaly, acute pancreatitis, chronic liver disease, hypo-/hyper-thyroidism, glucagonoma, pheochromocytoma, somatostatinoma, hyperaldosteronism, polycystic ovarian syndrome, hypertension, hyperlipidaemia)	
Recent healthcare use: frequency of hospitalisations within past year	Discrete: n of hospitalisations
Recent healthcare use: emergency department visits within past year	Discrete: n of emergency visits
Recent healthcare use: outpatient physician visits within past year	Discrete: n of outpatient visits
Prior history of acute complications of hyperglycaemia (e.g., diabetic ketoacidosis, hyperosmolar hyperglycaemic state)	Binary: yes, no
Calendar year of index date (2023, 2024, etc.)	Categorical: each year will form a category
HbA1c value	Binary: <8%, ≥8%

[a] Classification of patients with type 1 or type 2 diabetes will be done following an algorithm such as Sharma et al. (19) as described in section 9.3.3.3. More detail will be provided in the SAP.

[b] Postmenopausal status will be defined according to an algorithm (see below). More detail will be provided in the SAP.

[c] Proxy for pre- or peri-menopausal status in female patients, given recommended use in combination with capivasertib + fulvestrant for this population.

[d] Variable will not be included in exploratory objectives 4 or exploratory objectives 5 to 7 adjusted analyses.

[e] Anti-oestrogen therapies will include at least one of the following treatments: fulvestrant, tamoxifen, anastrozole, letrozole, exemestane, and oral selective oestrogen receptor degrader therapies.

Postmenopausal status

A female patient will be considered to be postmenopausal if they meet any of the following criteria:

1. Any record indicative of menopause in the look-back period, such as ICD-codes N95.1 (menopausal and female climacteric states), N95.0 (postmenopausal bleeding), or M80.0 (postmenopausal osteoporosis with pathological fracture); note: a list of all relevant codes will be developed in the SAP

2. A history of a bilateral oophorectomy, identified through procedure codes during the look-back period

3. Age 55 years or older at index date

The mean age at natural menopause in Europe is 51 years (41), but a study of 142,973 women in Australia found that an age threshold of 55 years was optimal for identifying menopause status (42). Other indicators, such as menopausal symptom treatments or hormone replacement therapy, are not applicable here because, according to the indication of capivasertib, patients will have ER+/HER2- breast cancer and hence, would likely avoid hormone therapies to prevent cancer growth.

9.4 Data sources

Considering the recent approval of capivasertib by the EMA during this protocol's development, there is uncertainty about which European countries will provide reimbursement. This uncertainty could impact the drug's uptake and, consequently, the selection of data sources.

The decision on which data sources to use was informed by a feasibility assessment conducted in July 2024 (see Appendix A). This assessment assumed that capivasertib would be present in the data sources if other drugs targeting the PI3K-AKT signalling pathway, such as alpelisib (a PI3K inhibitor) and everolimus (an mTOR inhibitor), were captured in the data source (if reimbursed in the country of the data source).

9.4.1 Feasibility assessment

The study will use existing secondary data from multiple European countries and the USA. A feasibility assessment was conducted in July 2024 with the aim to evaluate the most relevant data sources for addressing the research question and study objectives. The Feasibility Assessment Report is available as a stand-alone document, see Appendix A. There were several limitations to the feasibility assessment as it was conducted within 3 months of a positive CHMP opinion, prior to market availability of capivasertib in any of the EU member countries.

The feasibility assessment focused on a study population diagnosed with locally advanced or metastatic breast cancer, characterised by ER+ (or HR+)/HER2- status, with *PIK3CA*/*AKT1*/*PTEN* alterations, and a concurrent diagnosis of type 1 or 2 diabetes. Results from the feasibility assessment indicated that there was no single European data source that could capture data on biomarkers, genomic data, cancer stage at diagnosis, and information on acute complications of hyperglycaemia alongside management of diabetes. As discussed above, while most administrative health databases (i.e., claims data and EMRs) lack data on cancer staging and biomarker status, they collect comprehensive information on specific cancer treatments, diabetes management, and acute complications of hyperglycaemia in large, representative populations. Disease-specific data sources, such as cancer registries, collect comprehensive information on cancer characteristics (e.g., staging and biomarker status), but they lack key data on acute complications of hyperglycaemia, specific cancer treatments, and/or

comedication for diabetes. As a result, several elements of the study population definition (see section 9.2.1) were revised to address the challenges observed in the administrative health databases.

9.4.2 Selection of data sources

Regarding the selected data sources, one important caveat must be considered. Considering that capivasertib + fulvestrant has only recently been approved by the EMA, it is currently uncertain which European countries will provide reimbursement, which will affect drug uptake, and therefore, the final data source selection for this study. As a result, the European data sources recommended below as being suitable are subject to change depending on reimbursement status. To mitigate potential reimbursement challenges in the EU, one USA data source has been selected for the study as capivasertib was approved in the USA in November 2023 (7). The relevance of USA data to the European context will be supported by providing patient demographic distributions, considerations on treatment guidelines, and variation in treatment accessibility across geographies in the final study report.

Additional data sources detailed in Appendix C will be considered, should the options described below prove unsuitable due to capivasertib reimbursement status in the respective European countries.

The choice of final data sources was guided by the following criteria:

- Availability of the data required to meet the study objectives, including the ability to identify and describe the study population, to capture acute complications of hyperglycaemia, to apply an algorithm for progression, and availability of the covariates
- Size of the data source – the potential to identify a sample size of 150 patients. As explained in section 9.5.1, a sample size of 150 patients provides a similar precision to that observed in the Phase III trial (CAPItello-291) for both safety and effectiveness outcomes
- Representativeness of the overall population covered by the data source
- Possibility of linkage with, or integration of, cancer-specific data source(s)
- Possibility of linkage with, or integration of, laboratory data (specifically HbA1c values)

Based on the overall rating, the data sources currently selected for use in this PASS are:

- The Système National Des Données De Santé (SNDS) in France
- The Institute for Applied Health Research Berlin (InGef) in Germany

- The NPR in Denmark
- The Optum Market Clarity® dataset in the USA

General characteristics of these data sources and the availability of required data elements to address the research objectives are summarised in Table 6.

Table 6 Summary characteristics and availability of data in the data sources

Data source name (Country)	SNDS (France)	InGef (Germany)	NPR (Denmark)	Optum Market Clarity (USA)
Type of data source	Insurance claims	Insurance claims	EMRs	EMRs linked to claims
Data collection setting	Inpatient and outpatient	Inpatient, outpatient, and primary care	Inpatient and outpatient	Inpatient and outpatient
Period of data availability	2006-present	Last 6 years	1977-present	2007-present
Coverage	99% of French population	8% of German population, representative	100% of Denmark population	25% of the USA population
Coding system for diagnoses	ICD-10	ICD-10-GM	ICD-10	ICD-10-CM
Coding system for drugs	ATC, EphMRA, UCD/CIP	ATC and OPS	ATC	ATC and NDC
Ability to identify study population	Diabetes + BC diagnosis	Diabetes + BC diagnosis	Diabetes + BC diagnosis	Diabetes + BC diagnosis
Acute complications of hyperglycaemia	Yes, inpatient	Yes, inpatient and outpatient	Yes, inpatient and outpatient	Yes, inpatient and outpatient
Progression	Via algorithm	Via algorithm	Via algorithm	Via algorithm Yes (<10%)
Death	Yes	Yes	Yes	Yes
Cause of death	Yes	No	Yes	No
Cancer staging	No	No	Yes	Yes (<10%)
Biomarker data	No	No	Yes	Yes (<1%)
HbA1c value	No	No	Yes	Yes (<20%)

Abbreviations: ATC, Anatomical Therapeutic Chemical; BC, Breast Cancer; CM, Clinical Modification; CIP, Club Inter Pharmaceutique; EphMRA, European Pharmaceutical Market Research Association; GM, German Modification; ICD, International Classification of Diseases; NDC, National Drug Code; OPS, Operationen- und Prozedurenschlüssel; UCD, Unités Communes de Dispensation; USA, United States of America.

The assumptions used in selection of the databases will be monitored during the conduct of the study, as capivasertib market launch and reimbursement decisions in the EU are ongoing. If necessary, the following contingency plan will be considered:

1. If the selected European data sources (SNDS, InGef, or NPR) are no longer fit for the study conduct, alternative European data sources (provided in Appendix C) will be considered for replacement.

2. Study timelines could be extended, after consideration/discussions with the EMA, to allow for sufficient patient accrual over time in the selected European data source(s).

9.4.3 Details of data sources

The following data sources will be used to address the study objectives.

SNDS – France

SNDS is the largest and most comprehensive healthcare dataset available in Europe with a 10-year longitudinal follow-up for over 66 million patients (43). It covers 99% of the French population. SNDS includes anonymised administrative and healthcare claims data from the French national health care insurance system databases. In particular:

- The *Système national d'information interrégimes de l'Assurance maladie* contains demographic data, presence and date of chronic disease including a list of long-term diseases (*Affections de Longue Durée*), all outpatients reimbursed health expenditures (*Données de Consommation Inter-Régimes*), date and nature of all lab tests (but without the results), date and duration of hospital admissions, with diagnosis-related groups, among others (43). There is also information on in-hospital prescriptions for very expensive drugs not included in the hospital diagnosis-related groups (e.g., targeted cancer therapies and monoclonal antibodies).
- *Programme de Médicalisation des Systèmes d'Information* is the national hospital discharge database. In addition to admission date and duration of stay, it includes main, related, and associated diagnoses, as well as procedures and especially costly drugs.
- *Centre d'épidémiologie sur les causes médicales de Décès* is the national death registry, which includes causes of death.

These three databases are linked by a unique personal identification number to allow for follow-up across different settings of care. Access to only four years of database is routinely allowed by law but more years may be authorised upon validated request (43).

SNDS has proven to be a very useful and reliable tool for research purposes. It has been used extensively for studies on cancer, more specifically on breast cancer (44–50), as well as studies on progression-free survival of different cancers (not breast) (51–53).

InGef – Germany

The InGef Research Database is an anonymised claims database with approximately 70 German statutory health insurances contributing longitudinal data from approximately 6.7 million persons (54). It provides a readily available, reliable and representative data source for healthcare research (55).

This database contains information on hospitalisations, outpatient physician visits and outpatient drug prescriptions. The hospital data comprises information on the date of admission and discharge, the reason for discharge, diagnostic and therapeutic procedures with the exact date as well as diagnoses, which can be distinguished in hospital main discharge diagnoses and secondary diagnoses. The outpatient data also comprises information on diagnostic and therapeutic procedures with their exact date. Data on outpatient prescriptions of reimbursed drugs comprise information on the prescription, the date of prescription and the pharmaceutical reference number. The ATC code, the defined daily dose, the packaging size as well as the strength and formulation of the drug can be linked for each dispensed drug based on a pharmaceutical reference database (56).

The InGef database has been used for research on cancer (57–61), including breast cancer (62,63).

NPR – Denmark

The NPR is a population-based administrative health register, which has collected data from all Danish hospitals since 1977 with complete nationwide coverage (5.9 million inhabitants approximately). Reporting to the NPR became compulsory in 2003 for private hospitals and private outpatient specialty clinics, excluding private practice specialists and general practitioners (GPs). Its primary aim is continuous monitoring of hospital and health services utilisation for the Danish Health and Medicines Authority (64).

The content of the NPR is structured, with each variable having a finite number of possible values. Information reported to the NPR includes administrative data, diagnoses (including primary, secondary, referral and temporary diagnoses), in-hospital medication use, other treatments, and examinations (64).

The availability of patient-identifiable data in the NPR makes it technically easy to link to other Danish data sources using unique identifiers. Some of the data sources that it can be linked to are:

- The Danish Register of Causes of Death: contains information on date and cause of death since 1943 and has a data lag of approximately 13 months
- The Danish Cancer Registry: contains detailed cancer diagnoses since 1943
- The Danish Civil Registration System: contains information on everybody that has a civil registration number, e.g., emigration status, marriage status, whether person is alive or dead
- The Danish National Prescription Registry: records all prescription drugs filled by patients at community pharmacies since 1995
- The Danish National Pathology Registry and Blood Transfusion Databases: holds data on data of patient tissue samples and blood transfusions since 1997.
- The Clinical Laboratory Information System Database: collects laboratory information since 1985.

Numerous studies on breast cancer have been conducted in Denmark, many in collaboration with the Danish Breast Cancer Cooperative Group (65–69), with several specifically focused on cancer recurrence (31,70–72), collaboration with the Danish Breast Cancer Cooperative Group is not currently feasible due to operational constraints, and as a result, linkage will not be available for the present study.

Optum Market Clarity – USA

Optum Market Clarity contains EMR data with prescriptions, diagnoses, and provider information as well as practice management data and claims information for deterministically-matched patients. This dataset contains a combination of structured data (e.g., diagnoses, procedures, prescriptions) and information from unstructured data (e.g., drug rationale, provider notes) from the EMR and corresponding claims information for those instances. This observational study may use Optum Market Clarity with oncology enrichment if sufficient patient data is captured. Optum Market Clarity has a large network of EMRs that covers a broad swath of the USA population, with over 103 million patients coming from integrated delivery networks and ambulatory only facilities. The data source includes around 60 million patients with overlapping EMR data from large health systems linked to medical and pharmacy claims across payers, which will allow capture of encounters missed by EMR alone (73). Natural language processing is performed on provider notes to turn unstructured text into a variety of structured fields with models specifically developed for oncology.

This dataset has been used in oncology research and several studies on breast cancer have been published (74–79).

9.5 Study size

For this PASS, a sample size of 150 patients per country will enable estimation of the primary safety outcome with a precision of 4.1% (assuming incidence of acute complications of hyperglycaemia of 5.9%, providing an estimated 95% confidence interval, CI: 2.7%, 11.0%) and estimation of the primary effectiveness outcome (TFST) with a precision of ~1.7 months (using the observed clinical trial PFS of 7.3 months, providing an estimated 95% CI: 5.7, 9.1 months).

However, if within a given data source fewer patients are observed, alternative precision estimates and CIs have been considered for smaller sample sizes.

Details of the approach used to estimate sample size and varying precision levels for the primary safety and effectiveness objective are provided in sections 9.5.1.1 and 9.5.1.2, respectively.

9.5.1 Sample size calculation

9.5.1.1 Primary safety outcome: acute complications of hyperglycaemia

Table 7 presents the sample size and associated 95% CI width/precision to estimate the proportion experiencing acute complications of hyperglycaemia (diabetic ketoacidosis, hyperosmolar hyperglycaemic state, hyperglycaemic coma, hyperosmolar coma) during follow-up, i.e., between index date and up to 30 days after last capivasertib dose, or death, disenrolment/de-registering/emigration, or last available data (whichever occurs first).

The table presents a range of sample sizes and presumed proportions of acute complications of hyperglycaemia (1.9%, 2.3%, and 5.9%), which were based on observed incidences of grade ≥3 or serious hyperglycaemic adverse events in the CAPItello-291 trial, as described in the table.

The observed incidence of diabetic ketoacidosis and diabetic metabolic decompensation in the capivasertib + fulvestrant arm of the overall CAPItello-291 population (3/355 or 0.8%) was not used in these calculations, as this value (<1%) will underestimate the incidence of the safety outcome in the proposed study population.

Assuming 5.9% of the study population experiences an acute complication of hyperglycaemia [redacted], a sample size of 150 patients would provide a precision of 4.1%, i.e., corresponding 95% CI (2.7%, 11.0%). Sample sizes of 500 and 1000 would provide precision of 2.2% and 1.5% respectively.

Table 7 Sample size (number of patients) required to estimate a given proportion with acute complications of hyperglycaemia during follow-up at varying levels of precision

Proportion with acute complications of hyperglycaemia (%)						
	1.9		2.3		5.9	
CCI [redacted]	[redacted]		[redacted]		[redacted]	
Number of patients	**95% CI**	**Precision***	**95% CI**	**Precision***	**95% CI**	**Precision***
60	(0.1, 9.3)	4.6	(0.1, 10.0)	4.9	(1.5, 15.2)	6.9
80	(0.1, 7.8)	3.8	(0.2, 8.4)	4.1	(1.9, 13.5)	5.8
100	(0.2, 6.9)	3.3	(0.3, 7.5)	3.6	(2.2, 12.5)	5.1
120	(0.3, 6.2)	3.0	(0.4, 6.8)	3.2	(2.4, 11.7)	4.7
150	(0.4, 5.6)	2.6	(0.6, 6.2)	2.8	(2.7, 11.0)	4.1
500	(0.9, 3.5)	1.3	(1.2, 4.0)	1.4	(4.0, 8.3)	2.2
1000	(1.1, 3.0)	0.9	(1.5, 3.4)	1.0	(4.5, 7.5)	1.5

Abbreviations: AEs, adverse events; CI, confidence interval; CTCAE v5.0, Common Terminology Criteria for Adverse Events

Note: CCI [redacted]

* Precision is half the width of the 95% CI.

CCI [redacted]

If the cumulative incidence (proportion) of patients experiencing an acute complication of hyperglycaemia is 5.9% in each of the four databases selected for this study—with sample sizes of 1000 in France, 500 in Germany, 120 in Denmark, and 1000 in the USA—then applying a random-effect meta-analysis would yield a pooled cumulative incidence (proportion) of 5.9%, with a corresponding precision of 0.9% (corresponding 95% CI: 5.1, 6.9). Refer to section 9.7.6 for further details on the meta-analysis.

9.5.1.2 Primary effectiveness outcome: TFST

As discussed in section 8.1, TFST is used as the best measure of effectiveness in the selected real-world data and will thus be the primary effectiveness outcome in this study; as a proxy for the clinical trial outcome of PFS. Nevertheless, PFS estimates from the clinical trial have been used to estimate sample size calculations.

Table 8 presents the estimated sample sizes (number of patients required) to estimate a median rwPFS of 7.3 months at varying levels of precision (half 95% CI width of approximately 0.7 to 3.0 months), assuming a loss-to-follow-up rate of 10%. Furthermore, these calculations assume a data maturity of approximately 92%, with patients being accrued from November 2023 (earliest; in the USA) and followed until the end of all available data at the time of the end of data collection (data extraction planned on Q4 2029 for all countries). These precision calculations were based on a fixed parameter exponential failure distribution assuming a uniform dropout rate.

As shown in Table 8, 147 patients would be required to estimate a median PFS of 7.3 months with a precision of 1.7 months (95% CI: 5.7, 9.2), which is close to the level of precision (1.8 months) in the 95% CI for median PFS observed in the capivasertib + fulvestrant AKT-altered subgroup of CAPItello-291 (95% CI: 5.5, 9.0) (1). Larger sample sizes, as predicted by the feasibility assessment for two of the data sources, will lead to more precise estimates.

Table 8 Sample size (number of patients) required to estimate median PFS of 7.3 months at varying levels of precision and 10% loss-to-follow-up rate

Number of patients	95% CI for median PFS (months)	Precision* (months)
50	(4.6, 10.6)	3.0
70	(4.9, 10.1)	2.6
90	(5.2, 9.7)	2.3
112	(5.4, 9.5)	2.0
147	(5.7, 9.2)	1.7
500	(6.4, 8.3)	1.0
1000	(6.7, 8.0)	0.7

Abbreviations: PFS, progression-free survival.

Note: Estimated median progression-free survival was 7.3 months (95% CI: 5.5 to 9.0 months; precision = 1.75 months) in the AKT-altered subgroup of capivasertib–fulvestrant arm (n=155) in CAPItello-291 trial (1).

* Precision is half the width of the 95% CI.

9.5.1.3 Secondary effectiveness outcome: rwOS

Table 9 presents the sample size and associated 95% CI width/precision to estimate the overall survival at 12 months, i.e., between the index date and 12 months of follow-up.

The table presents a range of sample sizes and presumed overall survival (79.4%), CCI [redacted] assuming a

loss-to-follow-up rate of 10%. These precision calculations were based on a fixed parameter exponential failure distribution assuming a uniform dropout rate.

Assuming 79.4% of the study population survives CCI [redacted], a sample size of 150 patients would provide a precision of 6.7%, i.e., corresponding 95% CI (71.8, 85.2). Sample sizes of 500 and 1000 would provide a precision of 3.7% and 2.6% respectively.

