Observational Study Information/ Post Authorization Safety Study (PASS)

Acronym/Title	PRostAte Cancer vTe In SwEden: epidemiology and anticoagulation treatment of VTE **PRACTISE**
Protocol version and date	v 1.0 / 12 May 2019
IMPACT study number	20653
Study type / Study phase	Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN, B01A E07 DABIGATRAN ETEXILATE)
Medicinal product	Xarelto (Rivaroxaban), Eliquis (Apixaban), Dabigatran etexilate (Pradaxa)
Product reference	EU/1/08/472/001-041
Procedure number	EMEA/H/C/00944
Study Initiator and Funder	**Bayer AG**, Müllerstrasse 173, 13353 Berlin
Research question and objectives	This study aims to identify what the current landscape of VTE events and its treatment is for prostate cancer patients in Sweden.
Country(-ies) of study	Sweden
Author	CCI

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	CCI

The study will be conducted in compliance with the protocol

and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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2. List of abbreviations

ATC	Anatomical Therapeutic Chemical (Classification System)
CALLISTO	Cancer Associated thrombosis – expLoring soLutions for patients through Treatment and Prevention with RivarOxaban
CAT	Cancer associated thrombosis / Cancer associated VTE event
CDR	Cause of Death Register
COPD	Chronic obstructive pulmonary disorder
DVT	Deep vein thrombosis
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
LISA	Swedish longitudinal integration database for health insurance and labour market studies
LMWH	Low molecular weight heparin
MAH	Marketing Authorization Holder
NOAC	Non-vitamin K oral anticoagulation
NPCR	National Prostate Cancer Register
NPR	National Patient Register
NSAIDs	Nonsteroidal anti-inflammatory drugs
N/A	Not Applicable
OAC	Oral Anticoagulant
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PCa	Prostate cancer
PCBaSe	Prostate Cancer Database Sweden
PDR	Prescribed Drug Register
PE	Pulmonary embolism
PSA	Prostate specific antigen
QPPV	Qualified Person Responsible For Pharmacovigilance
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VTE	Venous thromboembolism
VKA	Vitamin K anticoagulants

3. Responsible parties

3.1 Study initiator and funder

Role: OS Conduct Responsible
Name: CCI
E-mail: CCI

Role: Qualified Person responsible for Pharmacovigilance (QPPV)
Name: CCI

Role: MAH contact person (Regulatory Affairs)
Name: CCI

Role: OS Safety Lead
Name: CCI

Role: OS Medical Expert
Name: CCI

Role: OS Medical Expert
Name: CCI

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Role: OS Epidemiologist
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Contact details of the responsible parties at Bayer AG are available upon request.

3.2 Collaborator(s)/External partner(s)/Committee(s)

CCI	Consultant Urologist	CCI	Principle Investigator

CCI	Senior Researcher	CCI	Senior statistician

4. Abstract

Acronym/Title	PRostAte Cancer vTe In SwEden: epidemiology and anticoagulation treatment of VTE **PRACTISE**
Protocol version and date	1.0, 12 May 2019
IMPACT study number	20653
Study type / Study phase	Observational, Phase IV
Author	CCI
Rationale and background	Patients with cancer are at a significantly increased risk of experiencing a venous thromboembolism (VTE). VTE is defined by deep vein thrombosis (DVT) or pulmonary embolism (PE) and is a leading cause of morbidity and death among cancer patients. A variety of anti-coagulants are available to treat VTE with treatments differing between cancer and non-cancer patients. The use of such treatments has changed over time with a shift towards the increased use of non-vitamin K oral anticoagulants (NOACs) due to their ease of administration. An increasing success of cancer treatments results in significant extension of survival, even in cases of metastatic diseases; therefore prevention of debilitating thrombotic events in these patients is gaining importance. Although prostate cancer (PCa) belongs to the cancer types with a relatively low risk of VTE, the burden of patients with PCa is high (the commonest cancer type in men); thus adequate treatment and secondary prophylaxis of VTE in this population is of clinical and public health importance.
Research question and objectives	This study aims to identify the current landscape of VTE events and its treatment in prostate cancer (PCa) patients in Sweden. The objectives include: **Primary objective** Among <u>all men with PCa</u>: 1. To describe socio-demographic and clinical characteristics at the date of an incident PCa diagnosis. 2. To estimate the occurrence of cancer-related VTE. 3. To describe the cancer therapies in PCa at the initial

	time after diagnosis. Among men with PCa and a first cancer-related VTE event: 4. To characterize the long-term anticoagulation treatment including choice of drug and duration of treatment. 5. To estimate the occurrence of recurrent VTE events by long-term anticoagulation treatment (LMWH, VKA or NOACs) and its estimated duration (up 3 months, 3-6 months, more than 6 months). 6. To determine the time between a first cancer-related and a recurrent VTE event. 7. To estimate the occurrence of post-VTE bleeding events leading to hospitalization, and mortality by anticoagulation treatment. **Secondary objectives** Among PCa-free men from the general population: 8. To describe socio- demographic and clinical characteristics at the date of inclusion into the database. 9. To estimate the occurrence of VTE events.
Study design	This is a retrospective cohort study based on an existing on-going registry of men with PCa and randomly selected men without PCa in Sweden.
Population	Included in this study will be all men with newly diagnosed PCa between 2007 -2016 as well as PCa-free men who have been frequency-matched to incident cases of PCa by birth year and county of residence.
Variables	Variables include characteristics of PCa and (where possible) PCa-free men related to socio-demographic and clinical parameters such as comorbidities, cancer-specific characteristics and therapies including anticoagulation therapies. Outcomes of interest include: In men with PCa: 1. DVT or PE; 2. Bleeding events leading to hospitalization; 3. Mortality. In PCa-free men: 4. DVT or PE.
Data sources	This study will use data from a research database, PCBaSe, which is a comprehensive database from Sweden encompassing information from over 180,000 prostate cancer patients identified from the national Cancer register and around 900,000 PCa-free men from the general population of Sweden (frequency matched on birth year and county) and selected

	from national population registers.
Study size	The full PCBaSe database contains data on 185 729 men diagnosed with PCa since 1998 and more than 900 000 PCa-free men. This study will utilize the period from 2007 and contain approximately 98 000 men with PCa and 500 000 PCa-free control men.
Data analysis	<u>Among men with PCa:</u> Descriptive statistics will be used to define the socio-demographic and clinical characteristics of all PCa patients at the date of incident PCa diagnosis (baseline) as well as main types of cancer therapies. The occurrence (incidence rate) of cancer-related VTE events, split into PE and DVT events will be also described by Kaplan-Meier curves in different strata. The anticoagulation (AC) treatment received by the PCa patients after the first cancer-related VTE event at an out-patient long-term basis will be reported by type of anticoagulation (LMWH, VKAs and NOACs) and its estimated duration (up to 3 months, 3-6 months, more than 6 months). Among this sub-group of patients, the occurrence (incidence rates) of recurrent VTE and the time to recurrence, post-VTE bleeding leading to hospitalisation, and mortality will be calculated by the type and duration of AC treatment. <u>Among PCa-free men:</u> Descriptive statistics will be used to define the socio-demographic and clinical characteristics of PCa-free men at the time of inclusion in PCBaSe (baseline). The occurrence of VTE events, split into PE and DVT events will be also described by Kaplan-Meier curves in different strata.
Milestones	The project is planned to begin in May 2019 and will end in April 2020.

5. Amendments

<None>

6. Milestones

Table 1: Milestones

Milestone	Planned date
Study start	May 2019
Submission of application form for approval from Research Ethics Board Uppsala	March 2019
Development of a study file containing the data	June 2019
Upload study file Research Platform	June 2019
Registration in the EU PAS register	April 2019
Study end	December 2019
Final report of study results	April 2020

7. Rationale and background

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a leading cause of morbidity and death for cancer patients. Approximately 20% of all VTE cases occur in patients with cancer and more than 20% of patients with cancer will experience VTE (1). There is some evidence that that patients with both cancer and VTE were at a four times increased risk of developing recurrent thromboembolic complications and twice as likely to develop major bleeding during anticoagulant (AC) treatment than those without cancer. This risk varies during the course of the disease with the highest risk immediately after the initiation of chemotherapy (2). Risk factors for developing VTE in cancer patients is multifold and is determined by patient-related, tumor-related, cancer treatment - related and biomarker-related factors. Hence, the population of cancer patients as well as the choice of cancer treatment is highly heterogeneous (3); patients' individual responses to cancer treatment are highly variable often prompting physicians to make tailored decisions regarding the choice of an anticoagulant and the duration of therapy.