Table 9 Sample size (number of patients) required to estimate a given overall survival at 12 months of follow-up at varying levels of precision

Overall survival (%)		
CCI	*Overall survival of 79.4%* CCI [redacted]	
Number of patients	**95% CI**	**Precision***
60	(66.4, 87.9)	10.7
80	(68.4, 87.0)	9.3
100	(69.8, 86.3)	8.3
120	(70.7, 85.8)	7.5
150	(71.8, 85.2)	6.7
500	(75.5,82.8)	3.7
1000	(76.7, 81.9)	2.6

Abbreviations: CI, confidence interval.

* Precision is half the width of the 95% CI.

CCI [redacted]

9.5.2 Estimation of patient counts

The methodology for estimating the patient counts in the potential data sources involved seven steps (also available in the Feasibility Assessment Report, Appendix A, except for the last step):

1. To estimate the number of adults diagnosed with breast cancer over a five-year period, using data from various different sources if not provided by the data source owners:

    - Direct estimates for number of patients with breast cancer from publicly available information for SNDS (80).

    - Direct estimates for number of patients with breast cancer and diabetes provided by InGef.

- Age-standardised incidence rates for breast cancer of 83.4 per 100,000 patient-years in the EU27 (81) were used for the NPR, as the NPR did not provide specific patient counts and no available information was found for number of patients with breast cancer. These rates were projected over five years, with CancerMPact/KANTAR data helping to estimate the proportion of newly recurrent patients eligible for capivasertib treatment. This proportion was used as an inflation factor to estimate the treatable population size drawn from the whole population covered by the NPR: 5.9 million inhabitants.

- Age-standardised incidence rates for breast cancer of 95.9 per 100,000 patient-years in the USA (81) were used for Optum Market Clarity. These rates were projected over five years, with CancerMPact/KANTAR data helping to estimate the proportion of newly recurrent patients eligible for capivasertib treatment. This proportion was used as an inflation factor to estimate the treatable population size.

2. CCI [redacted]

3. CCI [redacted]

4. CCI [redacted]

5. To estimate the proportion with *PIK3CA*/*AKT1*/*PTEN* alterations among patients with ER+/HER2- locally advanced or metastatic breast cancer and diabetes mellitus, the CAPItello-291 trial (1) showed that 40.8% of patients were found to have at least one AKT pathway alteration.

6. To estimate final patient counts, two scenarios based on predicted future capivasertib uptake are presented. Estimates of expected drug uptake are set at 40% and 80% during the five-

year study period, presenting two different scenarios, which will need to be further evaluated following market availability.

7. To estimate the number of insulin-dependent diabetic patients in the study population, the proportion of insulin-treated diabetic patients was retrieved from country-specific estimates using national statistics or published evidence on diabetes mellitus:

    - French national estimates for diabetes mellitus (n=4,300,000 in 2022 (83)) and insulin-treated patients (n=916,737 in 2020 (84)) were used to estimate the proportion of insulin-dependent diabetes mellitus (21.3%); this estimate was used for France.

    - A study using InGef database reported that 26.6% of patients having type 2 diabetes mellitus were treated with insulin (85); this estimate was used for Germany.

    - National estimates reported that approximately 17.5% of the Danish population with type 2 diabetes mellitus was treated with insulin (86); this estimate was used for Denmark.

    - National trends for diabetes mellitus from the National Health and Nutrition Examination Survey reported a proportion of 25.7% diabetic patients treated with insulin (87); this estimate was used for the USA.

An estimation of patient counts by data source is detailed in Table 10.

The assumptions used in making these estimates will need to be re-evaluated when capivasertib becomes available in the EU countries after product launch and reimbursement decisions become available. Based on previous experience, it is anticipated that 50% of the patients preselected by data sources would be eligible (meet all the inclusion and exclusion criteria) and may constitute the final valid sample (88–90).

Table 10 Estimation of patient counts

Estimated	SNDS (France)[a]	InGef (Germany)[b]	NPR (Denmark)[c]	Optum Market Clarity[d] (USA)
Total population in data source	65,000,000	10,000,000	5,900,000	77,000,000
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best-case scenario: 80% drug uptake	1,712	791	166	2,497
Worst-case scenario: 40% drug uptake	856	396	83	1,249
Insulin-dependent diabetes mellitus subgroup - Best-case scenario	365	210[e]	29[e]	642
Insulin-dependent diabetes mellitus subgroup - Worst-case scenario	182	105[e]	15[e]	321

Note: The intended population is the cumulative total of newly recurrent patients and new incidence cases

[a] SNDS (France): 455,711 patients diagnosed with breast cancer from 2010 to 2018 ([455,711/9 years]*5 year to yield 5-year incidence of 253,173).

[b] InGef (Germany): approximately 40,000 patients with both breast cancer and diabetes from 2015 to 2023.

[c] NPR (Denmark): covers around 5.9 million patients total.

[d] Optum Market Clarity (USA): total population based on feasibility report dated July 2024 – it includes around 60 million patients with overlapping EHR data linked to medical and pharmacy claims.

[e] Estimates are for patients with type 2 diabetes mellitus treated with insulin.

9.6 Data management

The processes for database management differ by country. Generally, the data are stored at the database level and analysed locally (e.g., SNDS, InGef, and NPR) and aggregate results are

provided. For data sources that provide patient-level data (e.g., Optum Market Clarity), the analysis will be conducted by the study team. High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. SAS software, R, or other statistical software will be utilised for access to the raw data, to manage the analytic datasets and to conduct data analysis. If the study is conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures.

This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (91), the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines for data management (92), and Module VIII of the EMA Guideline on good pharmacovigilance practices on post-authorisation safety studies (93).

9.7 Data analysis

9.7.1 General considerations

A SAP will be developed to include the operational definitions of variables for exposures, outcomes, covariates, and subgroups of interest. The SAP will detail the statistical analyses and include a full set of table shells. The SAP will be developed after final protocol approval and before data extraction. The SAP will also capture data nuances per selected data source through data source-specific adaptations, as necessary.

The analyses will be conducted using SAS version 9.4 or newer, R version 4.3.2 (31 OCT 2023) or newer, or other statistical software. All analyses will be conducted separately by data source.

Given the study objectives, analyses will be descriptive, except for exploratory objective 4 which assesses risk factors for acute complications of hyperglycaemia. Subgroups will be explored descriptively with no confirmatory statistical testing. If feasible, exploratory objectives 5 to 7 will assess the marginal effect of insulin-dependent (versus non-insulin-dependent) diabetes on acute complications of hyperglycaemia, TFST, and rwOS, separately.

Due to data protection regulations, and to avoid the identification of patients, data cells with small numbers of patients may not be reported in the data sources. The suppression limits of the selected data sources are <10 for SNDS, and <5 for InGef and NPR; there is no suppression limit for Optum Market Clarity. For the same reason, minimum and maximum values for individual variables may not be reported. The data will be presented in a format that complies with these regulations and prevents patient identification.

The planned analyses are summarised below.

9.7.2 Attrition and patient characteristics

The impact of inclusion and exclusion criteria on the number of patients in the study population will be described in an attrition table and a flowchart.

Patient baseline characteristics for the safety cohort, effectiveness cohort, and subgroups of interest will be assessed as described in section 9.3.4, and reported using descriptive statistics. Categorical variables will be summarised using patient counts and percentages, and continuous variables will be summarised using means with standard deviations (SD) and medians with interquartile ranges (as appropriate). Missing data will be quantified in terms of patient counts and percentages, but values will not be imputed.

A description of the follow-up period and censoring criteria will be provided for the safety cohort, the effectiveness cohort, and subgroups of interest.

9.7.3 Primary analysis

9.7.3.1 Safety outcome

The primary safety outcome of acute complications of hyperglycaemia (composite, including diabetic ketoacidosis; primary objective 1a) will be assessed across the safety follow-up period, as defined in section 9.2.2.5. The analyses will be unadjusted. The following safety outcomes will be reported among the patients in the safety cohort:

- The distribution of follow-up time among patients, reported as median follow-up time with corresponding range and interquartile range
- The total number of events and the number of events per patient (median and interquartile range) among patients who experience the composite outcome of acute complications of hyperglycaemia
- The cumulative incidence of acute complications of hyperglycaemia, defined as the proportion (with 95% CI) of patients who experience at least one event of the composite outcome of acute complications of hyperglycaemia between index date and up to 30 days after capivasertib discontinuation (as defined in section 9.3.2)

9.7.3.2 Effectiveness outcome

The primary effectiveness outcome of TFST (primary objective 1b) will be assessed across the effectiveness follow-up period, as defined in section 9.2.2.5. All effectiveness outcomes will be reported among the patients in the effectiveness cohort. The analyses will be unadjusted.

TFST (primary objective 1b) will be summarised using Kaplan-Meier (K-M) plots. The number of patients at risk and the number of events will be reported at 3 months, 6 months, and 12 months, and other time points as follow-up allows. Median K-M survival estimates with 95% CI will be reported.

A Sankey diagram will be used to illustrate the different treatment sequences from the index treatment to the first subsequent systemic anti-cancer therapy (as defined in section 9.3.2).

TFST will be categorised according to the type of first subsequent systemic anti-cancer therapy after discontinuation of capivasertib, as determined via examination of the Sankey diagram.

9.7.4 Secondary analyses

The secondary outcomes of rwOS (secondary objective 2a) and TTD (secondary objective 2b) will be assessed across the effectiveness follow-up period, as defined in section 9.2.2.5. All effectiveness outcomes will be reported among the patients in the effectiveness cohort. The secondary analyses will be unadjusted.

rwOS and TTD will be summarised separately using K-M plots, with the number of patients at risk and the number of events reported at 3 months, 6 months, 12 months, and other time points as follow-up allows. Median K-M survival estimates with 95% CI will be reported for TTD. For rwOS, the 12-month K-M survival rate with 95% CI will be reported.

In addition, the number and percentage of patients who experience the TTD outcome will be categorised based on capivasertib + fulvestrant treatment discontinuation or censoring (as defined in section 9.3.2):

- Discontinuation without replacement
- Add-on
- Switch
- Censoring at the end of follow-up

For capivasertib + fulvestrant treatment discontinuations due to add-on or switch, the number and percentages of subsequent systemic anti-cancer therapy will be reported. The definition of systemic anti-cancer therapy will be further detailed in the SAP.

9.7.5 Exploratory analyses

9.7.5.1 Exploratory objective 3

The exploratory outcome of rwPFS will be assessed across the effectiveness follow-up period, as defined in section 9.2.2.5. rwPFS will be summarised using K-M plots, with the number of patients at risk and the number of events reported at 3 months, 6 months, 12 months, and other time points as follow-up allows. Median K-M survival estimates with 95% CI will be reported. This exploratory analysis will be unadjusted.

9.7.5.2 Exploratory objective 4

Risk factors for acute complications of hyperglycaemia (composite, including diabetic ketoacidosis) will be assessed using a time-to-event analysis. A Cox proportional hazards model will be used to examine the association of patient baseline characteristics with the occurrence of acute complications of hyperglycaemia as a composite outcome over follow-up; each baseline risk factor will be the independent variable for the unadjusted Cox model. The dependent variable is defined as having an acute complication of hyperglycaemia (composite) any time during follow-up. Pre-selected patient baseline characteristics were defined based on prior published evidence and expert input (refer to section 9.3.4 for details on covariate selection). Patients will be censored as specified in section 9.2.2.5.

The number of events in the study cohort will be examined to determine the feasibility of developing Cox models. If the number of events will support a Cox model, the proportional hazards assumption will be assessed by 1) visually inspecting the K-M curves to ensure that the hazards for the safety cohort are constant over time and 2) visually inspecting a plot of Schoenfeld residuals to ensure the residuals are independent of time. Unadjusted hazard ratios (HR) with 95% CI will be reported for all pre-selected variables with respect to the outcome. Two-sided p-values will be reported with a pre-specified significance level of 0.05. Additionally, multivariable adjusted HR with 95% CI will be reported for significant variables considered with respect to the outcome after adjusting for all pre-selected variables. Pearson correlation coefficient between the dependent variable and the pre-selected variables will be estimated to assess collinearity. Collinear variables, defined as those with a correlation coefficient greater than or equal to 0.7 (94), will be removed from the model using a sequential approach and model will be refitted. Backward stepwise elimination will be considered to optimize the model. Further details on the model specifications will be given in the SAP.

In addition to assessing the risk factors for acute complications of hyperglycaemia (composite, including diabetic ketoacidosis), the following will be reported:

- The time to first event of the composite outcome of acute complications of hyperglycaemia (median and interquartile range) among those having an event.

- The survival function for the time to composite outcome of acute complications of hyperglycaemia will be visualised using a Kaplan-Meier (K-M) plot.

9.7.5.3 Exploratory objectives 5-7: unadjusted analysis

Exploratory objective 5: The cumulative incidence of acute complications of hyperglycaemia adverse events (composite, including diabetic ketoacidosis) stratified into insulin-dependent diabetes and non-insulin-dependent diabetes at index date will be calculated as described in section 9.7.3.1.

Exploratory objectives 6 and 7: The estimation of unadjusted TFST (for exploratory objective 6) and rwOS (for exploratory objective 7) stratified into insulin-dependent diabetes and non-insulin-dependent diabetes at index date will follow the same approach as described for the overall population after including the stratification variable in the K-M analysis in sections 9.7.3.2 and 9.7.4.

9.7.5.4 Exploratory objectives 5-7: adjusted analysis

Adjusted analyses will be considered to assess the marginal effect of having insulin-dependent diabetes on acute complications of hyperglycaemia (composite), TFST, and rwOS, separately.

For each patient, a propensity score (PS) will be calculated via multivariable logistic regression as the probability of having insulin-dependent diabetes conditional on measured covariates. The outcome variable in the PS model will be insulin-dependent diabetes and the independent variables will be covariates identified *a priori* as potential confounders (see Appendix B). Although this list was selected *a priori,* covariates may be removed from the PS model if there are not enough patients to support the number of covariates (for example, 10-20 exposed patients per covariate) (95). Covariates considered not likely to be a confounder, as specified in Appendix B, will be the first to be removed. Collinear covariates will be defined as any covariates with a Pearson correlation coefficient greater than or equal to 0.7 (94). Collinear variables will be removed from the PS model, using a sequential approach.

Given that the insulin-dependent diabetes group (i.e., exposed patients) is expected to have a limited size (13-22% of type 2 diabetes mellitus patients are treated with insulin) (96), an inverse probability of treatment weighting (IPTW) approach will be applied. This PS application approach will weight exposed and referent (i.e., non-insulin-dependent diabetes) patients on the inverse probability of receiving the treatment they actually received, conditional on observed covariates included as independent variables in the PS model. Inverse probability of treatment weights will be calculated as 1/PS for patients with insulin-dependent diabetes (i.e., the exposure) and as 1/(1-PS) for patients in the referent group.

The distribution of weights will be evaluated by insulin-dependency status. Weight truncation or trimming (e.g., using 1st and 99th percentile) will be considered when extreme weights are encountered, typically when the PS is close to 0 for a treated patient or 1 for a referent. To assess covariate balance, the absolute standardised difference (ASD) for each covariate before and after weighing will be reported, with an ASD <0.10 considered to indicate sufficient covariate balance. If the baseline covariates are not deemed to be balanced across groups, revisions to the PS model or alternative weighting methods may be considered. These alternative weighting methods will be further detailed in the SAP.

Weighting the outcome model by the IPTW results in a pseudo-population in which patients with a high probability of having their observed exposure (insulin-dependent or non-insulin-dependent diabetes) have a smaller weight and patients with a low probability of having their observed exposure have a larger weight (97,98). The resulting effect estimate when utilizing IPTW will estimate the average treatment effect (ATE) in the population. This estimand provides the average treatment effect assuming that every patient in the study population would be observed under assignment of treatment and under assignment of no treatment. A robust variance estimator will be utilised in the outcome models to account for the weighted design. This method will be further detailed in the SAP.

9.7.5.5 Exploratory objective 8

In data sources where biomarker and cancer staging information is available, the following analyses will be assessed among patients with known ER+/HER2- locally advanced or metastatic breast cancer with ≥1 *PIK3CA/AKT1/PTEN* alterations:

- Primary safety objective analyses for the acute complications of hyperglycaemia (composite, including diabetic ketoacidosis), as defined in section 9.7.3.1, in the safety cohort;

- Primary effectiveness analyses for TFST, as defined in section 9.7.3.2, in the effectiveness cohort.

9.7.5.6 Exploratory objective 9

In data sources where HbA1c level data is available, the primary safety outcome of acute complications of hyperglycaemia (composite, including diabetic ketoacidosis) as defined in section 9.7.3.1, will be assessed among patients having a recorded baseline HbA1c level ≥ 8.0% in the safety cohort.

9.7.5.7 Exploratory objective 10

The primary safety outcome, as defined in section 9.7.3.1, will be assessed in the safety cohort for each individual component of acute complications of hyperglycaemia (i.e. diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome).

9.7.5.8 Exploratory objective 11

A descriptive analysis of anti-diabetic treatment patterns will be assessed across the treatment patterns follow-up period, as defined in section 9.2.2.5. The following endpoints will be calculated among patients in the safety cohort:

- The number and percentage of patients with anti-diabetic treatment, overall and by class, at index date.
- The number and percentage of patients who change anti-diabetic treatment class during the follow-up period.
- The number and percentage of patients who discontinue anti-diabetic treatment, overall and by class, during the follow-up period (see section 9.3.3.3 Exploratory objective 11 for definition).
- The time to anti-diabetic treatment discontinuation, overall and by class, during the follow-up period, reported as median time with corresponding interquartile range.
- Time to first subsequent anti-diabetic treatment after discontinuation among those experiencing discontinuation, overall and by class, during the follow-up period, reported as median time with corresponding interquartile range.
- The number and percentage of patients who change anti-diabetic drug dosage during the follow-up period, defined as any reduction in daily dose during the follow-up period compared to the daily dose at index date. Daily dose will be derived from prescription information (e.g. dispensed quantity, strength, drug fill duration). This will be further detailed in the SAP.
- Time to first change in anti-diabetic drug dosage during the follow-up period among those with a drug dosage change, reported as the median time with corresponding interquartile range.

9.7.6 Meta-analysis

As described in section 9.7.1, each outcome will be analysed separately within each data source, as pooling patient-level data across geographies is not feasible due to data restrictions. Thus, a

meta-analysis is proposed to provide unadjusted pooled estimates for primary outcomes (acute complications of hyperglycaemia [composite, including diabetic ketoacidosis] and TFST) and secondary outcomes (rwOS and TTD), overall and stratified by insulin dependency status, across geographies.

Forest plots for unadjusted cumulative incidence (proportion) with 95% CI of acute complications of hyperglycaemia (composite) and median survival time with 95% CI for TFST, rwOS, and TTD will be reported for all data sources, overall and stratified by insulin-dependent diabetes.

For the primary safety endpoint (acute complications of hyperglycaemia), a pooled cumulative incidence estimate (proportion) with 95% CI will be estimated using a meta-analysis of cumulative incidence (proportion) from the database-specific cumulative incidence results (99). The inverse variance method assuming a binomial distribution of risk estimates will be used. The double arcsine transformation will be considered to stabilise the variance and avoid the possible estimation of a lower confidence interval limit below zero in instances of rare outcomes (100).

Pooled survival probability estimate and summary survival curve will be generated for rwOS, TFST, and TTD, separately, using a multivariate DerSimonian and Laird methodology (101).

A random-effect meta-analysis model will be considered to allow for the possibility that the underlying true effect may not be the same for all database-specific analyses. This model will consider hidden or unmeasured sources of variability by incorporating such variability when computing the weighted average summary estimate, producing wider confidence intervals compared to a fixed-effect model (102).

The I^2 statistic will be used to quantify the study results variability (103). It estimates the proportion of variability in point estimates due to heterogeneity rather than sampling error.

τ^2 will be used to quantify the between-study variance. It estimates the variance of the underlying distribution of true effect sizes and can be computed using a moment-based approach (104,105) with CI (106).