Low-molecular-weight heparin (LMWH) is the standard initial treatment for cancer-associated VTE (CAT) (4). For long term treatment, a vitamin K antagonist (VKA), warfarin, is the recommended treatment for several types of cancer including prostate, lung and breast cancers (5). More recently, the role of non-vitamin K oral anticoagulant agents (NOACs) is being assessed in several clinical trials. As the risk of thrombotic event depends on the 'cancer activity' that is variable in different

cancers, no reliable data are available on the risk-benefit balance of the anticoagulation therapy extended beyond 6 months in cancer patients.

An increasing success of cancer treatments results in significant extension of survival, even in cases of metastatic diseases; therefore prevention of debilitating thrombotic events in these patients is gaining importance. Although prostate cancer (PCa) belongs to the cancer types with a relatively low risk of VTE, the burden of patients with PCa is high; thus adequate treatment and secondary prophylaxis of VTE in this population is of clinical and public health importance.

A recent retrospective study analyzing the data from a large US administrative database showed that the majority of prostate cancer patients received warfarin for VTE treatment with an equal proportions of patients receiving LMWH and NOACs, of which rivaroxaban was mostly common. Reduced hazard of bleeding for NOACs versus warfarin and for NOACs versus LMWH was observed (6). An analysis of RIETE Registry showed a relatively low risk of bleeding but a substantial rate of VTE recurrences in PCa patients (7); however the patients' sample was limited and geographically diverse due to the nature of the Registry.

Rivaroxaban (Xarelto) is indicated for the treatment of DVT, PE and prevention of recurrence; its label that does not have a warning regarding its use in patients with active cancer. Demonstrating opportunities for use of oral anticoagulants such as rivaroxaban in cancer patients is thus essential.

The on-going 'Cancer Associated thrombosis – expLoring soLutions for patients through Treatment and Prevention with RivarOxaban' (CALLISTO) programme encompasses several initiatives, including both clinical trials as well as non-interventional studies and a survey. Nevertheless, several gaps in knowledge remain as some of the research questions will not be feasible to answer within the planned activities. Real-life data reflecting current practice are needed to address those gaps. In particular, there is a need to describe:

- Clinical characterization (staging, presence of metastasis, types of cancer therapy etc.) of cancer patients with an emphasize on most common cancers (prostate, lung, breast, colorectal etc.) in order to understand risk of thrombotic and bleeding events in this population.
- AC treatment of patients with cancer experiencing an acute VTE event, its duration, dose variation and switching against the background of different cancer treatment in order to understand prescription patterns of clinicians.
- Risk of recurrent thrombotic and bleeding events after the initiation of different AC therapies.

Non-interventional observational research data originating from cancer cohorts can provide relevant real-world clinical evidence and would be important complementing data from RCT´s . As cancer patients are very heterogeneous in their clinical characteristics, it would be extremely difficult to construct a trial addressing all questions of interest; hence an observational study design based on data from clinical practice will provide a deeper understanding the consequences of current clinical practice for anticoagulation approaches in treatment of cancer patients and how the choice of a regimen influences risk of thrombotic and bleeding events. Generated evidence will support physicians in their treatment decisions.

Sweden offers a unique opportunity to study routine clinical practice and associated outcomes in cancer patients as notification of cancer has been mandatory in all Nordic countries for decades, and the Swedish Cancer Registry was established already in 1958. The completeness of data on incident cases is considered to be very high.

The study will focus on prostate cancer (PCa), the most common cancer form in men. It will be based on the data from the Prostate Cancer Database Sweden (PCBaSe), containing information from many national registries other than the Cancer register, such as Patient register, Dispensed drug register, Cause of Death registry and Population registries. In total, over 180,000 newly diagnosed cases of PCa in Sweden between 1996 to 2017 (currently available) together with a random sample of about 900,000 men from the general population without PCa in the same age group and area of residence as prostate cancer cases, are included into the PCBaSe.