Prior to conducting meta-analysis, the study team and biostatistics experts will perform an inspection of the data. Further details on the type of data inspection—including but not limited to considerations of each data source's nuances, data source-specific outcome definitions, and forest plots with data source-specific estimates—will be described in the SAP. If the team considers the data to be heterogeneous, meta-analysis would be considered inappropriate and a narrative review will be conducted instead.

9.7.7 Sensitivity analysis

Primary safety outcome

Patients may index on either capivasertib or fulvestrant, whichever comes first (see section 9.2.2.1). Among those in the safety cohort who initiate on the index date with fulvestrant and subsequently begin combination treatment with capivasertib on a later date, the following information will be reported:

- The number and percentage of patients who receive fulvestrant first
- The distribution of time between the first prescription of fulvestrant and first prescription of capivasertib, reported as median time with corresponding interquartile range
- The number and percentage of acute hyperglycaemic events, overall and per patient, that occur in the period between the index date and the date of first prescription of capivasertib

Among the overall safety cohort, the number and percentage of acute complications of hyperglycaemia that occur after the discontinuation of anti-diabetic treatment (see section 9.3.3.3 exploratory objective 11 for definition) will also be summarised.

Primary effectiveness outcome

In this sensitivity analysis, the add-on and switch scenarios as defined in section 9.3.2 will not be considered as capivasertib treatment discontinuation for TFST outcome definition (see section 9.3.3.1 for outcome definition). Instead, add-on and switch to another anti-cancer therapy will be considered as the first subsequent anti-cancer therapy.

This sensitivity analysis will include K-M plots. The number of patients at risk and the number of events will be reported at 3 months, 6 months, 12 months, and other time points as follow-up allows. Median K-M survival estimates with 95% CI will be reported.

Exploratory effectiveness outcome

To assess the robustness of the rwPFS definition in this study (refer to section 9.3.3.3), the rwPFS will be calculated for a cohort of Optum Market Clarity patients using the disease-state information from the enriched oncology data. The agreement between the algorithm-defined rwPFS (as defined in section 9.3.3.3) and the disease-state rwPFS among patients with disease-state rwPFS information will be described using a Bland-Altman plot (107) (further details are provided in the SAP). The following will be assessed:

- The difference versus mean for time to progression event (excluding censors)

- The difference versus mean for time to censoring event

The plot will be used to visually assess the agreement between the two definitions of rwPFS, with no statistical analysis beyond the plot description.

Meta-analysis

If a meta-analysis is deemed feasible (as described in section 9.7.6) and is performed in at least 3 data sources, including the USA and ≥2 European countries, a sensitivity analysis including only the European countries will be performed.

Diabetes diagnosis

One of the criteria to identify patients with Type 1 diabetes (presence of a type 2 diabetes mellitus code only or unspecific diagnostic codes, a prescription for insulin only, and an incident case of diabetes mellitus or diagnosed with diabetes mellitus at <35 years of age (see section 9.3.1). It is conceivable that a patient with clinically confirmed type 2 diabetes may meet these criteria and be wrongly labelled as having type 1 disease. To assess the potential impact, the number and percentage of patients who are classified as having type 1diabetes based on these criteria will be reported.

9.7.8 Handling of missing data

No data imputation strategies are anticipated to supplement missing data on patient characteristics or the outcome variables. The number of cases with missing information will be described separately within the summary for each variable. General rules for the derivation of incomplete dates and handling of inconsistent or invalid dates, and handling of inconsistent continuous variables (e.g., outlier for age, laboratory result) will be detailed in the SAP.

9.7.9 Interim analysis

The primary and secondary analyses (see section 9.7.3 and section 9.7.4, respectively, for further details) will be conducted where sufficient data will have accrued in the selected data sources at the time of the interim analysis. The interim analysis will focus on reporting the number of eligible patients and foundational demographic information; these analyses will be further detailed in the SAP.

9.8 Quality control

The study will use existing databases in different countries, which are being used widely for research. The study will be executed in line with all applicable regulations and guidelines – such as best-practice guidelines applicable to NIS, including but not limited to the ENCePP Guide

on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols (see Appendix D), and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology as well as the specific Standard Operating Procedures of each contractor. All study programs, log files, and output files will be stored on a secure server.

The study team will ensure quality control procedures are followed throughout the project. Where the study team have access to the raw data, the following process would be applied to ensure the quality of the data and analyses for all the data management and statistical analyses tasks. All programming will be undertaken in SAS (currently version 9.4) or equivalent software (e.g., R) and all code will be quality checked. Where possible, tests on data coherence will be performed (e.g., age distribution as expected). Queries or issues on the data will be raised, documented, and resolved.

In countries where patient-level data will not be available to the study team, the study team will liaise closely on a regular basis with the relevant local team who are conducting the data management and analyses in each country. The study team will communicate the same assumptions and methods needed to clean and derive the necessary variables and to conduct the statistical analyses to ensure that there is methodological consistency across the different countries. Quality checks of the data will be required within each country. Once results have been produced, the study team will review thoroughly to ensure, where possible, that the variable specifications have been met and that the results appear sensible. All queries will be discussed with the relevant teams in each country to be resolved. All study documents will be stored on Microsoft SharePoint. Data will be encrypted at rest and in transit, using several strong encryption protocols, and technologies that include Transport Layer Security/Secure Sockets Layer, Internet Protocol Security and Advanced Encryption Standard.

9.9 Limitations of the research methods

This study is conducted using secondary data sources that were not collected for the purposes of research. Such studies are potentially subject to biases due to their observational nature. Potential limitations relevant to this study are detailed below.

Selection bias

- Although all patients meeting the eligibility criteria will be included in the study, the data sources in the different countries differ in terms of content and expected coverage. In Europe, SNDS (France) and the NPR (Denmark) cover close to 100% of the population (see section 9.4.2), while InGef covers only 8% of the German population, although it has been shown to be representative of the broader population (55). Therefore, the potential risk of selection bias in terms of access to medical care is

considered to be low across European countries. Optum Market Clarity (USA) is comprised of patients receiving care from large integrated delivery networks across the USA and, for our study cohort, further restricted to those with commercial insurance coverage. The selection of patients with both EMR data and claims data coverage will restrict the representativeness of this data to those commercially insured in the USA. However, its key strength for this study lies in the availability of biomarker and breast cancer characteristic data, which is essential for addressing exploratory objective 8.

- Patients with diabetes who have not interacted with the healthcare system in the 12 months prior to the index date may be missed due to the variability in continuous enrolment periods allowed. Studies indicate that longer enrolment periods generally yield higher prevalence estimates (18). However, the proportion of missed patients is expected to be very low. A Dutch study found that patients with diabetes and a non-diabetes-related comorbidity (including breast cancer) had a mean (SD) of 2.3 (2.3) hospital admissions, 14.3 (9.1) GP contacts, and 2.8 (1.8) consultations per year. These figures increased to 2.9 (2.5), 23.2 (14.0), and 3.6 (2.2), respectively, when diabetes-related comorbidities were present (108). Given these findings, and assuming that healthcare utilisation would likely be even higher with an advanced breast cancer diagnosis, 12 months of continuous enrolment prior to the index date should be sufficient to minimise selection bias.

- Some patients may be included in the study population despite not meeting the label's indication criteria. Capivasertib could be reimbursed for patients outside these criteria due to factors such as disease severity, lack of alternative treatments, or evidence of potential benefit (109). However, the absence of genomic and staging data in most of the data sources means it will not be possible to confirm whether patients were diagnosed at an advanced stage of ER+/HER2- breast cancer or have the required *PIK3CA*/*AKT1*/*PTEN* alterations specified by the label. This limitation will be addressed by assessing the results among those with known ER+/HER2- advanced breast cancer with ≥1 *PIK3CA/AKT1/PTEN* alteration (see section 9.3.3.3) in the data source(s) that record all those parameters.

- Patients will be included if they have previous endocrine treatment and excluded if they received more than two different endocrine treatments within the past 12 months. This exclusion criterion is consistent with the previous CAPItello trial (1), where patients were allowed up to two lines of endocrine therapy and one line of chemotherapy for advanced disease. Given the challenges in real-world data, such as the inability to identify advanced disease, this criterion could exclude patients who receive endocrine therapy in a non-advanced setting. A feasibility assessment conducted in July 2024 using a US data source indicate that the impact of this exclusion criterion will be minimal. The feasibility counts show that 72.5% of patients who began treatment with capivasertib

and fulvestrant as second-line therapy had received between one and two endocrine therapies in the past 12 months.

Misclassification bias

- Prescriptions may be issued but not dispensed or dispensed but not used. No information will be available to confirm if the medication is actually taken by the patient. When available, dispensing data will be preferred over prescription data to minimise the risk of misclassification of the population. However, given the nature of the condition, i.e. patients with advanced breast cancer who have failed a previous therapy, and close follow-up by oncology units, adherence to medication is likely to be high.

- There is a possibility of exposure misclassification for diabetes in any administrative health database without diagnosis validation or adjudication. Several validated algorithms exist, typically requiring at least one diabetes-related claim and one prescription for anti-diabetic medication (23). The validated algorithm by Sharma et al. (22) will be used to identify type 1 and type 2 diabetes mellitus. However, this algorithm has only been validated in the data source THIN in the UK and its performance cannot be assessed in the rest of the data sources. Nonetheless, the literature indicates that diagnostic criteria for diabetes are largely comparable at an international level. One study that evaluated the validity of diabetes diagnoses by comparing clinical information with the World Health Organization's criteria, found that the majority of diagnoses (82%) aligned with these standards, with minimal variation between countries (110). Additionally, a patient with clinically confirmed type 2 diabetes may be misclassified in this study as having type 1 diabetes if they received an unspecific diagnostic code, a prescription for insulin only (111), and diagnosed with diabetes mellitus at <35 years of age (112). To mitigate this concern, the number and percentage of patients who meet these criteria will be reported.

- There is also a risk of outcome misclassification:

    - Acute complications of hyperglycaemia:

        * One limitation inherent to secondary data is that only complications which require medical attention are included, which mostly concerns the more severe and acute events. Those acute complications that do not require medical attention will not be captured, which may result in underestimation of the true incidence of acute complications of hyperglycaemia.

        * Since the index date is defined as the first prescription of either capivasertib or fulvestrant (section 9.2.2.1), there is a risk of exposure misclassification given outcomes may be observed and attributed to exposed time before

initiation of capivasertib. As explained in section 9.7.3.1, in the cases where the index date is the date of the record for fulvestrant, the counts of acute hyperglycaemic events occurred in the period between the index date and the date of first prescription of capivasertib will be reported separately.

- rwPFS
    - Conventional PFS, as measured in a clinical trial (such as CAPItello-291), is based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria (113) for disease progression, where detailed measurements and tests are performed at frequent, scheduled visits. However, rwPFS in disease-specific data sources is defined using physician assessments occurring during routine care, which are likely to occur at less frequent intervals for a given individual than trial-based assessments. In real-world data sources like administrative health databases, disease progression is also typically not available. Therefore, algorithms are often used to determine real-world progression. As a result, rwPFS may misclassify conventional progression-free survival.
    - The algorithm used in this study for detecting events of progression (Figure 6) has been designed using proxies where these are not clearly identified in the data sources. The following considerations should be taken into account:
        - The first criterion of the algorithm requires a comprehensive list of adverse events for capivasertib and fulvestrant. However, some adverse events, such as diarrhoea, nausea, fatigue, decreased appetite, and rash may be inconsistently recorded in secondary data. As a result, treatment discontinuations might be incorrectly classified as disease progression instead of being attributed to toxicity.
        - The algorithm may fail to identify patients for whom treatments are initially contraindicated due to comorbidities or those who decline surgical intervention. These patients might later undergo surgery if their condition improves or if they change their preference, which may not necessarily indicate disease progression. However, this is not expected to be a significant limitation, as the number of such cases is anticipated to be low.
        - The algorithm by Xu et al. (35) includes “death caused by cancer” as opposed to death from any cause. However, since cause of death is not always recorded or has significant limitations in secondary data, this criterion was broadened to include all causes of death. This limitation is not anticipated to have an impact since deaths not caused by the breast cancer are expected to be very

low in this population. Moreover, while the data sources accurately record death information, there can be a data lag which may result in a lower observed rate of progression events.

* The date of defining progression is important to calculate rwPFS, but there may be inaccuracies due to potential errors in the recorded dates or because the date of discharge is used instead of the actual event date. However, it is anticipated that the dates will closely approximate the true event timing.

- Baseline characteristics associated with risk of acute complications of hyperglycaemia: there is a risk of misclassification of these covariates identified as potential risk factors for acute complications of hyperglycaemia or the unavailability of information on the potential risk factors as some covariates may not be available in all data sources. Moreover, where available, the accuracy of some covariates will not be certain. For example, the algorithm by Sharma et al. (22) to distinguish diabetes type relies, among other criteria, on identifying incident versus prevalent cases and the age at the first diabetes record. With only a one-year look-back period, this may not be possible, although these are the least important criteria in descending importance. Similarly, the algorithm used to identify postmenopausal status has not been validated, which may impact its reliability.

Confounding bias

- Confounding is expected to be low in this study. Although factors such as the quality of diabetes management may not be recorded in secondary data, multiple relevant covariates have been considered (see Appendix B). For exploratory adjusted analyses, propensity scores will be applied to account for potential confounders if sample size allows (i.e., sufficient number of patients per covariate). Residual confounding may remain where covariates cannot be captured in one data source.

Other information bias

- Patients may discontinue fulvestrant but continue capivasertib, which could influence the effect estimates observed.

- Being a multi-country study, the data sources may adhere to varying standards and practices for recording information. Efforts will be made to standardise the data to minimise discrepancies, but differences in practices and regulations across countries may still impact the uniformity of the recorded data.

- Some variables may have missing data. As explained in section 9.7.8, the number of cases with missing information will be described separately within the summary for each

variable. This approach will help understand the extent of the impact of missing data, if any.

Other limitations

- Market launch and reimbursement decisions in European countries are ongoing. Consequently, the final selection of the data sources may change based on market launch and reimbursement status of capivasertib + fulvestrant in each European country.

- Given the recent approval of capivasertib by the EMA, there may be limited real-world data on patients who have been treated with capivasertib in the early years following reimbursement. Moreover, it is anticipated that 50% of the patients preselected by data sources would be eligible (meet all the inclusion and exclusion criteria) and may constitute the final valid sample. These limitations could reduce the overall sample size and therefore affect the robustness of the study's findings, potentially impacting the generalisability or requiring a longer study. To address this limitation, a fourth US data source was added, which increases the sample size and extends the post-approval observation period for capivasertib + fulvestrant (approved in November 2023 by FDA). Further, a meta-analytic approach has been proposed and will be conducted if, after inspection of the data by the study team and expert biostatisticians, heterogeneity is deemed a non-issue.

10. PROTECTION OF HUMAN SUBJECTS

The study will be conducted in agreement with the Regulation EU 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (114).

The analysis for this study is based on secondary data use. No identifying data will be collected in any of the planned approaches. Regulatory and ethical requirements will be followed in each country where the respective countries databases are used. The study will comply with the Module VIII of the Good Pharmacovigilance Practices (93).

The study will be submitted to ethical review boards for approval wherever required by local laws. Regulatory authorities will be notified, and approval sought as required by local laws and regulations.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is based on the secondary use of data from the country-specific databases. As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products, Revision 2, from 2017) for these studies, the submission of suspected adverse reactions in the form of individual case safety reports is not required (115).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered in the HMA-EMA Catalogue of real-world data in https://catalogues.ema.europa.eu/catalogue-rwd-studies, which replaces the European post-authorisation study (EU PAS) Register®.

An interim report and a final study report with the results of the study will be reported to the EMA in line with the Risk Management Plan (14). The dates for these milestones have been agreed with the EMA (see section 6). The interim and final study results will also be communicated in the periodic safety update reports submitted to the EMA.

The results of this observational study are intended to be published in a peer-reviewed journal and could also be presented as abstracts/presentations at medical congresses under the oversight of the Marketing Authorization Holder. Current guidelines and recommendation on good publication practice will be followed (e.g., Good Publication Practice Guidelines, Strengthening the Reporting of Observational Studies in Epidemiology) (116,117).

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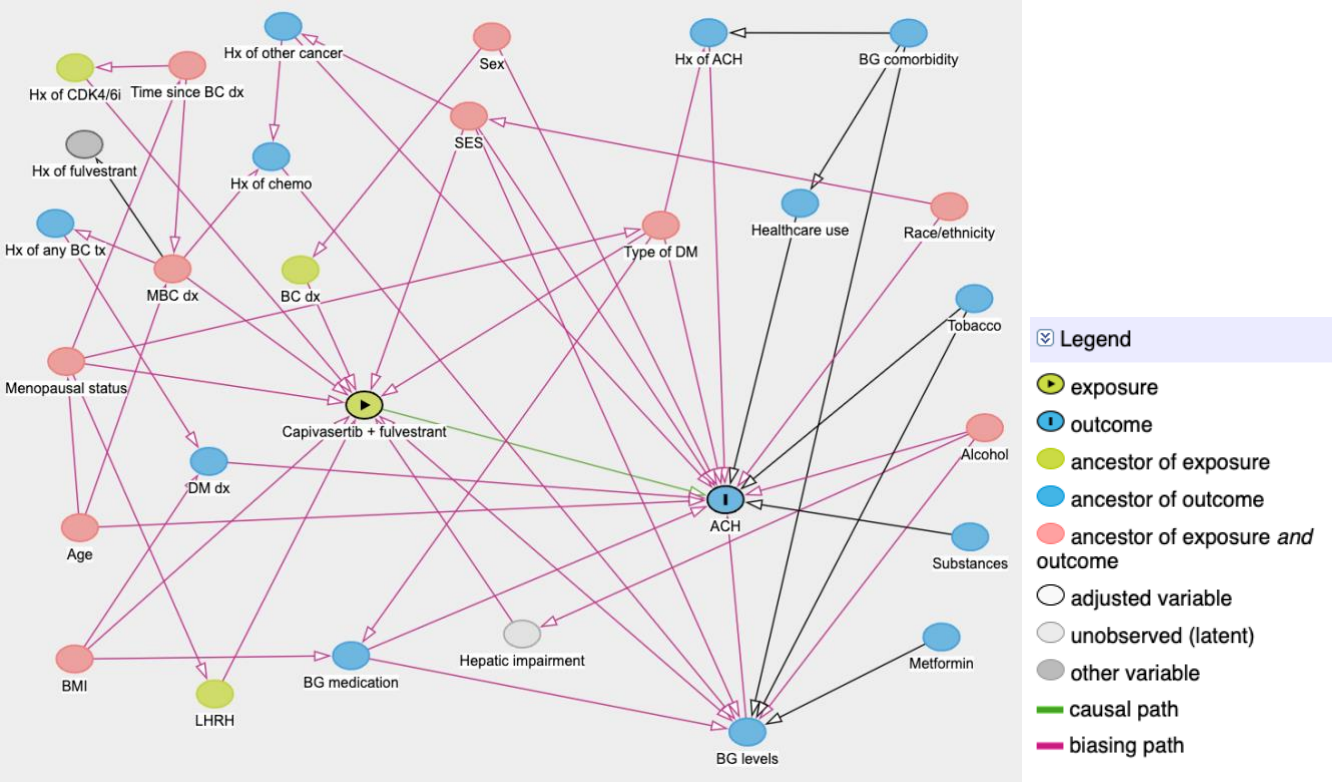
Appendix A List of stand-alone documents

Number	Document reference number	Date	Title
1	D3612R00020_Datasource_FAR_v1.0	17 July 2024	Feasibility Assessment Report

Appendix B Directed acyclic graph of relationships between variables

The relationship and supporting evidence between variables for Exploratory Objectives 4 to 7 are provided in the SPACE (Structured Preapproval and Postapproval Comparative study design framework to generate valid and transparent real-world Evidence) tables below.

Figure B1. Directed acyclic graph of the relationship among capivasertib + fulvestrant, risk for acute complications of hyperglycaemia, and baseline characteristics (Exploratory Objective 4)



Abbreviations: ACH, acute complications of hyperglycaemia; BC, breast cancer; BG, blood glucose; BMI, body mass index; CDK4/6i, CDK4/6 inhibitors; chemo, chemotherapy; DM, diabetes mellitus; dx, diagnosis; hx, history; LHRH, luteinizing hormone-releasing hormone; MBC, metastatic breast cancer; SES, socioeconomic status; tx, treatment.

Table B1. Supporting evidence among capivasertib + fulvestrant, risk for acute complications of hyperglycaemia, and baseline characteristics (Exploratory Objective 4)

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
Age at index date	Capivasertib in combination with fulvestrant (capivasertib + fulvestrant) is indicated in adult patients with hormone receptor-positive (HR+)/human epidermal growth factor 2 negative (HER2-) locally advanced or metastatic breast cancer. Diagnosis for HR+/HER2- locally advanced or metastatic breast cancer typically occurs at older ages (50-64 years; Giaquinto 2024). In CAPItello-291, the median age of participants was 58 years and 77.3% of patients in CAPItello-291 were postmenopausal (Turner 2023). Given that patients are typically diagnosed with HR+/HER2- breast cancer at an older age, the median age of patients receiving capivasertib in the real-world setting is expected to be higher. Age was not found to be a covariate for the pharmacokinetics of capivasertib (Fernandez-Teruel 2024).	Diabetic ketoacidosis (DKA) is more frequently reported in younger patients with type 1 diabetes while hyperglycaemic hyperosmolar states (HHS) is more commonly observed in older patients with type 2 diabetes (Benoit 2020; Umpierrez 2024).	Yes, potential confounder.	Yes
Sex	Capivasertib + fulvestrant is used to treat adult patients with HR+/HER2- locally advanced or metastatic breast cancer, a condition that is more commonly diagnosed in females than	DKA is more frequently reported in women versus men with type 1 diabetes (Farsani 2017; McCoy 2021).	Yes, potential confounder. For	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	males (Giaquinto 2024). A targeted literature review found no reported evidence of the relationship between sex and capivasertib + fulvestrant.	Sex dimorphic traits may influence the risk of ACH. For example, males are at higher risk to develop insulin resistance than healthy premenopausal females, and endogenous oestrogens influences pancreatic endocrine function (Tramunt 2020).	capivasertib + fulvestrant, the relationship with sex is mediated by breast cancer diagnosis.	
Race/ethnicity	There is limited evidence that race/ethnicity influences the pharmacokinetics of capivasertib. In a pharmacokinetic study, the combined study population was 74.1% white, and race/ethnicity was not significantly associated with capivasertib pharmacokinetics (Fernandez-Teruel 2024). In the United States, race/ethnicity is related to factors such as access to healthcare and differences in treatment adherence or availability (Macias-Konstantopoulos 2023), which may indirectly affect the use, effectiveness, and safety of capivasertib. In Europe, over half of the countries collect data on ethnicity. In other countries, country of origin is often collected as a proxy for race/ethnicity (van Apeldoorn 2022).	Evidence suggests that race/ethnicity significantly influences the risk of DKA. In particular, African American and Hispanic individuals have been reported to have a higher risk for DKA compared to other races (Ebekozien 2021; McCoy 2021). However, these disparities are likely intertwined with socioeconomic factors and healthcare access in certain populations in the United States (Macias-Konstantopoulos 2023).	Yes, potential confounder. For capivasertib + fulvestrant, the relationship with race/ ethnicity is mediated by SES	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
Body mass index (BMI)	A pharmacokinetics study reported slower clearance of capivasertib in those with lower body weight (47 kg vs 67 kg). However, the effects on the exposure were predicted to have minimal impact and were not expected to be clinically relevant (Fernandez-Teruel 2024). In CAPItello-291, patients in the capivasertib-fulvestrant arm with a higher BMI had more frequent adverse events of hyperglycaemia compared to those with a lower BMI: 21.2% (14/66) of patients with BMI ≥30 kg/m^2 had a hyperglycaemia AE versus 16.1% (46/285) of patients with BMI <30 kg/m^2 (Rugo 2024).	There is strong evidence that both a rapid increase and consistently high BMI are strongly associated with the subsequent risk of developing type 2 diabetes and hyperglycaemia compared with a stable normal BMI (Kan 2022). However, risk of HHS or DKA is higher in those with lower BMI in existing type 1 and type 2 diabetes due to poor metabolic control (Tittel 2020, Ross 2022).	Yes, potential effect modifier for capivasertib + fulvestrant. For ACH, the relationship with BMI is mediated by the presence of diabetes.	Yes
Socio-economic status (SES)	A targeted literature review found no reported evidence of the relationship between SES and the effectiveness, safety, or pharmacokinetics of capivasertib + fulvestrant. The impact of SES on healthcare access varies by geographic location and type of available healthcare (i.e., universal healthcare vs privatized). In the United States, due to privatized healthcare, SES has a greater impact on healthcare access compared to Europe (Avendano 2009). Consequently, in the current study, although SES is unlikely to influence the	In countries where healthcare is not universal or public, SES can impact access to healthcare, which has been reported to impact the ability to control hyperglycaemia and prevent ACH (Liu 2020; Everett 2019).	Yes, potential confounder in countries with privatized healthcare.	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	likelihood of receipt of capivasertib or its effectiveness in the European populations due to the availability of universal healthcare, SES may influence the likelihood of receipt of capivasertib and/or its effectiveness in the United States population.			
Tobacco use	In a pharmacokinetics study, tobacco was not predicted to impact the efficacy or safety of capivasertib + fulvestrant (Fernandez-Teruel 2024). Smoking status was not reported in CAPItello-291, the phase 3 pivotal trial (Turner 2023). A targeted literature review found no additional reported evidence of the relationship between tobacco use and capivasertib + fulvestrant.	Substantial research has demonstrated that nicotine can elevate blood glucose levels, disrupt glucose homeostasis, and induce insulin resistance, all of which are risk factors for ACH, especially in diabetic patients with infections or illness (Chen 2023). A prospective study reported that patients with type 1 diabetes who smoked at least one cigarette per day had an increased risk for DKA compared to non-smokers (Thomas 2020). Chronic tobacco use is associated with an increased risk of type 2 diabetes, which leads to an increased risk for ACH (Willi 2007). Short-term tobacco use decreases cells' sensitivity to insulin and increases the risk of ACH (Bergman 2012).	Yes, potential effect modifier for ACH. For ACH, the relationship with tobacco may be direct as well as mediated by diabetes status and blood glucose levels. There is a lack of sufficient evidence to determine if there is a relationship with	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
			capivasertib + fulvestrant.	
Alcohol abuse	A targeted literature review found no reported evidence of a direct relationship between alcohol use and capivasertib + fulvestrant. Alcohol use can cause liver impairment. Although alcohol abuse has not been directly studied, hepatic function was found to not be a significant variable for the pharmacokinetics of capivasertib (Fernandez-Teruel 2024). The Summary of Product Characteristics (SmPC) states that based on population pharmacokinetic analyses, capivasertib concentrations were higher in patients with mild hepatic impairment (based on bilirubin, ULN, and AST levels) compared to patients with normal hepatic function. In patients with moderate hepatic impairment, capivasertib concentrations were 13-17% higher compared to normal hepatic function. There is limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment (Capivasertib SmPC 2024). In the general population, alcohol consumption is associated with adverse oncologic outcomes	Those patients who use alcohol in excess or chronically are more likely to have hepatic impairment and/or metabolic dysfunction that is associated with an increased risk for ACH (Osna 2017). A prospective study reported that patients with type 1 diabetes and higher alcohol consumption were at an increased risk for DKA (Thomas 2020). A separate study reported that patients with alcohol disorder were at an increased risk for DKA (French 2019).	Yes, potential confounder. For both capivasertib + fulvestrant as well as ACH, this potential relationship with alcohol abuse is likely mediated by hepatic impairment.	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	among individuals with a diagnosis of cancer, specifically as it relates to hepatic impairment (Shi 2023).			
Drug or substance abuse	A targeted literature review found no reported evidence of a relationship between drug abuse and capivasertib + fulvestrant. Given the high prevalence of substance use in cancer patients, illicit drug use should be considered when evaluating drug safety and effectiveness. A study analysing data from the National Survey on Drug Use and Health (2015-2020) found that substance use disorder prevalence is higher among survivors of certain types of cancer, such as head and neck cancer survivors and cervical cancer survivors. This study also reported that approximately 4% of adult cancer survivors had an active substance use disorder (Jones 2024).	There is weak evidence that supports a higher risk of ACH in patients with substance use disorder, specifically as it relates to mental health and difficulties or inability to adequately manage existing diabetes or related conditions (Isidro 2013).	Unknown, due to lack of sufficient evidence.	Yes
Type of diabetes	Patients were not included in the CAPItello-291 trial if they had diabetes requiring insulin or had a baseline glycated haemoglobin level of ≥8.0% (Turner 2023). Therefore, there is a lack of evidence on those with insulin-dependent or uncontrolled type 2 diabetes. Evidence suggests that capivasertib + fulvestrant may be more appropriate for those	Historically, patients with type 1 diabetes had a higher risk for ACH, however, this has recently changed due to complexities of type 1 diabetes (Randazzese 2024). ACH, such as DKA, may occur in patients with either type 1 or type 2 diabetes as DKA has been reported in nearly 25-30% of patients with type 1 diabetes and in 4-29% of younger, newly	Yes, potential effect modifier for ACH. There is a lack of sufficient evidence to determine if	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	with well-controlled type 2 diabetes given the potential safety risks associated with capivasertib + fulvestrant.	diagnosed type 2 diabetics (Desai 2018). Patients with type 2 diabetes who experience a DKA event have more severe health outcomes compared to patients with type 1 diabetes who experience a DKA event (Barski 2013; Ata 2023).	there is a relationship with capivasertib + fulvestrant.	
Post-menopausal status (for female participants only)	Recent trends indicate that rates of premenopausal breast cancer are increasing equal to postmenopausal breast cancer, and that this differs by high-income versus developing countries (Heer 2020). Importantly, menopause status can influence the type of treatment of breast cancer in HR+ patients. For example, treatment with aromatase inhibitors is more effective in postmenopausal patients as the ovaries have stopped producing oestrogen. Recent clinical trials seek to find treatments that are effective regardless of menopause status (Sledge 2020). The CAPItello trial enroled women of any menopausal status and 77.3% of patients were postmenopausal (Turner 2023). In the subgroup analysis, postmenopausal women had improved PFS in comparison to pre-menopausal women (Turner 2023).	Menopause may increase the risk of type 2 diabetes due to metabolic changes that make women more susceptible to the condition, including a higher likelihood of upper body fat accumulation and increased insulin resistance. These factors may, in turn, contribute to an elevated risk of ACH. Furthermore, in those with type 1 or type 2 diabetes, menopause can cause difficulties with glycaemic control, thus increasing the risk of ACH (Lambrinoudaki 2022).	Yes, potential confounder. For ACH, the relationship is mediated by type of diabetes.	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
Concurrent use of luteinizing hormone-releasing hormone (LHRH) agonist	LHRH is indicated as a comedication in pre- and peri-menopausal women to improve the effectiveness of capivasertib + fulvestrant via ovarian function suppression (Capivasertib SmPC 2024).	Risk of development of type 2 diabetes and metabolic dysfunction appears to be higher in men receiving androgen therapy, however, in females, the relationship between LHRH and diabetes and metabolic dysfunction is less evident (Navarro 2015). LHRH treatment in HR+ breast cancer patients has been reported as safe and not associated with increased risk of HHS or DKA (Lu 2021), although research on LHRH therapy in HR+ breast cancer patients with diabetes and risk of DKA/HHA specifically is lacking.	Evidence suggests no.	Yes
Metastatic breast cancer diagnosis	Capivasertib has been approved by the EMA for the treatment of adult patients with HR+/HER2- locally advanced or metastatic breast cancer based on CAPItello-291 phase 3 efficacy and safety results (Turner 2023).	Some treatments for metastatic breast cancer (e.g., alpelisib) are associated with an increased risk of developing diabetes and hyperglycaemia (André 2019). Presence of diabetes and/or uncontrolled hyperglycaemia leads to an increased risk for hyperglycaemic crises.	May be a potential confounder, however, the relationship between metastatic breast cancer and ACH is indirect and mediated by both the history of any	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
			breast cancer treatment and diabetes diagnosis.	
Time since advanced breast cancer diagnosis	A large subset of patients with advanced disease develop resistance to 1st-line therapies (Zhou 2023). For example, a review describes the successful but inevitable resistance of CDK4/6 inhibitors and challenges for patients with recurring breast cancer of HR+ subtype (Huang 2022). Consequently, patients prescribed capivasertib + fulvestrant may be more likely to have increased severity of breast cancer disease, higher immune resistance, or more comorbidities, leading to a higher risk for occurrence of a related safety event.	There is a lack of evidence to support that length of time since breast cancer diagnosis is directly related to increased risk of AHC. In those patients with a longer time since breast cancer diagnosis, more metabolic changes may have occurred when compared to women recently diagnosed or on their first round of treatment. For example, one population-based study found that excess risk of diabetes diagnosis was temporary and related to breast cancer treatment (Kjærgaard 2024). The longer a patient undergoes breast cancer treatment, the greater the risk of metabolic changes that may result in glycaemic dysregulation in individuals with diabetes.	Unknown, due to lack of sufficient evidence. For capivasertib + fulvestrant, time since advanced breast cancer may be an effect modifier, with the relationship mediated by prior CDK4/6i use.	Yes
History of other cancers	A targeted literature review found no reported evidence of a relationship between a history of other cancers and capivasertib + fulvestrant.	History of cancer may be linked to both metabolic changes or exposure to cancer treatments that can influence the risk of diabetes or lead to a diagnosis of diabetes	Yes, potential effect modifier for ACH.	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	Patients with a history of other cancers may have decreased biological response (i.e., resistance) to capivasertib if they have previously received therapies targeting the same pathway as capivasertib (AKT/PIK3/mTOR pathway), however, this has yet to be shown. Note: patients were required to have no previous exposure to AKT, PI3K, or mTOR inhibitor drugs in CAPItello-291 (Turner 2023). Additionally, adherence or the likelihood of being prescribed capivasertib + fulvestrant may be influenced by past treatment toxicities for the non-breast cancer; similarly, this has yet to be shown.	after cancer. The risk of hyperglycaemia and ACH are likely higher in these patients. Emerging evidence suggests that a history of a cancer diagnosis may increase the risk of subsequent diabetes mellitus type 2 diagnosis. This association can vary depending on the type of cancer and the treatments employed. Notably, pancreas, kidney, liver, breast, stomach, and thyroid have been associated with increased diabetes risk (Hwangbo 2018).	There is a lack of sufficient evidence to determine if there is a relationship with capivasertib + fulvestrant.	
Previous CDK4/6 inhibitors (CDK4/6i)	Most patients diagnosed with HR+/HER2− metastatic breast cancer are treated with a CDK4/6i early in their endocrine-based therapy. However, despite therapy effectiveness, these agents face acquired resistance, which can be due to mechanisms involving the oestrogen receptor (ER) pathway or cell cycle regulation, ultimately leading to disease progression (Giordano 2024). A preclinical study reported that concurrent inhibition of AKT and ER signalling through	A recent review of the safety profile for CDK4/6i-related treatment-associated adverse events did not find that hyperglycaemia, blood glucose dysregulation or ACH as potential side effects for CDK4/6i. Of note, abemaciclib significantly reduces the renal clearance of metformin, which in turn could affect the blood glucose homeostasis of a patient with diabetes. However, previous use of CDK4/6i is not associated with an increased risk of ACH (Wekking 2023).	Yes, potential effect modifier for capivasertib + fulvestrant.	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	capivasertib and fulvestrant, respectively, are effective in palbociclib-resistant cell lines (Hopcroft 2023). In CAPItello-291, 69.1% of patients had prior exposure to a CDK4/6i. Patients receiving capivasertib + fulvestrant had a longer median PFS compared to patients receiving placebo + fulvestrant in both patients with previous CDK4/6i exposure and without CDK4/6i exposure. However, among patients receiving capivasertib + fulvestrant, the median PFS was 5.5. months among those with prior CDK4/6i exposure and 10.9 months among those with no prior CDK4/6i exposure (Turner 2023). Therefore, patients may have a differential overall health status after treatment with a CDK4/6i, resulting in differences in the effectiveness of capivasertib.			
Previous fulvestrant use	A targeted literature review found no reported evidence of a relationship between prior fulvestrant use and capivasertib + fulvestrant. Prior use of fulvestrant in CAPItello-291 trial was an exclusion criterion (Turner 2023). Prior fulvestrant use may influence the efficacy	A targeted literature review found no reported evidence of a relationship between prior fulvestrant use and ACH.	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letro

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	of capivasertib + fulvestrant if acquired resistance is present. The objective response rate observed with fulvestrant in patients who had received multiple lines of prior endocrine therapy for ER+ advanced breast cancer was typically ≤10% (Bardia 2019). Evidence shows that combination regimens significantly increase PFS, however, 'patients eventually relapse and will require additional therapies in the second-line setting' and beyond, leading to acquired resistance (Bardia 2019).			zole/exemestane/any other oral SERD)
Prior primary tumour surgery (e.g., mastectomy, lumpectomy)	A targeted literature review found no reported evidence of a relationship between prior primary tumour surgery and capivasertib + fulvestrant. In the FAKTION trial, a phase 2 trial examining the efficacy of capivasertib + fulvestrant versus placebo, the majority of patients had a history of breast surgery (Howell 2022). The proportion of patients with prior breast surgery was not reported in the CAPItello-291 trial (Turner 2023).	A targeted literature review found no reported evidence of the relationship between previous tumour surgery and risk of ACH. Patients with existing diabetes may be more likely to delay surgery as treatment for breast cancer (Lawrenson 2023).	Unknown, due to lack of sufficient evidence.	Yes
Number of prior	There is currently no direct evidence of the relationship between the number of tamoxifen therapies and capivasertib + fulvestrant.	A targeted literature review found no reported evidence of a relationship between the number of prior tamoxifen therapies and ACH.	Evidence suggests no.	Yes, as number of prior anti-oestrogen

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
tamoxifen therapies	Tamoxifen is a commonly used SERM and attenuates oestrogen-stimulated ER signalling in the breast (Howell 2023). ER+ breast cancer can develop resistance to endocrine therapies like SERMs (tamoxifen) and aromatase inhibitors (anastrozole, letrozole, exemestane, fulvestrant), often leading to the need for chemotherapy (Howell 2022). In the FAKTION and CAPItello-291 trials, 60% and 44% of patients, respectively, had previously received tamoxifen (Howell 2022; Capivasertib NDA 2021). Notably, tamoxifen is commonly prescribed to pre-menopausal women, who may be slightly healthier or have different metabolisms compared to postmenopausal women. There is evidence to suggest that ER+ breast cancer can become resistant to SERMs (e.g. tamoxifen). For example, ER-positive breast cancer can escape endocrine therapy through the presence of ER itself which can activate the ER signalling pathway. When progression is observed, it is typically via the "ligand-independent activation through direct mutation of ER or phosphorylation of ER or its	Hyperglycaemia or risk of diabetes is not recognized as a side effect of tamoxifen, however, one case report reported a male breast cancer patient who experienced HHS while on tamoxifen, which resolved once tamoxifen was discontinued (Radovic 2020). A population-based study found that tamoxifen therapy is associated with an increased incidence of diabetes compared to no tamoxifen use in older breast cancer survivors. This increased risk for diabetes was only observed in current or recent users of tamoxifen. Patients who received tamoxifen more than 6 months before the study index date did not have an increased risk for diabetes compared to patients with no history of tamoxifen (Lipscombe 2012).		therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	coregulators through signalling pathways such as PI3K-AKT-mTOR" (Patel 2023). While there is no evidence to support a differential efficacy of capivasertib + fulvestrant in those with previous tamoxifen therapies, this variable could be indicative of a person's overall health status or influence the likelihood of being treated with capivasertib + fulvestrant in the real-world setting.			
Number of prior anastrozole therapies	There is currently no direct evidence of the relationship between the number of anastrozole therapies and capivasertib + fulvestrant. ER+ breast cancer can develop resistance to endocrine therapies like aromatase inhibitors (anastrozole, letrozole, exemestane, fulvestrant), often leading to the need for chemotherapy. The CAPItello-291 and FAKTION trials evaluated capivasertib + fulvestrant in patients whose disease had progressed after an aromatase inhibitor, however, the relationship between the number of prior anastrozole treatments and capivasertib efficacy and safety were not reported (Howell 2022; Turner 2023).	A targeted literature review found no reported evidence of a relationship between the number of prior anastrozole therapies and ACH. Aromatase inhibitors have been suggested to increase the risk for insulin resistance and diabetes among women with breast cancer, however, the evidence is inconclusive due to small sample sizes and inadequate follow-up times (Hamood 2018; Gibb 2019; Buch 2019).	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
Number of prior letrozole therapies	There is currently no direct evidence of the relationship between the number of letrozole therapies and capivasertib + fulvestrant. ER+ breast cancer can develop resistance to endocrine therapies like aromatase inhibitors (anastrozole, letrozole, exemestane, fulvestrant), often leading to the need for chemotherapy. The CAPItello-291 and FAKTION trials evaluated capivasertib + fulvestrant in patients whose disease had progressed after an aromatase inhibitor, however, the relationship between the number of prior letrozole treatments and capivasertib efficacy and safety were not reported (Howell 2022; Turner 2023).	A targeted literature review found no reported evidence of a relationship between the number of prior letrozole therapies and ACH. Aromatase inhibitors have been suggested to increase the risk for insulin resistance and diabetes among women with breast cancer, however, the evidence is inconclusive due to small sample sizes and inadequate follow-up times (Hamood 2018; Gibb 2019; Buch 2019).	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Number of prior exemestane therapies	There is currently no direct evidence of the relationship between the number of exemestane therapies and capivasertib + fulvestrant. ER+ breast cancer can develop resistance to endocrine therapies like aromatase inhibitors (anastrozole, letrozole, exemestane, fulvestrant), often leading to the need for chemotherapy. The CAPItello-291 and FAKTION trials evaluated capivasertib +	A targeted literature review found no reported evidence of a relationship between the number of prior exemestane therapies and ACH. Aromatase inhibitors have been suggested to increase the risk for insulin resistance and diabetes among women with breast cancer, however, the evidence is inconclusive due to small sample sizes and inadequate follow-up	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	fulvestrant in patients whose disease had progressed after an aromatase inhibitor, however, the relationship between the number of prior exemestane treatments and capivasertib efficacy and safety were not reported (Howell 2022; Turner 2023).	times (Hamood 2018; Gibb 2019; Buch 2019).		
Number of prior oral selective oestrogen receptor degrader therapies	There is currently no direct evidence of the relationship between the number of prior oral selective oestrogen receptor degrader therapies and capivasertib + fulvestrant.	A targeted literature review found no reported evidence of a relationship between the number of prior oral selective oestrogen receptor degrader therapies and ACH.	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Prior chemotherapy	The relationship between prior chemotherapy and the efficacy, safety, or pharmacokinetics of capivasertib + fulvestrant remains unclear. Evidence suggests that capivasertib likely improves overall survival and PFS when in combination with chemotherapeutic agents, though the influence of previous chemotherapy use on the efficacy and safety of capivasertib is less studied (Turner 2019; Schmid 2020; Fabi 2021).	Evidence suggests that chemotherapy treatment in patients with diabetes is correlated with a risk of ACH. Hyperglycaemia develops in about 10% to 30% of patients undergoing chemotherapy (Hwangbo 2017). Evidence shows that breast cancer patients with diabetes respond less well to chemotherapy due to hyperglycaemia-induced chemoresistance in ER+ breast cancer cells (Zeng 2016). Furthermore, patients with	Yes, potential effect modifier for ACH. For ACH, the relationship with prior chemotherapy is mediated by blood glucose	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
	In the CAPItello-291 trial, 18.2% of capivasertib + fulvestrant arm had previously received neoadjuvant/adjuvant chemotherapy for advanced cancer (Turner 2023).	diabetes undergoing chemotherapy are less able to manage the acute stress from chemotherapy treatment. Stress, in addition to the chemotherapeutic agents, exacerbates insulin resistance, leading to increased blood glucose levels and increased risk of complications such as DKA (Hwangbo 2017).	levels. There is a lack of sufficient evidence to determine if there is a relationship with capivasertib + fulvestrant.	
Concomitant use of other medications affecting blood glucose level, regardless of type	A targeted literature review found no reported evidence of a relationship between concomitant use of medications affecting blood glucose level and capivasertib + fulvestrant. In CAPItello-291, a higher percentage of patients received concomitant glucocorticosteroids in the capivasertib + fulvestrant arm compared to the placebo + fulvestrant arm (Canadian Drug Agency 2025).	Though there is a paucity of strong evidence for the relationship between concomitant use of other medications affecting blood glucose levels and risk of ACH, this relationship is strongly influenced by levels of glycemia. These medications can indirectly increase risk of ACH given their effect on blood glucose levels (i.e., steroids). For example, studies found that corticosteroid use increased the risk of incident type 2 diabetes, related to both dose and duration response (Ambery 2022) and in some cases, induced DKA, though rare (Cavataio 2022). Specific to populations diagnosed with cancer, incidence of hyperglycaemia and use of PI3K/AKT/mTOR inhibitors has been found in ranges of 12%-	Yes, potential effect modifier for ACH. For ACH, the relationship with concomitant use of medications affecting blood glucose levels is mediated by blood glucose levels.	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
		50%, though rare and transient (Yim 2021, Ziegengeist 2024). While there is no systematic review or meta-analysis that has quantified the exact incidence of DKA/HHS in patients with breast cancer and diabetes with concomitant use of other medications affecting blood glucose levels, this variable is clinically relevant when addressing the risk of ACH, given the pathophysiology of ACH and the mechanism of action as it relates to blood glucose in this drug class (French 2019).	There is a lack of sufficient evidence to determine if there is a relationship with capivasertib + fulvestrant.	
Concurrent metformin use	A targeted literature review found no reported evidence of a relationship between current metformin use and capivasertib + fulvestrant. In CAPItello-291, 53.3% of patients in the capivasertib + fulvestrant arm were receiving antidiabetic medications at baseline. Hyperglycaemia adverse events were observed for 28 patients in the capivasertib + fulvestrant (28/60 patients with an event; 46.7%), most of whom (18/28, 64.3%) received metformin as treatment (Rugo 2024).	Metformin has antihyperglycemic effects and improves insulin sensitivity in patients with type 2 diabetes (Foretz 2023).	Yes, potential effect modifier for ACH. For ACH, the relationship with concurrent metformin use is mediated by blood glucose levels. There is a lack	Yes

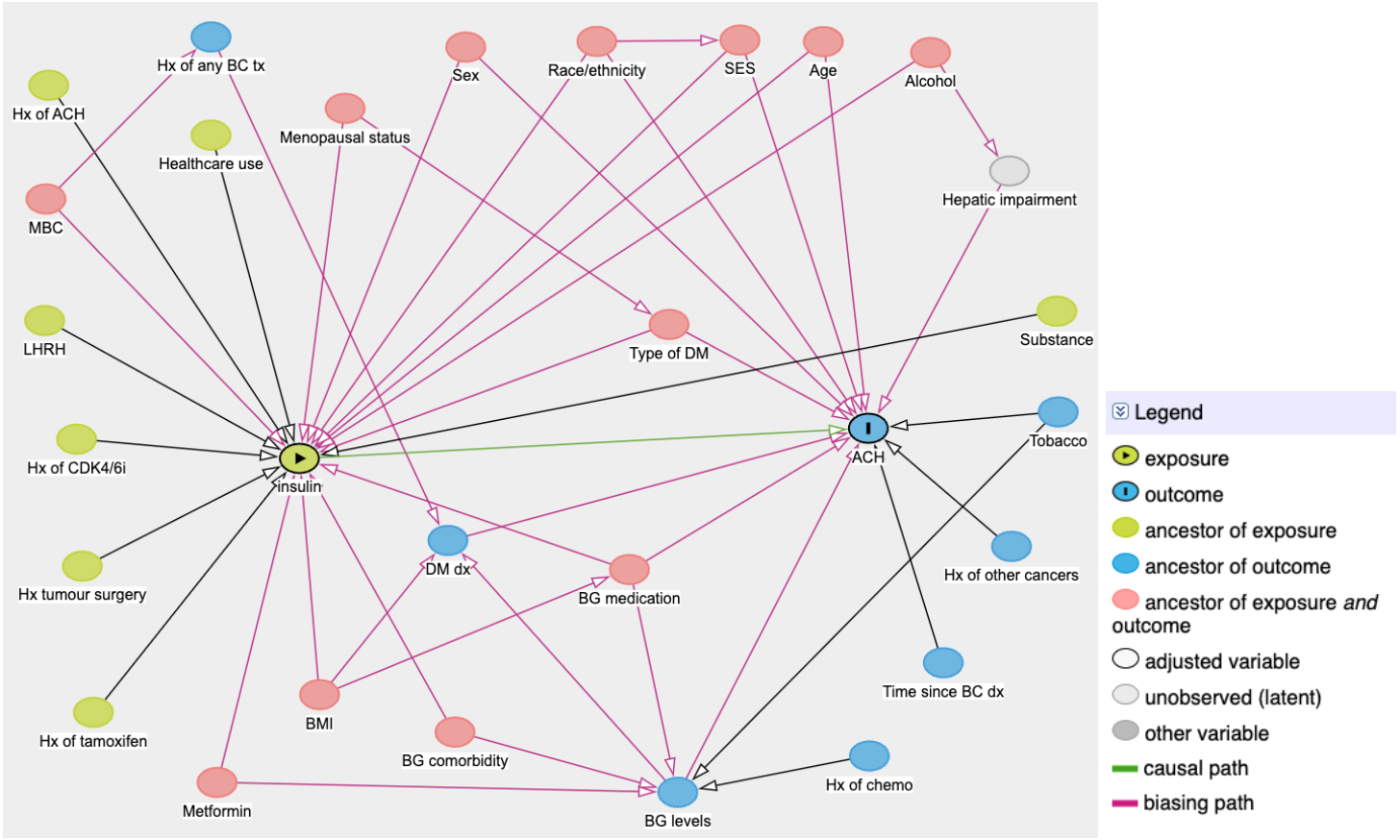
	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
			of sufficient evidence to determine if there is a relationship with capivasertib + fulvestrant.	
Comorbidity that interferes with blood glucose levels	There is currently no direct evidence of the relationship between comorbidities that interfere with blood glucose levels and the effectiveness and safety of capivasertib, however, hyperglycaemia is a known adverse event for capivasertib (Turner 2023). Patients with a medical history of diabetes or risk factors for hyperglycaemia (e.g., BMI ≥30) are recommended to have their fasting glucose frequently monitored while on capivasertib and to withhold, reduce the dose, or permanently discontinue capivasertib if severe hyperglycaemia occurs (Capivasertib SmPC 2024). Therefore, baseline comorbidities that affect blood glucose levels may impact adherence to capivasertib.	If a diabetic patient has a comorbidity that affects blood glucose levels, they are inherently at risk for DKA/HHS (Umpierrez 2024).	Yes, potential confounder. For both capivasertib + fulvestrant as well as ACH, this relationship with comorbidity that interferes with blood glucose levels is mediated by blood glucose levels.	Yes

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
Recent healthcare use: frequency of hospital-isations within past year	A targeted literature review found no reported evidence of a relationship between recent healthcare use: frequency of hospitalisations within past year and capivasertib + fulvestrant.	Recent hospitalizations reflect additional disease pathologies and pharmaceutical exposures that account for health status at baseline but do not directly affect a patient's risk of ACH. There is limited direct evidence examining the association between ACH and a patient's history of recent healthcare use. While certain cancer therapies, particularly PI3K/AKT pathway inhibitors, have been associated with severe hyperglycaemic events, the specific impact of prior hospitalizations on the risk of ACH in this population remains under-researched (Umpierrez 2024).	Unknown, due to lack of sufficient evidence.	Yes, as poly-morbidity marker
Recent healthcare use: emergency department visits within past year	A targeted literature review found no reported evidence of a relationship between recent healthcare use: emergency department visits within past year and capivasertib + fulvestrant.	Recent emergency department visits reflect additional disease pathologies and pharmaceutical exposures that account for health status at baseline but do not directly affect a patient's risk of ACH. There is limited direct evidence examining the association between ACH and a patient's history of recent healthcare use. While certain cancer therapies, particularly PI3K/AKT pathway inhibitors, have been associated with severe hyperglycaemic events, the specific impact of prior emergency department visits on the risk of ACH in this population remains under-researched (Umpierrez 2024).	Unknown, due to lack of sufficient evidence.	Yes, as poly-morbidity marker

	Type and strength of evidence for a relationship with capivasertib + fulvestrant[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate? (Yes/No)
Recent healthcare use: outpatient physician visits within past year	A targeted literature review found no reported evidence of a relationship between recent healthcare use: outpatient physician visits within past year and capivasertib + fulvestrant.	Recent outpatient physician visits reflect additional disease pathologies and pharmaceutical exposures that account for health status at baseline but do not directly affect a patient's risk of ACH. There is limited direct evidence examining the association between ACH and a patient's history of recent healthcare use. While certain cancer therapies, particularly PI3K/AKT pathway inhibitors, have been associated with severe hyperglycaemic events, the specific impact of prior physician visits on the risk of ACH in this population remains under-researched (Umpierrez 2024).	Unknown, due to lack of sufficient evidence.	Yes, as poly-morbidity marker
Prior history of acute complications of hyper-glycaemia	There is currently no direct evidence of the relationship between efficacy, effectiveness, or pharmacokinetics of capivasertib + fulvestrant and prior history of ACH. Patients with a history of insulin-dependent or type 1 diabetes were excluded from CAPItello-291.	History of ACH is a risk factor for recurrence; however, this is likely due to the poor overall health status or uncontrolled, related pathophysiology (McCoy 2018; French 2019).	Unknown, due to lack of sufficient evidence.	Yes

a. The source of information for the relationships was from published studies. Full citations are provided at the end of Appendix B.

Figure B2. Directed acyclic graph of the relationship among insulin, acute complications of hyperglycaemia, and baseline characteristics (Exploratory Objective 5)



Abbreviations: ACH, acute complications of hyperglycaemia; BC, breast cancer; BG, blood glucose; BMI, body mass index; CDK4/6i, CDK4/6 inhibitors; chemo, chemotherapy; DM, diabetes mellitus; dx, diagnosis; hx, history; LHRH, luteinizing hormone-releasing hormone; MBC, metastatic breast cancer; SES, socioeconomic status; tx, treatment.

Table B2. Supporting evidence among insulin, acute complications of hyperglycaemia, and baseline characteristics (Exploratory Objective 5)

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Age at index date	Older age is associated with an increased risk of insulin resistance (Kolb 2023). Age-related changes have been reported to contribute to this increased risk including impaired beta-cell function, reduced insulin sensitivity, and decreased beta-cell response to incretins (Chang 2003). While circulating insulin levels may remain similar to those of younger individuals, the ability to effectively use insulin declines. This leads to a higher risk of glucose intolerance and type 2 diabetes in older adults (Zhao 2023).	Diabetic ketoacidosis (DKA) is more frequently reported in younger patients with type 1 diabetes while hyperglycaemic hyperosmolar states (HHS) is more commonly observed in older patients with type 2 diabetes (Benoit 2020; Umpierrez 2024).	Yes, potential confounder.	Yes
Sex	Insulin resistance and type 2 diabetes are more prevalent in males than in females (Geer 2009; Varlamov 2015). Oestrogen has been suggested to have a protective effect against insulin resistance in females (Varlamov 2015).	DKA is more frequently reported in women versus men with type 1 diabetes (Farsani 2017; McCoy 2021). Sex dimorphic traits may influence the risk of ACH. For example, males are at higher risk to develop insulin resistance than healthy premenopausal females, and endogenous oestrogens influences pancreatic endocrine function (Tramunt 2020).	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Race/ethnicity	Insulin resistance, prediabetes, and diabetes are more prevalent in racial and ethnic minorities compared to non-Hispanic Whites (Zhu 2019; Raygor 2019).	Evidence suggests that race/ethnicity significantly influences the risk of DKA. In particular, African American and Hispanic individuals have been reported to have a higher risk for DKA compared to other races (Ebekozien 2021; McCoy 2021). However, these disparities are likely intertwined with socioeconomic factors and healthcare access in certain populations in the United States (Macias-Konstantopoulos 2023).	Yes, potential confounder.	Yes
Body mass index (BMI)	High BMI and obesity are related to insulin resistance, with insulin resistance increasing incrementally according to BMI levels (Martinez 2017).	There is strong evidence that both a rapid increase and consistently high BMI are strongly associated with the subsequent risk of developing type 2 diabetes and hyperglycaemia compared with a stable normal BMI (Kan 2022). However, risk of HHS or DKA is higher in those with lower BMI in existing type 1 and type 2 diabetes due to poor metabolic control (Tittel 2020, Ross 2022).	Yes, potential effect modifier for insulin. For ACH, the relationship with BMI is mediated by the presence of diabetes.	Yes
Socioeconomic status (SES)	Individuals with lower SES exhibit a higher risk of diabetes compared to those with higher SES, suggesting a potential link to increased insulin resistance (Liu 2023). Data from the	In countries where healthcare is not universal or public, SES can impact access to healthcare, which has been reported to	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	CDC (2019–2021) show that adults with family incomes above 500% of the federal poverty level have the lowest diabetes prevalence. Additionally, individuals with lower SES demonstrate poorer glycaemic control, a key factor associated with increased insulin resistance (Houle 2016).	impact the ability to control hyperglycaemia and prevent ACH (Liu 2020; Everett 2019).		
Tobacco use	Smoking can elevate the risk of developing insulin resistance (Cho 2022; Bergman 2012).	Substantial research has demonstrated that nicotine can elevate blood glucose levels, disrupt glucose homeostasis, and induce insulin resistance, all of which are risk factors for ACH, especially in diabetic patients with infections or illness (Chen 2023). A prospective study reported that patients with type 1 diabetes who smoked at least one cigarette per day had an increased risk for DKA compared to non-smokers (Thomas 2020). Chronic tobacco use is associated with an increased risk of type 2 diabetes, which leads to an increased risk for ACH (Willi 2007). Short-term tobacco use decreases cells'	Yes, potential confounder. For ACH, the relationship with tobacco may be direct as well as mediated by diabetes status and blood glucose levels.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		sensitivity to insulin and increases the risk of ACH (Bergman 2012).		
Alcohol abuse	In nondiabetic patients, moderate alcohol consumption may lower fasting insulin and HbA1c concentrations. In women, alcohol consumption might improve insulin sensitivity (Schrieks 2015).	Those patients who use alcohol in excess or chronically are more likely to have hepatic impairment and/or metabolic dysfunction that is associated with an increased risk for ACH (Osna 2017). A prospective study reported that patients with type 1 diabetes and higher alcohol consumption were at an increased risk for DKA (Thomas 2020). A separate study reported that patients with alcohol disorder were at an increased risk for DKA (French 2019).	Yes, potential confounder. For ACH, this potential relationship with alcohol abuse is likely mediated by hepatic impairment.	Yes
Drug or substance abuse	Individuals with substance use disorders exhibit higher levels of insulin resistance than individuals with no substance use disorder (Ojo 2018).	There is weak evidence that supports a higher risk of ACH in patients with substance use disorder, specifically as it relates to mental health and difficulties or inability to adequately manage existing diabetes or related conditions (Isidro 2013).	Yes, potential effect modifier for insulin. There is lack of sufficient evidence to determine if there is a	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
			relationship with ACH.	
Type of diabetes	Type 1 diabetes is an autoimmune condition in which your immune system attacks the insulin-producing cells in your pancreas. It eventually results in a total lack of natural insulin. Insulin treatment is the foundational treatment for type 1 diabetes (Burrack 2017). Type 2 diabetes happens when insulin resistance is too strong for your pancreas to overcome, resulting in high blood sugar (Swinnen 2009). Insulin treatment is used across 12-30% of patients with type 2 diabetes (Jorgensen 2016, UK NHS 2023, US CDC NHANES 2024).	Historically, patients with type 1 diabetes had a higher risk for ACH, however, this has recently changed due to complexities of type 1 diabetes (Randazzese 2024). ACH, such as DKA, may occur in patients with either type 1 or type 2 diabetes as DKA has been reported in nearly 25-30% of patients with type 1 diabetes and in 4-29% of younger, newly diagnosed type 2 diabetics (Desai 2018). Patients with type 2 diabetes who experience a DKA event have more severe health outcomes compared to patients with type 1 diabetes who experience a DKA event (Barski 2013; Ata 2023).	Yes, potential confounder.	Yes
Postmenopausal status (for female participants only)	Insulin and oestrogen may have a reciprocal relationship that significantly elevates the risk of endocrine-related cancers, particularly in postmenopausal women (Ferroni 2015). Insulin sensitivity has been reported to be lower in early postmenopausal women	Menopause may increase the risk of type 2 diabetes due to metabolic changes that make women more susceptible to the condition, including a higher likelihood of upper body fat accumulation and increased insulin resistance. These factors may, in turn, contribute to an elevated risk of ACH. Furthermore, in those with type 1 or type 2	Yes, potential confounder. For ACH, the relationship is mediated by	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	compared to premenopausal women (Mandrup 2018). In addition, menopausal status and risk for type 2 diabetes have been reported (Ahanchi 2024).	diabetes, menopause can cause difficulties with glycaemic control, thus increasing the risk of ACH (Lambrinoudaki 2022).	type of diabetes.	
Concurrent use of luteinizing hormone-releasing hormone (LHRH) agonist	Evidence suggests that the use of LHRH may influence insulin sensitivity. Transgender youth undergoing gonadotropin-releasing hormone agonist (GnRHa) treatment tend to have reduced insulin sensitivity, along with increased glycaemic markers and body fat, compared to cisgender peers with similar characteristics (Nokoff 2021). However, in patients with central precocious puberty, GnRHa treatment did not result in significant changes in insulin sensitivity after 6 and 12 months (Guo 2024). Additionally, patients receiving LHRH agonists demonstrated a less favourable progression of HOMA-IR (homeostasis model assessment-insulin resistance) compared to those who underwent bilateral orchiectomy (Zhang 2023).	Risk of development of type 2 diabetes and metabolic dysfunction appears to be higher in men receiving androgen therapy, however, in females, the relationship between LHRH and diabetes and metabolic dysfunction is less evident (Navarro 2015). LHRH treatment in HR+ breast cancer patients has been reported as safe and not associated with increased risk of HHS or DKA (Lu 2021), although research on LHRH therapy in HR+ breast cancer patients with diabetes and risk of DKA/HHA specifically is lacking.	Yes, effect modifier for insulin.	Yes
Metastatic breast cancer diagnosis	Some treatments for metastatic breast cancer (e.g., alpelisib) are associated with an increased risk of developing diabetes and hyperglycaemia (André 2019).	Some treatments for metastatic breast cancer (e.g., alpelisib) are associated with an increased risk of developing diabetes and hyperglycaemia (André 2019). Presence of diabetes and/or uncontrolled hyperglycaemia	May be a potential confounder, however, the relationship	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		leads to an increased risk for hyperglycaemic crises.	between metastatic breast cancer and ACH is indirect and mediated by both the history of any breast cancer treatment and diabetes diagnosis. For insulin, the relationship with metastatic breast cancer is mediated by the selected treatment for metastatic breast cancer.	
Time since advanced breast cancer diagnosis	Evidence suggests that insulin levels are elevated in breast cancer patients, with these insulin levels increasing with higher disease stage (Ferroni 2016).	There is a lack of evidence to support that length of time since breast cancer diagnosis is directly related to increased risk of AHC.	Yes, potential effect modifier for insulin.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		In those patients with a longer time since breast cancer diagnosis, more metabolic changes may have occurred when compared to women recently diagnosed or on their first round of treatment. For example, one population-based study found that excess risk of diabetes diagnosis was temporary and related to breast cancer treatment (Kjærgaard 2024). The longer a patient undergoes breast cancer treatment, the greater the risk of metabolic changes that may result in glycaemic dysregulation in individuals with diabetes.	There is lack of sufficient evidence to determine if there is a relationship with ACH.	
History of other cancers	Patients with a cancer diagnosis are more likely to be insulin-resistant compared to healthy controls. This increased resistance leads to metabolic dysfunction, increased recurrence, and reduced survival (Marmol 2023). A targeted literature review found no reported evidence of the relationship between a history of other cancers and insulin.	History of cancer may be linked to both metabolic changes or exposure to cancer treatments that can influence the risk of diabetes or lead to a diagnosis of diabetes after cancer. The risk of hyperglycaemia and ACH are likely higher in these patients. Emerging evidence suggests that a history of a cancer diagnosis may increase the risk of subsequent diabetes mellitus type 2 diagnosis. This association can vary depending on the type of cancer and the treatments employed. Notably, pancreas, kidney, liver, breast, stomach, and thyroid	Yes, potential effect modifier for ACH. There is a lack of sufficient evidence to determine if there is a relationship with insulin.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		have been associated with increased diabetes risk (Hwangbo 2018).		
Previous CDK4/6 inhibitors (CDK4/6i)	While direct evidence linking CDK4/6i to insulin resistance is limited, a preclinical study demonstrated that CDK4 enhances insulin sensitivity in insulin-responsive tissues such as adipose and liver in mouse models (Stamateriset 2023).	A recent review of the safety profile for CDK4/6i-related treatment-associated adverse events did not find that hyperglycaemia, blood glucose dysregulation or ACH as potential side effects for CDK4/6i. Of note, abemaciclib significantly reduces the renal clearance of metformin, which in turn could affect the blood glucose homeostasis of a patient with diabetes. However, previous use of CDK4/6i is not associated with an increased risk of ACH (Wekking 2023).	Yes, potential effect modifier for insulin.	Yes
Previous fulvestrant use	A targeted literature review found no reported evidence of a relationship between prior fulvestrant use and insulin.	A targeted literature review found no reported evidence of a relationship between prior fulvestrant use and ACH.	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (ful-vestrant/tamoxifen/anastrozole/letrozole/exemestane/any

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
				other oral SERD)
Prior primary tumour surgery (e.g., mastectomy, lumpectomy)	It has been found that breast surgery resulted in increased whole-body protein breakdown and synthesis, independent of the presence of cancer. Various factors may contribute to the upregulated protein turnover following surgery, including an enhanced systemic inflammatory response and elevated insulin resistance, as reflected by an increased HOMA index (Engelen 2017).	A targeted literature review found no reported evidence of the relationship between previous tumour surgery and risk of ACH. Patients with existing diabetes may be more likely to delay surgery as treatment for breast cancer (Lawrenson 2023).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with ACH.	Yes
Number of prior tamoxifen therapies	Despite lowering body weight in obese women, tamoxifen may increase the incidence of diabetes as tamoxifen treatment has been shown to lead to early hepatic insulin resistance (Kloting 2020).	A targeted literature review found no reported evidence of a relationship between the number of prior tamoxifen therapies and ACH. Hyperglycaemia or risk of diabetes is not recognized as a side effect of tamoxifen; however, one case report reported a male breast cancer patient who experienced HHS while on tamoxifen, which resolved once tamoxifen was discontinued (Radovic 2020). A population-based study found that tamoxifen therapy is associated with an	Yes, potential effect modifier for insulin.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		increased incidence of diabetes compared to no tamoxifen use in older breast cancer survivors. This increased risk for diabetes was only observed in current or recent users of tamoxifen. Patients who received tamoxifen more than 6 months before the study index date did not have an increased risk for diabetes compared to patients with no history of tamoxifen (Lipscombe 2012).		other oral SERD)
Number of prior anastrozole therapies	A targeted literature review found no reported evidence of a relationship between the number of prior anastrozole therapies and insulin. While no direct evidence exists, one study reported that in healthy men, anastrozole has been shown to reduce insulin sensitivity by lowering the glucose disposal rate during insulin infusion (Gibb 2016).	A targeted literature review found no reported evidence of a relationship between the number of prior anastrozole therapies and ACH. Aromatase inhibitors have been suggested to increase the risk for insulin resistance and diabetes among women with breast cancer, however, the evidence is inconclusive due to small sample sizes and inadequate follow-up times (Hamood 2018; Gibb 2019; Buch 2019).	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Number of prior letrozole therapies	A targeted literature review found no reported evidence of a relationship between the number of prior letrozole therapies and insulin.	A targeted literature review found no reported evidence of a relationship between the number of prior letrozole therapies and ACH.	Unknown, due to lack of	Yes, as number of prior anti-oestrogen

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	A study demonstrated that letrozole treatment resulted in a rapid increase in glucose and insulin levels after 1 week of treatment (Skarra 2017).	Aromatase inhibitors have been suggested to increase the risk for insulin resistance and diabetes among women with breast cancer, however, the evidence is inconclusive due to small sample sizes and inadequate follow-up times (Hamood 2018; Gibb 2019; Buch 2019).	sufficient evidence.	therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Number of prior exemestane therapies	A targeted literature review found no reported evidence of a relationship between the number of prior exemestane therapies and insulin. However, current exemestane use is associated with lower insulin sensitivity (Senkus-konefka 2008).	A targeted literature review found no reported evidence of a relationship between the number of prior exemestane therapies and ACH. Aromatase inhibitors have been suggested to increase the risk for insulin resistance and diabetes among women with breast cancer, however, the evidence is inconclusive due to small sample sizes and inadequate follow-up times (Hamood 2018; Gibb 2019; Buch 2019).	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Number of prior oral selective oestrogen receptor	A targeted literature review found no reported evidence of a relationship between the number	A targeted literature review found no reported evidence of a relationship between	Unknown, due to lack of	Yes, as number of prior anti-oestrogen

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
degrader therapies	of prior oral selective oestrogen receptor degrader therapies and insulin.	the number of prior oral selective oestrogen receptor degrader therapies and ACH.	sufficient evidence.	therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Prior chemotherapy	A targeted literature review found no reported evidence of a relationship between prior chemotherapy and insulin. Studies have reported that women may have increased blood glucose and insulin levels while on adjuvant chemotherapy, most likely due to increased weight or change in body composition (Buch 2019).	Evidence suggests that chemotherapy treatment in patients with diabetes is correlated with a risk of ACH. Hyperglycaemia develops in about 10% to 30% of patients undergoing chemotherapy (Hwangbo 2017). Evidence shows that breast cancer patients with diabetes respond less well to chemotherapy due to hyperglycaemia-induced chemoresistance in ER+ breast cancer cells (Zeng 2016). Furthermore, patients with diabetes undergoing chemotherapy are less able to manage the acute stress from chemotherapy treatment. Stress, in addition to the chemotherapeutic agents, exacerbates insulin resistance, leading to increased blood glucose levels and increased risk of	Yes, potential effect modifier for ACH. For ACH, the relationship with prior chemotherapy is mediated by blood glucose levels. There is a lack of sufficient evidence to determine if there is a	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		complications such as DKA (Hwangbo 2017).	relationship with insulin.	
Concomitant use of other medications affecting blood glucose level, regardless of type	Systemic corticosteroids: prior research has reported systemic corticosteroids to induce insulin resistance, leading to elevated blood glucose levels and in some cases, steroid-induced diabetes mellitus. This effect has been reported to be associated with corticosteroids increasing gluconeogenesis (Geer 2014). Statins: There is mixed and inconclusive evidence regarding the association between statins and insulin intolerance. A prior systematic review provides evidence suggesting that statins might have an adverse effect on insulin sensitivity and increase insulin resistance (Dabhi 2023). Quinolones: A study examining the effect of past quinolones exposure on diabetes risk reported that treatment with more than five courses of quinolones was associated with an increased risk of developing diabetes (Boursi 2015). Thiazide-like diuretics: Evidence suggests that	Though there is a paucity of strong evidence for the relationship between concomitant use of other medications affecting blood glucose levels and risk of ACH, this relationship is strongly influenced by levels of glycemia. These medications can indirectly increase risk of ACH given their effect on blood glucose levels (i.e., steroids). For example, studies found that corticosteroid use increased the risk of incident type 2 diabetes, related to both dose and duration response (Ambery 2022) and in some cases, induced DKA, though rare (Cavataio 2022). Specific to populations diagnosed with cancer, incidence of hyperglycaemia and use of PI3K/AKT/mTOR inhibitors has been found in ranges of 12%-50%, though rare and transient (Yim 2021, Ziegengeist 2024). While there is no systematic review or meta-analysis that has quantified the exact incidence of DKA/HHS in patients with breast cancer and diabetes with concomitant use of other medications affecting blood	Yes, potential confounder. For ACH, the relationship with concomitant use of medications affecting blood glucose levels is mediated by blood glucose levels.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	patients receiving thiazide diuretics may have a higher risk of impaired glucose tolerance. Additionally, a higher incidence of diabetes has been reported across patients receiving thiazide diuretics (Zhang 2016). Atypical antipsychotics: A systematic review and meta-analysis of trials conducted in healthy volunteers reports that atypical antipsychotics may decrease insulin sensitivity and increase weight (Burghardt 2018). Calcineurin inhibitors: Prior research has suggested that calcineurin inhibitors, including tacrolimus and cyclosporine, decrease insulin sensitivity. In a study involving hemodialysis patients, treatment with tacrolimus and cyclosporine resulted in a 13% and 22% reduction in insulin sensitivity, respectively (Ozbay 2012).	glucose levels, this variable is clinically relevant when addressing the risk of ACH, given the pathophysiology of ACH and the mechanism of action as it relates to blood glucose in this drug class (French 2019).		
Concurrent metformin use	Metformin has antihyperglycemic effects and improves insulin sensitivity in patients with type 2 diabetes (Foretz 2023).	Metformin has antihyperglycemic effects and improves insulin sensitivity in patients with type 2 diabetes (Foretz 2023).	Yes, potential confounder. For ACH, the relationship	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
			with metformin is mediated by blood glucose levels.	
Comorbidity that interferes with blood glucose levels	Previous research has reported that patients with Cushing's disease are highly susceptible to developing impaired glucose tolerance and secondary diabetes as a result of hypercortisolism (Colao 2014). Pasireotide-induced hyperglycaemia has been linked to both reduced insulin secretion and diminished incretin response. Therefore, anti-hyperglycaemic treatment in patients with Cushing's disease receiving pasireotide should primarily target these two underlying mechanisms. (Colao 2014).	If a diabetic patient has a comorbidity that affects blood glucose levels, they are inherently at risk for DKA/HHS (Umpierrez 2024).	Yes, potential confounder. For ACH, the relationship with comorbidity that interferes with blood glucose levels is mediated by blood glucose levels.	Yes
Recent healthcare use: frequency of hospitalisations within past year	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown	Recent hospitalizations reflect additional disease pathologies and pharmaceutical exposures that account for health status at baseline but do not directly affect a patient's risk of ACH. There is limited direct evidence examining the association between ACH and a patient's history of recent healthcare use. While certain cancer therapies, particularly	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if	Yes, as polymorbidity marker

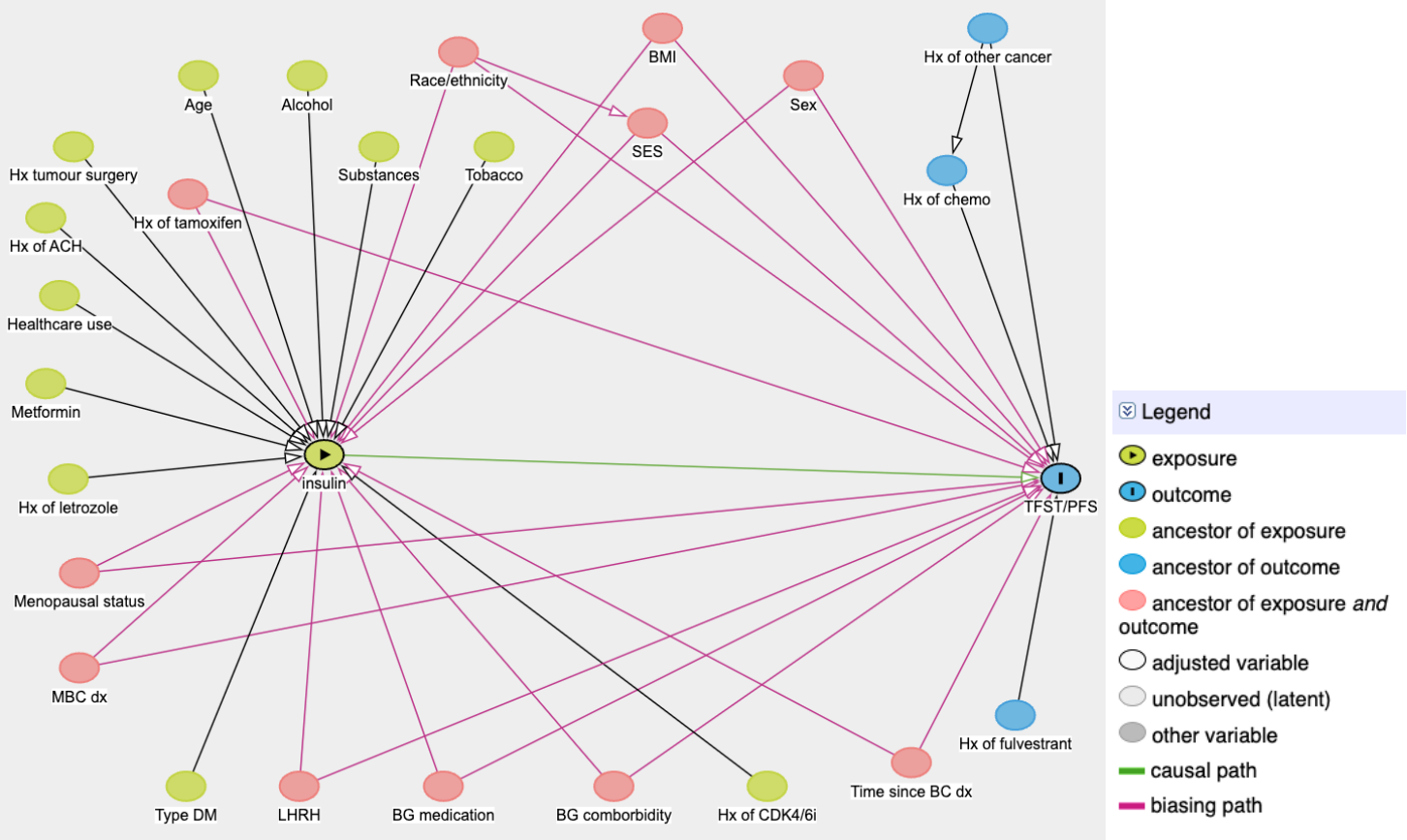
	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	to be a predictor of higher healthcare use in the following years (Alkhaddo 2022).	PI3K/AKT pathway inhibitors, have been associated with severe hyperglycaemic events, the specific impact of prior hospitalizations on the risk of ACH in this population remains under-researched (Umpierrez 2024).	there is a relationship with ACH.	
Recent healthcare use: emergency department visits within past year	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Recent emergency department visits reflect additional disease pathologies and pharmaceutical exposures that account for health status at baseline but do not directly affect a patient's risk of ACH. There is limited direct evidence examining the association between ACH and a patient's history of recent healthcare use. While certain cancer therapies, particularly PI3K/AKT pathway inhibitors, have been associated with severe hyperglycaemic events, the specific impact of prior emergency department visits on the risk of ACH in this population remains under-researched (Umpierrez 2024).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with ACH.	Yes, as polymorbidity marker
Recent healthcare use: outpatient	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department	Recent outpatient physician visits reflect additional disease pathologies and pharmaceutical exposures that account for health status at baseline but do not directly affect a patient's risk of ACH. There is	Yes, potential effect modifier for insulin. There is a lack	Yes, as polymorbidity marker

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
physician visits within past year	visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	limited direct evidence examining the association between ACH and a patient's history of recent healthcare use. While certain cancer therapies, particularly PI3K/AKT pathway inhibitors, have been associated with severe hyperglycaemic events, the specific impact of prior physician visits on the risk of ACH in this population remains under-researched (Umpierrez 2024).	of sufficient evidence to determine if there is a relationship with ACH.	
Prior history of acute complications of hyperglycaemia	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory	History of ACH is a risk factor for recurrence; however, this is likely due to the poor overall health status or uncontrolled, related pathophysiology (McCoy 2018; French 2019).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with ACH.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with acute complications of hyperglycaemia (ACH) [a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).			

a. The source of information for the relationships was from published studies. Full citations are provided at the end of Appendix B.

Figure B3. Directed acyclic graph of the relationship among insulin, time to first subsequent therapy (TFST)/progression-free survival (PFS), and baseline characteristics (Exploratory Objective 6)



Abbreviations: ACH, acute complications of hyperglycaemia; BC, breast cancer; BG, blood glucose; BMI, body mass index; CDK4/6i, CDK4/6 inhibitors; chemo, chemotherapy; DM, diabetes mellitus; dx, diagnosis; hx, history; LHRH, luteinizing hormone-releasing hormone; MBC, metastatic breast cancer; PFS, progression-free survival; SES, socioeconomic status; TFST, time to first subsequent therapy; tx, treatment.

Table B3. Supporting evidence among insulin, TFST/PFS, and baseline characteristics (Exploratory Objective 6)

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Age at index date	Older age is associated with an increased risk of insulin resistance (Kolb 2023). Age-related changes have been reported to contribute to this increased risk including impaired beta-cell function, reduced insulin sensitivity, and decreased beta-cell response to incretins (Chang 2003). While circulating insulin levels may remain similar to those of younger individuals, the ability to effectively use insulin declines. This leads to a higher risk of glucose intolerance and type 2 diabetes in older adults (Zhao 2023).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential effect modifier for insulin.	Yes
Sex	Insulin resistance and type 2 diabetes are more prevalent in males than in females (Geer 2009; Varlamov 2015). Oestrogen has been suggested to have a protective effect against insulin resistance in females (Varlamov 2015).	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).		
Race/ethnicity	Insulin resistance, prediabetes, and diabetes are more prevalent in racial and ethnic minorities compared to non-Hispanic Whites (Zhu 2019; Raygor 2019).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential confounder.	Yes
Body mass index (BMI)	High BMI and obesity are related to insulin resistance, with insulin resistance increasing incrementally according to BMI levels (Martinez 2017).	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).		
Socio-economic status (SES)	Individuals with lower SES exhibit a higher risk of diabetes compared to those with higher SES, suggesting a potential link to increased insulin resistance (Liu 2023). Data from the CDC (2019–2021) show that adults with family incomes above 500% of the federal poverty level have the lowest diabetes prevalence. Additionally, individuals with lower SES demonstrate poorer glycaemic control, a key factor associated with increased insulin resistance (Houle 2016).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential confounder.	Yes
Tobacco use	Smoking can elevate the risk of developing insulin resistance (Cho 2022; Bergman 2012).	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		(Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	relationship with TFST/PFS.	
Alcohol abuse	In nondiabetic patients, moderate alcohol consumption may lower fasting insulin and HbA1c concentrations. In women, alcohol consumption might improve insulin sensitivity (Schrieks 2015).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with TFST/PFS.	Yes
Drug or substance abuse	Individuals with substance use disorders exhibit higher levels of insulin resistance than	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of	Yes, potential effect modifier for insulin.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	individuals with no substance use disorder (Ojo 2018).	body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	There is a lack of sufficient evidence to determine if there is a relationship with TFST/PFS.	
Type of diabetes	Type 1 diabetes is an autoimmune condition in which your immune system attacks the insulin-producing cells in your pancreas. It eventually results in a total lack of natural insulin. Insulin treatment is the foundational treatment for type 1 diabetes (Burrack 2017). Type 2 diabetes happens when insulin resistance is too strong for your pancreas to overcome, resulting in high blood sugar (Swinnen 2009). Insulin treatment is used across 12-30% of	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	patients with type 2 diabetes (Jorgensen 2016, UK NHS 2023, US CDC NHANES 2024).		with TFST/PFS.	
Post-menopausal status (for female participants only)	Insulin and oestrogen may have a reciprocal relationship that significantly elevates the risk of endocrine-related cancers, particularly in postmenopausal women (Ferroni 2015). Insulin sensitivity has been reported to be lower in early postmenopausal women compared to premenopausal women (Mandrup 2018). In addition, menopausal status and risk for type 2 diabetes have been reported (Ahanchi 2024).	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	Yes, potential confounder.	Yes
Concurrent use of luteinizing hormone-releasing	Evidence suggests that the use of LHRH may influence insulin sensitivity. Transgender youth undergoing gonadotropin-releasing hormone agonist (GnRHa) treatment tend to have reduced insulin sensitivity, along with increased	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
hormone (LHRH) agonist	glycaemic markers and body fat, compared to cisgender peers with similar characteristics (Nokoff 2021). However, in patients with central precocious puberty, GnRHa treatment did not result in significant changes in insulin sensitivity after 6 and 12 months (Guo 2024). Additionally, patients receiving LHRH agonists demonstrated a less favourable progression of HOMA-IR (homeostasis model assessment-insulin resistance) compared to those who underwent bilateral orchiectomy (Zhang 2023).	visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).		
Metastatic breast cancer diagnosis	Some treatments for metastatic breast cancer (e.g., alpelisib) are associated with an increased risk of developing diabetes and hyperglycaemia (André 2019).	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of	May be a potential confounder, depending on the selected treatment for metastatic breast cancer. For insulin, the relationship with metastatic breast cancer	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	is mediated by the selected treatment for metastatic breast cancer.	
Time since advanced breast cancer diagnosis	Evidence suggests that insulin levels are elevated in breast cancer patients, with these insulin levels increasing with higher disease stage (Ferroni 2016).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential confounder.	Yes
History of other cancers	Patients with a cancer diagnosis are more likely to be insulin-resistant compared to healthy controls. This increased resistance leads to metabolic dysfunction, increased recurrence, and reduced survival (Marmol 2023). A targeted literature review found no reported evidence of the relationship between a history of other cancers and insulin.	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but	Yes, potential effect modifier for TFST/PFS. There is a lack of sufficient evidence to determine if there is a relationship with insulin.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).		
Previous CDK4/6 inhibitors (CDK4/6i)	While direct evidence linking CDK4/6i to insulin resistance is limited, a preclinical study demonstrated that CDK4 enhances insulin sensitivity in insulin-responsive tissues such as adipose and liver in mouse models (Stamateriset 2023).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with TFST/PFS.	Yes
Previous fulvestrant use	A targeted literature review found no reported evidence of a relationship between prior fulvestrant use and insulin.	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high	Yes, potential effect modifier for TFST/PFS. There is a lack of sufficient evidence to determine if	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastro

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	there is a relationship with insulin.	zole/letrozole/exemestane/any other oral SERD)
Prior primary tumour surgery (e.g., mastectomy, lumpectomy)	It has been found that breast surgery resulted in increased whole-body protein breakdown and synthesis, independent of the presence of cancer. Various factors may contribute to the upregulated protein turnover following surgery, including an enhanced systemic inflammatory response and elevated insulin resistance, as reflected by an increased HOMA index (Engelen 2017).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential effect modifier for insulin.	Yes
Number of prior tamoxifen therapies	Despite lowering body weight in obese women, tamoxifen may increase the incidence of diabetes as tamoxifen treatment has been shown to lead to early hepatic insulin resistance (Kloting 2020).	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of	Yes, potential confounder.	Yes, as number of prior anti-oestrogen therapy (fulvestra

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).		nt/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Number of prior anastrozole therapies	A targeted literature review found no reported evidence of a relationship between the number of prior anastrozole therapies and insulin. While no direct evidence exists, one study reported that in healthy men, anastrozole has been shown to reduce insulin sensitivity by lowering the glucose disposal rate during insulin infusion (Gibb 2016).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Number of prior letrozole therapies	A targeted literature review found no reported evidence of a relationship between the number of prior letrozole therapies and insulin. A study demonstrated that letrozole treatment resulted in a rapid increase in glucose and insulin levels after 1 week of treatment (Skarra 2017).	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	Unknown, due to lack of sufficient evidence. The evidence available suggests prior letrozole use may be potential effect modifier for insulin.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Number of prior exemestane therapies	A targeted literature review found no reported evidence of a relationship between the number of prior exemestane therapies and insulin. However, current exemestane use is associated with lower insulin sensitivity (Senkus-konefka 2007).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxif

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		to be a predictor of higher healthcare use in following years (Alkhaddo 2022).		en/anastrozole/letrozole/exemestane/any other oral SERD)
Number of prior oral selective oestrogen receptor degrader therapies	A targeted literature review found no reported evidence of a relationship between the number of prior oral selective oestrogen receptor degrader therapies and insulin.	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Prior chemotherapy	A targeted literature review found no reported evidence of a relationship between prior chemotherapy and insulin. Studies have reported that women may have increased blood glucose and insulin levels while on adjuvant chemotherapy, most likely due to increased weight or change in body composition (Buch 2019).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential effect modifier for TFST/PFS. There is a lack of sufficient evidence to determine if there is a relationship with insulin.	Yes
Concomitant use of other medications affecting blood glucose level, regardless of type	Systemic corticosteroids: prior research has reported systemic corticosteroids to induce insulin resistance, leading to elevated blood glucose levels and in some cases, steroid-induced diabetes mellitus. This effect has been reported to be associated with corticosteroids increasing gluconeogenesis (Geer 2014). Statins: There is mixed and inconclusive evidence regarding the association between statins and insulin intolerance. A prior systematic review provides evidence suggesting that statins might have an adverse effect on insulin sensitivity and increase insulin resistance (Dabhi 2023).	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of	Yes, potential confounder depending on concomitant medication.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	Quinolones: A study examining the effect of past quinolones exposure on diabetes risk reported that treatment with more than five courses of quinolones was associated with an increased risk of developing diabetes (Boursi 2015). Thiazide-like diuretics: Evidence suggests that patients receiving thiazide diuretics may have a higher risk of impaired glucose tolerance. Additionally, a higher incidence of diabetes has been reported across patients receiving thiazide diuretics (Zhang 2016). Atypical antipsychotics: A systematic review and meta-analysis of trials conducted in healthy volunteers reports that atypical antipsychotics may decrease insulin sensitivity and increase weight (Burghardt 2018). Calcineurin inhibitors: Prior research has suggested that calcineurin inhibitors, including tacrolimus and cyclosporine, decrease insulin sensitivity. In a study involving haemodialysis patients, treatment with tacrolimus and	sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).		

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	cyclosporine resulted in a 13% and 22% reduction in insulin sensitivity, respectively (Ozbay 2012).			
Concurrent metformin use	Metformin has antihyperglycemic effects and improves insulin sensitivity in patients with type 2 diabetes (Foretz 2023).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential effect modifier for insulin.	Yes
Comorbidity that interferes with blood glucose levels	Previous research has reported that patients with Cushing's disease are highly susceptible to developing impaired glucose tolerance and secondary diabetes as a result of hypercortisolism (Colao 2014). Pasireotide-induced hyperglycaemia has been linked to both reduced insulin secretion and diminished incretin response. Therefore, anti-hyperglycaemic treatment in patients with Cushing's disease receiving pasireotide should primarily target these two underlying mechanisms. (Colao 2014)	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of	Yes, potential confounder depending on comorbidity.	Yes

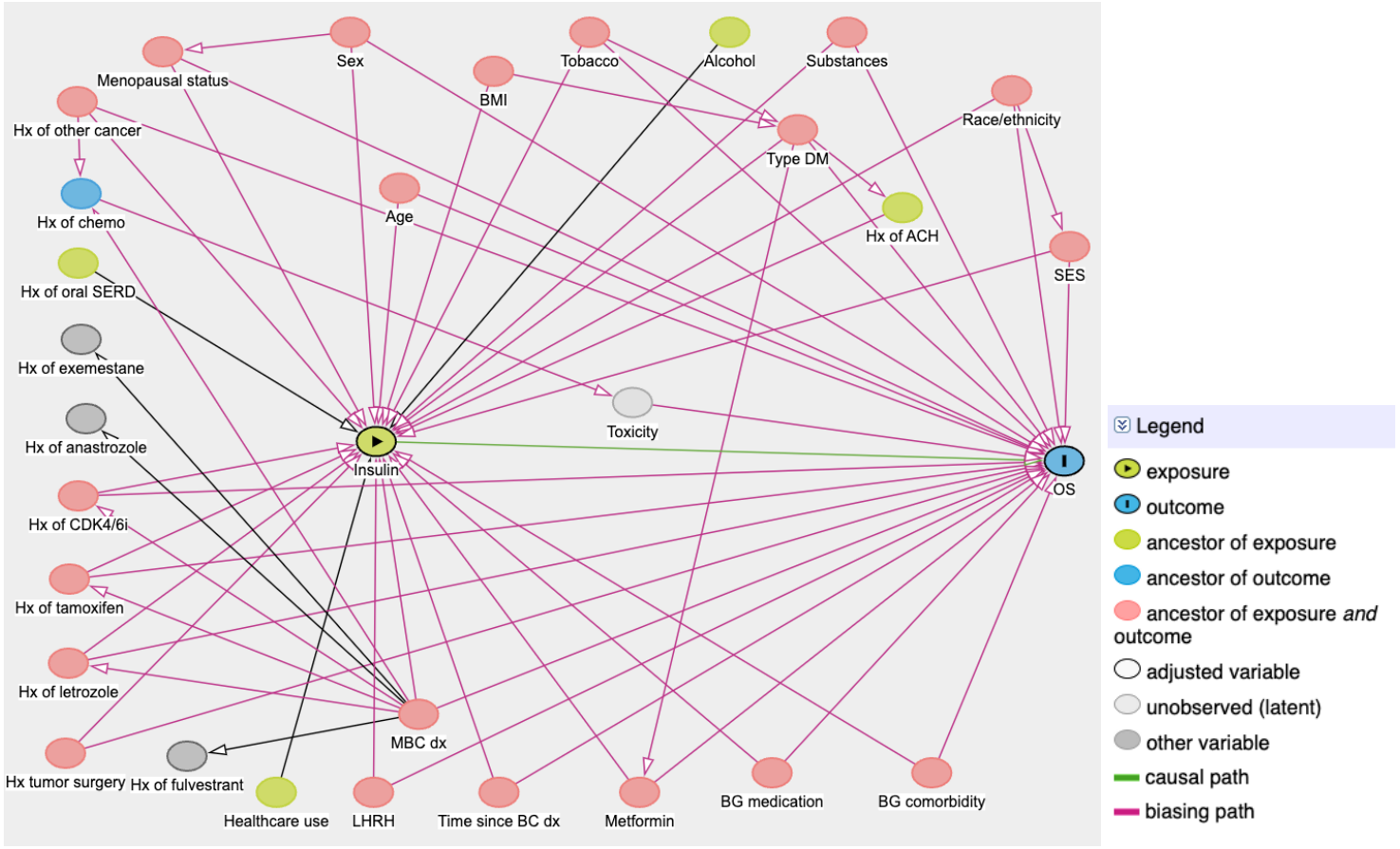
	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).		
Recent healthcare use: frequency of hospital-isations within past year	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in the following years (Alkhaddo 2022).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with TFST/PFS.	Yes, as poly-morbity marker
Recent healthcare use: emergency department visits within past year	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship	Yes, as poly-morbidity marker

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	with TFST/PFS.	
Recent healthcare use: outpatient physician visits within past year	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with TFST/PFS.	Yes, as poly-morbidity marker
Prior history of acute complications of	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose	Yes, potential effect modifier for insulin. There is a lack	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for TFST/PFS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
hyper-glycaemia	production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	of sufficient evidence to determine if there is a relationship with TFST/PFS.	

a. The source of information for the relationships was from published studies. Full citations are provided at the end of Appendix B.

Figure B4. Directed acyclic graph of the relationship among insulin, overall survival (OS), and baseline characteristics (Exploratory Objective 7)



Abbreviations: ACH, acute complications of hyperglycaemia; BC, breast cancer; BG, blood glucose; BMI, body mass index; CDK4/6i, CDK4/6 inhibitors; chemo, chemotherapy; DM, diabetes mellitus; dx, diagnosis; hx, history; LHRH, luteinizing hormone-releasing hormone; MBC, metastatic breast cancer; OS, overall survival; SERD, selective oestrogen receptor degrader; SES, socioeconomic status; tx, treatment.

Table B4. Supporting evidence among insulin, OS, and baseline characteristics (Exploratory Objective 7)

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Age at index date	Older age is associated with an increased risk of insulin resistance (Kolb 2023). Age-related changes have been reported to contribute to this increased risk including impaired beta-cell function, reduced insulin sensitivity, and decreased beta-cell response to incretins (Chang 2003). While circulating insulin levels may remain similar to those of younger individuals, the ability to effectively use insulin declines. This leads to a higher risk of glucose intolerance and type 2 diabetes in older adults (Zhao 2023).	Older age is associated with decreased OS in women with breast cancer worldwide (Howell 2022). Older age has been reported as a significant factor for diabetes mellitus–related mortality (Raghaven 2019).	Yes, potential confounder.	Yes
Sex	Insulin resistance and type 2 diabetes are more prevalent in males than in females (Geer 2009; Varlamov 2015). Oestrogen has been suggested to have a protective effect against insulin resistance in females (Varlamov 2015).	Among patients with breast cancer, men have lower OS compared to women (Wang 2019). Limited evidence is available, however, a United States real-world study reported women with breast cancer and diabetes have lower OS compared to women with breast cancer and no diabetes (Shao 2018).	Yes, potential confounder.	Yes
Race/ethnicity	Insulin resistance, prediabetes, and diabetes are more prevalent in racial and ethnic minorities compared to non-Hispanic Whites (Zhu 2019; Raygor 2019).	Non-Hispanic Black/African American women experience higher mortality rates compared to non-Hispanic White women (Giaquinto 2024; Holmes 2010). From 2011	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		to 2015, non-Hispanic Black women in the US had a 41% higher death rate from breast cancer than non-Hispanic White women (DeSantis 2017). Although racial and ethnic differences in diabetes mortality rates have recently declined in the United States, American Indian or Alaska Native and Black/African American populations continue to have higher mortality rates compared to White, Asian, and Latino populations (Nassereldine 2025). In the United States, race/ethnicity is related to factors such as access to healthcare and differences in treatment adherence or availability (Macias-Konstantopoulos 2023), which may indirectly affect OS.		
Body mass index (BMI)	High BMI and obesity are related to insulin resistance, with insulin resistance increasing incrementally according to BMI levels (Martinez 2017).	The relationship between BMI and OS among cancer patients remains unclear. Some studies have shown that high BMI and obesity are associated with worse overall survival among breast cancer patients, while other studies have reported no differences (Lammers 2024; Carter 2021).	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		Among women diagnosed with breast cancer, those with type 2 diabetes have been reported to present a higher risk of mortality in comparison to those without diabetes (Shao 2018). Additionally, patients with both obesity and diabetes mellitus have been reported to have worse disease-free survival and OS compared to those without obesity and diabetes (Buono 2017).		
Socioeconomic status (SES)	Individuals with lower SES exhibit a higher risk of diabetes compared to those with higher SES, suggesting a potential link to increased insulin resistance (Liu 2023). Data from the CDC (2019–2021) show that adults with family incomes above 500% of the federal poverty level have the lowest diabetes prevalence. Additionally, individuals with lower SES demonstrate poorer glycaemic control, a key factor associated with increased insulin resistance (Houle 2016).	Lower SES is associated with worse OS in breast cancer patients. Women with no education beyond high school have a 39% higher risk of breast cancer mortality compared to college graduates, while those with household incomes below 2.5 times the poverty level face a 44% higher risk compared to those with incomes ≥5 times the poverty level (Sprague 2011). Neighborhood-level deprivation independently predicts poorer survival outcomes in nonmetastatic breast cancer patients (Cheng 2021). Similarly, lower SES has been reported to significantly reduce OS in patients with	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		diabetes. Prior research indicates that both individual and neighbourhood-level SES factors contribute to mortality rates among DM patients (Rawshani 2016).		
Tobacco use	Smoking can elevate the risk of developing insulin resistance (Cho 2022; Bergman 2012).	Smoking at the time of breast cancer diagnosis may be associated with increased risk of breast cancer-specific and other-cause mortality. Quitting smoking is associated with improved survival among breast cancer patients who smoked at the time of diagnosis (Raghavendra 2022; Izano 2015). In individuals with type 2 diabetes, smoking has been reported as a prominent modifiable risk factor for OS. Specifically, smokers with diabetes have been reported to exhibit a higher risk of all-cause mortality compared to non-smokers. Additionally, smoking cessation may improve survival outcomes in patients with diabetes (Laurberg 2024).	Yes, potential confounder.	Yes
Alcohol abuse	In nondiabetic patients, moderate alcohol consumption may lower fasting insulin and HbA1c concentrations. In women, alcohol consumption might improve insulin sensitivity (Schrieks 2015).	Alcohol intake is not associated with all-cause mortality in patients with breast cancer and might actually reduce the risk of non–breast cancer death, with evidence also suggesting that alcohol consumption around the time of and up to six months after breast	Yes, potential effect modifier for insulin.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		cancer diagnosis is linked to lower all-cause mortality risk in obese women (Kwan 2010; Kwan 2023). In patients with diabetes, a study has shown no association between current alcohol consumption (>6 g/d) and mortality risk compared with lower alcohol consumption (<6 g/d) (Sluik 2012).		
Drug or substance abuse	Individuals with substance use disorders exhibit higher levels of insulin resistance than individuals with no substance use disorder (Ojo 2018).	Women with drug use disorders have a higher risk of fatal breast cancer and metastasized breast cancer, suggesting worse OS outcomes in this population (Dahlman 2021). Higher rates of diabetes complications, hospital admissions, and overall mortality have been reported among patients with both diabetes and a history of drug abuse (Aregbesola 2018; Saunders 2004).	Yes, potential confounder.	Yes
Type of diabetes	Type 1 diabetes is an autoimmune condition in which your immune system attacks the insulin-producing cells in your pancreas. It eventually results in a total lack of natural insulin. Insulin treatment is the foundational treatment for type 1 diabetes (Burrack 2017).	Patients with type 1 diabetes have a lower life expectancy than patients with type 2 diabetes (Tachkov 2020; Heald 2020; Arffman 2023). Patients with both breast cancer and any	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	Type 2 diabetes happens when insulin resistance is too strong for your pancreas to overcome, resulting in high blood sugar (Swinnen 2009). Insulin treatment is used across 12-30% of patients with type 2 diabetes (Jorgensen 2016, UK NHS 2023, US CDC NHANES 2018).	diabetes or type 2 diabetes have been shown to have poorer overall survival compared to patients with breast cancer and no diabetes (Zhou 2015; Zhao 2016; Shao 2018; Maskarinec 2019). A targeted literature review found no reported evidence of a relationship between type of diabetes in breast cancer patients and OS.		
Postmenopausal status (for female participants only)	Insulin and oestrogen may have a reciprocal relationship that significantly elevates the risk of endocrine-related cancers, particularly in postmenopausal women (Ferroni 2015). Insulin sensitivity has been reported to be lower in early postmenopausal women compared to premenopausal women (Mandrup 2018). In addition, menopausal status and risk for type 2 diabetes have been reported (Ahanchi 2024).	In 2018, the global age-standardized mortality rate was 4.1 per 100,000 for premenopausal breast cancer patients and 48.9 per 100,000 for postmenopausal breast cancer (Heer 2020). Prior research has reported that patients diagnosed with breast cancer and type 2 diabetes mellitus have an increased risk of mortality in comparison with those with breast cancer and no diabetes. This association was observed across various subgroups stratified by menopausal status. Specifically, postmenopausal women with type 2 diabetes exhibited a higher mortality risk compared to non-diabetic postmenopausal women (Shao 2018).	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Concurrent use of luteinizing hormone-releasing hormone (LHRH) agonist	Evidence suggests that the use of LHRH may influence insulin sensitivity. Transgender youth undergoing gonadotropin-releasing hormone agonist (GnRHa) treatment tend to have reduced insulin sensitivity, along with increased glycaemic markers and body fat, compared to cisgender peers with similar characteristics (Nokoff 2021). However, in patients with central precocious puberty, GnRHa treatment did not result in significant changes in insulin sensitivity after 6 and 12 months (Guo 2024). Additionally, patients receiving LHRH agonists demonstrated a less favourable progression of HOMA-IR (homeostasis model assessment-insulin resistance) compared to those who underwent bilateral orchiectomy (Zhang 2023).	LHRH has been shown to improve overall survival in breast cancer patients when used in combination with cancer drugs (Tancredi 2018). A targeted literature review found no reported evidence of a relationship between LHRH agonists and OS in patients with diabetes.	Yes, potential confounder.	Yes
Metastatic breast cancer diagnosis	Some treatments for metastatic breast cancer (e.g., alpelisib) are associated with an increased risk of developing diabetes and hyperglycaemia (André 2019).	Patients with metastatic breast cancer have lower overall survival compared to patients with lower stage (i.e., non-metastatic) breast cancer (Giaquinto 2024). Among patients with metastatic breast cancer, one study found no difference in 5-year OS in patients with diabetes compared to those without diabetes. Among those who	May be a potential confounder, depending on the selected treatment for metastatic breast cancer.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
		survived at least 8 years from metastatic diagnosis, patients with diabetes had a worse 10-year OS compared to those without diabetes (Cheung 2022).	For insulin, the relationship with metastatic breast cancer is mediated by the selected treatment for metastatic breast cancer.	
Time since advanced breast cancer diagnosis	Evidence suggests that insulin levels are elevated in breast cancer patients, with these insulin levels increasing with higher disease stage (Ferroni 2016).	OS varies for patients with recurrent versus de novo metastatic breast cancer, with patients with recurrent metastatic breast cancer having slightly worse OS compared to those with de novo metastatic breast cancer (Valachis 2022).	Yes, potential confounder.	Yes
History of other cancers	Patients with a cancer diagnosis are more likely to be insulin-resistant compared to healthy controls. This increased resistance leads to metabolic dysfunction, increased recurrence, and reduced survival (Marmol 2023). A targeted literature review found no reported	A history of previous cancer and diabetes has been reported to increase the overall mortality in breast cancer patients (Wu 2015).	Yes, potential effect modifier for OS. There is a lack of sufficient evidence to determine if there is a	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	evidence of the relationship between a history of other cancers and insulin.		relationship with insulin.	
Previous CDK4/6 inhibitors (CDK4/6i)	While direct evidence linking CDK4/6i to insulin resistance is limited, a preclinical study demonstrated that CDK4 enhances insulin sensitivity in insulin-responsive tissues such as adipose and liver in mouse models (Stamateriset 2023).	One study reported that combining first-line endocrine therapy with a CDK4/6i resulted in a 41% reduction in mortality rates compared to endocrine therapy alone (Goyal 2023). Treatment with abemaciclib plus fulvestrant resulted in a statistically significant and clinically meaningful median OS improvement compared to placebo + fulvestrant (Sledge Jr. 2020).	Yes, potential confounder.	Yes
Previous fulvestrant use	A targeted literature review found no reported evidence of a relationship between prior fulvestrant use and insulin.	A targeted literature review found no reported evidence of a relationship between prior fulvestrant use and OS. However, fulvestrant has been shown to reduce OS in breast cancer patients who are actively receiving fulvestrant (Howell 2004; Howell 2005; Di Leo 2014).	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
				other oral SERD)
Prior primary tumour surgery (e.g., mastectomy, lumpectomy)	It has been found that breast surgery resulted in increased whole-body protein breakdown and synthesis, independent of the presence of cancer. Various factors may contribute to the upregulated protein turnover following surgery, including an enhanced systemic inflammatory response and elevated insulin resistance, as reflected by an increased HOMA index (Engelen 2017).	Patients with breast cancer who receive surgery have been shown to have better OS compared to those who do not receive surgery (Carter 2021).	Yes, potential confounder.	Yes
Number of prior tamoxifen therapies	Despite lowering body weight in obese women, tamoxifen may increase the incidence of diabetes as tamoxifen treatment has been shown to lead to early hepatic insulin resistance (Kloting 2020).	Ten years of tamoxifen treatment has been shown to reduce breast cancer recurrence and improve survival (Davies 2013).	Yes, potential confounder.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Number of prior anastrozole therapies	A targeted literature review found no reported evidence of a relationship between the number of prior anastrozole therapies and insulin. While no direct evidence exists, one study reported that in healthy men, anastrozole has been shown to reduce insulin sensitivity by lowering the glucose disposal rate during insulin infusion (Gibb 2016).	A targeted literature review found no reported evidence of a relationship between the number of prior anastrozole therapies and OS. Anastrozole has been shown to improve survival in patients with breast cancer, either alone or in combination with other therapies (Kümler 2016; Iwase 2023).	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Number of prior letrozole therapies	A targeted literature review found no reported evidence of a relationship between the number of prior letrozole therapies and insulin. A study demonstrated that letrozole treatment resulted in a rapid increase in glucose and insulin levels after 1 week of treatment (Skarra 2017).	A targeted literature review found no reported evidence of a relationship between the number of prior letrozole therapies and OS. However, an additional 5 years of treatment with the aromatase inhibitor letrozole improved survival outcomes in patients with breast cancer (Jin 2012).	Unknown, due to lack of sufficient evidence. The evidence available suggests prior letrozole use may be potential confounder.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Number of prior exemestane therapies	A targeted literature review found no reported evidence of a relationship between the number of prior exemestane therapies and insulin. However, current exemestane use is associated with lower insulin sensitivity (Senkus-konefka 2008).	A targeted literature review found no reported evidence of a relationship between the number of prior exemestane therapies and OS. Exemestane has been shown to have comparable OS to other breast cancer treatments (Kümler 2016).	Unknown, due to lack of sufficient evidence.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)
Number of prior oral selective oestrogen receptor degrader therapies	A targeted literature review found no reported evidence of a relationship between the number of prior oral selective oestrogen receptor degrader therapies and insulin.	Oral selective oestrogen receptor degrader therapies therapy is associated with improved survival outcomes in patients with breast cancer (Neupane 2024). There is a lack of direct research specifically evaluating the association of oral selective oestrogen receptor degrader therapies therapy and OS in patients with both diabetes and metastatic breast cancer.	Yes, potential effect modifier for OS. There is a lack of sufficient evidence to determine if there is a relationship with insulin.	Yes, as number of prior anti-oestrogen therapy (fulvestrant/tamoxifen/anastrozole/letrozole/exemestane/any other oral SERD)

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Prior chemotherapy	A targeted literature review found no reported evidence of a relationship between prior chemotherapy and insulin. Studies have reported that women may have increased blood glucose and insulin levels while on adjuvant chemotherapy, most likely due to increased weight or change in body composition (Buch 2019).	Currently, there is a lack of direct research specifically evaluating the association of prior chemotherapy on OS in patients with both diabetes and metastatic breast cancer. However, there is some indirect evidence: 1. The length of OS has been shown to decrease with each successive round of chemotherapy (Tolaney 2024). 2. Patients who have breast cancer and diabetes are at increased risk of chemotherapy-related toxicities compared with nondiabetic patients who are receiving chemotherapy and have higher all-cause mortality (Srokowski 2009).	Yes, potential effect modifier for OS. There is a lack of sufficient evidence to determine if there is a relationship with insulin.	Yes
Concomitant use of other medications affecting blood glucose level, regardless of type	Systemic corticosteroids: prior research has reported systemic corticosteroids to induce insulin resistance, leading to elevated blood glucose levels and in some cases, steroid-induced diabetes mellitus. This effect has been reported to be associated with corticosteroids increasing gluconeogenesis (Geer 2014). Statins: There is mixed and inconclusive evidence regarding the association between	The use of sulfonylureas has been associated with poorer survival outcomes in breast cancer patients with diabetes (Baglia 2019).	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	statins and insulin intolerance. A prior systematic review provides evidence suggesting that statins might have an adverse effect on insulin sensitivity and increase insulin resistance (Dabhi 2023). Quinolones: A study examining the effect of past quinolones exposure on diabetes risk reported that treatment with more than five courses of quinolones was associated with an increased risk of developing diabetes (Boursi 2015). Thiazide-like diuretics: Evidence suggests that patients receiving thiazide diuretics may have a higher risk of impaired glucose tolerance. Additionally, a higher incidence of diabetes has been reported across patients receiving thiazide diuretics (Zhang 2016). Atypical antipsychotics: A systematic review and meta-analysis of trials conducted in healthy volunteers reports that atypical antipsychotics may decrease insulin sensitivity and increase weight (Burghardt 2018).			

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	Calcineurin inhibitors: Prior research has suggested that calcineurin inhibitors, including tacrolimus and cyclosporine, decrease insulin sensitivity. In a study involving hemodialysis patients, treatment with tacrolimus and cyclosporine resulted in a 13% and 22% reduction in insulin sensitivity, respectively (Ozbay 2012).			
Concurrent metformin use	Metformin has antihyperglycaemic effects and improves insulin sensitivity in patients with type 2 diabetes (Foretz 2023).	Concurrent metformin use has been associated with decrease in all-cause mortality in patients with breast cancer (Zhao 2016, Dowling 2015, Baglia 2019, Ferroni 2015, Yang 2016 and Tang 2018)	Yes, potential confounder.	Yes
Comorbidity that interferes with blood glucose levels	Previous research has reported that patients with Cushing's disease are highly susceptible to developing impaired glucose tolerance and secondary diabetes as a result of hypercortisolism (Colao 2014). Pasireotide-induced hyperglycaemia has been linked to both reduced insulin secretion and diminished incretin response. Therefore, anti-hyperglycaemic treatment in patients with Cushing's disease receiving pasireotide	Diabetes in individuals with acromegaly have been reported to be associated with a higher morbidity and mortality (Storman 2024). Among breast cancer patients, patients with cirrhosis have a higher mortality rate compared to patients without cirrhosis. Among women over 60 years of age with breast cancer, presence of hyperthyroidism has been shown to have an increased risk of death compared to those without thyroid	Yes, potential confounder.	Yes

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
	should primarily target these two underlying mechanisms (Colao 2014).	disease (Jogendran 2025). Chronic proinflammatory conditions and oxidative stress induced by impaired glucose metabolism have been reported to promote tumour initiation and progression (Zhao 2016). Among breast cancer patients, OS has been inversely associated with existing comorbidity including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease (Baglia 2019).		
Recent healthcare use: frequency of hospital-isations within past year	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in the following years (Alkhaddo 2022).	A targeted literature review found no reported evidence of the relationship between frequency of hospitalizations and OS among patients with diabetes and metastatic breast cancer. However, patients who have both cancer and diabetes have been shown to have higher healthcare resource utilization than those with cancer only (Jo 2024).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with OS.	Yes, as poly-morbidity marker

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Recent healthcare use: emergency department visits within past year	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	A targeted literature review found no reported evidence of the relationship between the frequency of emergency department visits and OS among patients with diabetes and metastatic cancer. A study found that patients with diabetes had higher utilization of emergency department services and a higher frequency of unplanned inpatient admissions compared to those without diabetes. Additionally, poor glycemic control was associated with increased healthcare utilization and adverse effects during chemotherapy (Phillips 2023).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with OS.	Yes, as poly-morbidity marker
Recent healthcare use: outpatient physician visits within past year	Patients who have insulin-dependent diabetes have higher healthcare utilization and higher spending than patients without diabetes. Higher numbers of healthcare use (composite of hospitalizations, emergency department visits, and outpatient visits) have been shown to be a predictor of higher healthcare use in following years (Alkhaddo 2022).	A targeted literature review found no reported evidence of the relationship between the frequency of outpatient visits and OS among patients with diabetes and metastatic cancer.	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with OS.	Yes, as poly-morbidity marker

	Type and strength of evidence for a relationship with insulin[a]	Type and strength of evidence for a relationship with OS[a]	Confounder or effect modifier?	Priority covariate ? (Yes/No)
Prior history of acute complications of hyperglycaemia	In patients with type 1 diabetes, diabetic ketoacidosis occurs as a consequence of insufficient insulin. The absence of insulin production triggers significant breakdown of body tissues, resulting in elevated glucose production, increased breakdown of glycogen and fats, and muscle protein breakdown. These processes lead to high blood sugar levels and osmotic diuresis (Castellanos 2020). HHS is marked by extreme hyperglycaemia, high osmolality, and dehydration, but without significant ketoacidosis. These metabolic disturbances arise from a lack of sufficient insulin and a rise in counterregulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone (Kitabchi 2009).	There is limited evidence on the relationship of a prior history of acute complications of hyperglycaemia and OS in breast cancer patients. A Dutch prospective study found that poor glycemic control before breast cancer diagnosis can lead to poorer OS (Haan-Du 2023). Other studies have reported that patients with pre-existing diabetes at breast cancer diagnosis have poorer OS compared to patients with no diabetes, however, the presence of acute complications of hyperglycaemia were not described (Peairs 2011).	Yes, potential effect modifier for insulin. There is a lack of sufficient evidence to determine if there is a relationship with OS.	Yes

a. The source of information for the relationships was from published studies. Full citations are provided at the end of Appendix B.

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Appendix C Other potentially feasible back-up data sources

Order of priority	Data source (Country)	Estimated N of patients under best-case scenario[a]	Estimated N of patients under worst- case scenario[b]	Reason for Initial Non-Selection
1	PHARMO (Netherlands)	160	80	The sample size available in this database according to the patient counts provided is limited and would require several linkages that may reduce eligible numbers further
2	VID (Spain)	416	208	Hospital-administered medications are not mandatorily reported by hospitals to VID, posing a risk of insufficient patient identification.
3	SIDIAP (Spain)	410	205	Treatment information includes drugs prescribed in primary care and hospital medications for outpatient dispensing, posing a risk of under identifying the exposure of interest.

VID: Valencia Health System Integrated Database; SIDIAP: Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

[a] Best case scenario: 80% drug uptake

[a] Worst case scenario: 40% drug uptake

Appendix D ENCePP checklist for study protocols

Study title: CAPIseid

Safety and Effectiveness of Capivasertib with Fulvestrant in Patients with Advanced Breast Cancer and Diabetes – an Observational Study using Secondary Real-World Data

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[16]	☒	☐	☐	6 and 9.2.2.1
1.1.2 End of data collection[17]	☒	☐	☐	6 and 9.2.2.1
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Progress reports not requested by the EMA

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2 and 8.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2, 8.3, and 8.4
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Given the study objectives, analyses will be descriptive, with no hypothesis testing.

[16] Date from which information on the first study subject is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[17] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.2.1.1
	4.2.3 Country of origin	☒	☐	☐	9.2.1.1 and 9.3.4
	4.2.4 Disease/indication	☒	☐	☐	9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.2.5
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1.1 and 9.2.1.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.2
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.2
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.2

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.2
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Given the descriptive nature of the study objectives, all patients are exposed to the drug: no comparative analysis is contemplated.

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.3
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.3
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.3
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.3.4

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.5.4 and 9.9
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.3.3 and 9.3.4 and Appendix B

Comments:

Covariates will be added in the models for adjusted analysis if sample size permits, and specific stratifications

will also account for effect modifiers

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.2 and 9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.3 and 9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.4 and 9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4.2
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4.2
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4.2
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.2
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.2
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Full detail on the type and availability of information from the data source(s) has been provided in a previous Feasibility Assessment Report and will depend on the final selection of data sources. Specific codes are provided for exposure, and primary outcomes. The coding systems are described but will be mapped to the relevant dictionaries during the SAP development. Linkage method between data sources is not described as they will not be linked with each other.

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.2, 9.7.3 and 9.7.4
10.4	Are stratified analyses included?	☒	☐	☐	9.7.5
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.8
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

No sensitivity analyses will be performed. Covariates will be added in the models for adjusted analysis if sample size permits.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

The study will be submitted to ethical review boards for approval wherever required by local laws.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD (AstraZeneca)

Date:

Signature: _____