8. Research questions and objectives

This study aims to identify the current landscape of VTE events and its treatment in prostate cancer (PCa) patients in Sweden.

8.1 Primary objective

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Among all men with PCa:

- To describe socio-demographic and clinical characteristics at the date of an incident PCa diagnosis.
- To estimate the occurrence of cancer-related VTE.
- To describe the cancer therapies in PCa at the initial time after diagnosis.

Among men with PCa and a first cancer-related VTE event:

- To characterize the long-term anticoagulation treatment including choice of drug and duration of treatment.
- To estimate the occurrence of recurrent VTE events by long-term anticoagulation treatment (LMWH, VKA or NOAC) and its estimated duration (up 3 months, 3-6 months, more than 6 months).
- To determine the time between a first cancer-related and a recurrent VTE event.
- To estimate the incidence rates of post-VTE bleeding events leading to hospitalization, and mortality by anticoagulation treatment.

8.2 Secondary objectives

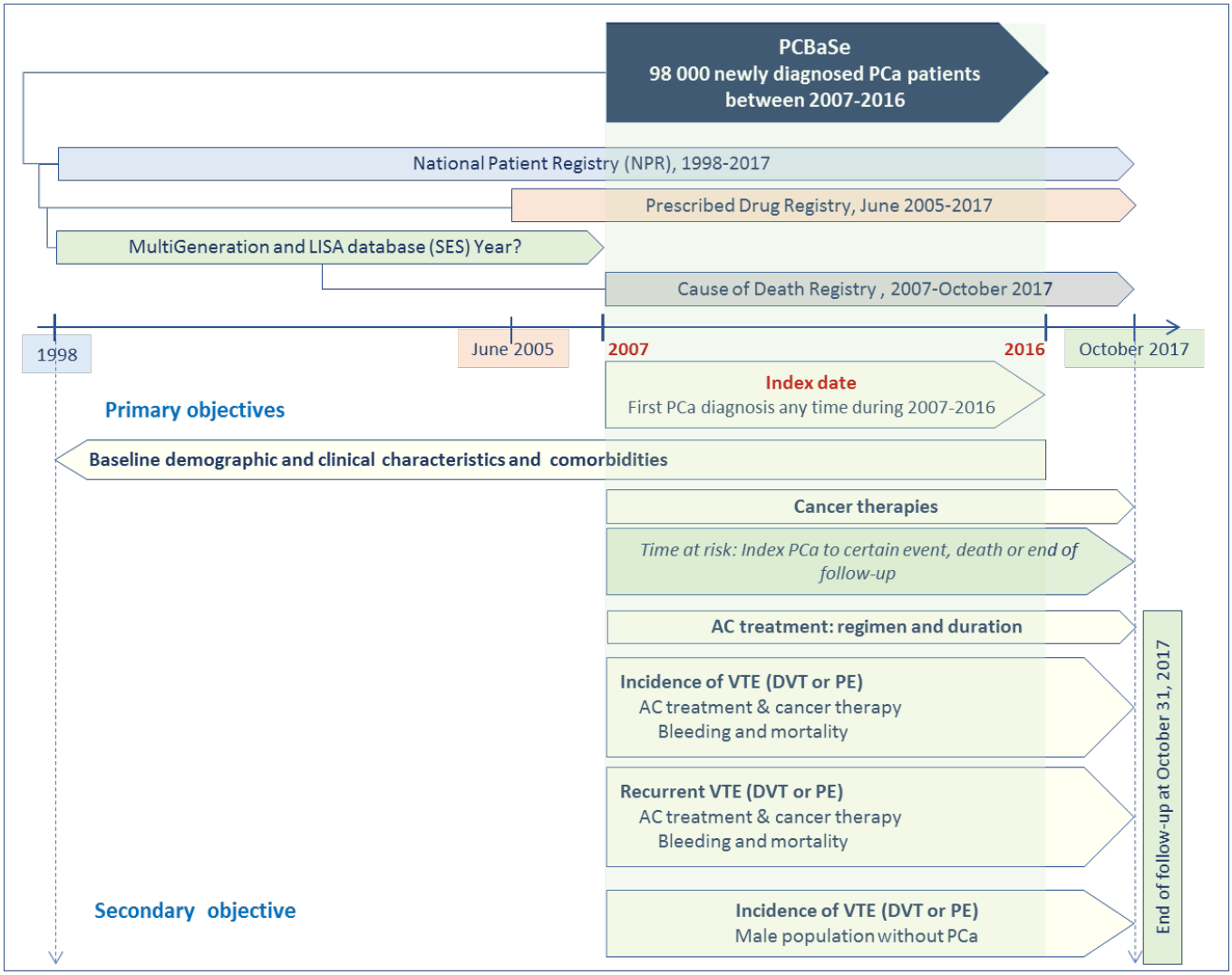
Among PCa-free men from the general population:

- To describe socio- demographic and clinical characteristics at the time of inclusion into the database.
- To estimate the occurrence of VTE events.

9. Research methods

Overview of study methodology and the process through which the study cohort will be selected is outlined in Figure 1.

Figure 1. Overview of study methodology



9.1 Study design

This is a retrospective cohort study based on on-going registry of men with PCa as well as men without PCa (PCa-free men) in Sweden.

9.2 Setting

9.2.1 Study population

The population will be selected from the PCBaSe 4.0 database that contains patients with PCa as well as PCa-free men from the general population in Sweden who have been frequency-matched to incident cases of PCa by birth year and county of residence. A sub-population will include PCa patients with a cancer-related VTE event (8).

9.2.2 Study time frame

The study will capture the observation period of 2007-2016, hence focusing on the period when the Prescribed Drug Registry became available.

9.2.3 Selection criteria from PCBaSe

PCa patients

Inclusion criteria

Initially all patients newly diagnosed with PCa between 2007-2016 with at least one year before the end of follow up date (31 December 2017) will be included.

From this population, a sub-population of PCa patients with a first cancer-related VTE event will be selected.

Exclusion criteria

No exclusions will be made.

Men without PCa

Inclusion criteria

All PCa-free men included in PCBaSe who are randomly selected from the general population of Sweden with the same birth year and county of residence of PCa patients diagnosed between 2007-2016.

Exclusion criteria

A PC free men diagnosed with a prostate cancer during the follow up will be identified and censured.

9.2.4 Representativeness

The study cohort will include 98% of all newly diagnosed PCa patients in Sweden between 2007-2016 (8). PCBaSe contains information from multiple national health care registries such as The Patient Registry, The Prescribed Drug Registry, The Cause of Death Registry, The Registry of the Total Population and Population Changes, The Registries of Immigration and Emigration and The Longitudinal database on socioeconomic factors (LISA) with data on educational level, marital status, and income.

Included in the full dataset (starting from 1998) are PCa-free men selected from the general population of Sweden for every PCa incident case (in the ratio 1 PCa patient : 5 PCa-free men) who were frequency-matched on birth year and county of residence. To date, over 180,000 incident cases of PCa, together with 900,000 PCa-free men are included in the PCBaSe. Since all PCa and non-PCa patients have the same source of information on their clinical and demographic characteristics, comparisons can be made with consideration of these baseline characteristics between the populations.

This study consisting of all men with PCa and men without PCa in Sweden observed during 2007-2016 is clearly representative of treatment patterns and occurrences of outcomes of interest in Sweden during period of time.

9.3 Variables

Baseline is defined as:

- in men with PCa: a date of an incident PCa
- in PCa-free men: a date of selection of PCa-free men (who are alive) into the database corresponding to the date of diagnosis for the index case

Index date is defined as:

- in men with PCa:
    - a date of a first cancer-related VTE event that is a VTE event related to the diagnosis of PCa (to define the relatedness, different time-frames will be specified and applied);
- in PCa-free men:
    - a date of selection into the database for defining a first recorded VTE event.

9.3.1 Characteristics of PCa and (where possible) PCa-free men:

- Age at PCa diagnosis
- Age at VTE
- Charlson Comorbidity Index (CCI) based on discharge diagnosis (including variables included into CCI)
- Specific events at baseline (that occurred prior and at the baseline) define by ICD codes for:
    - intracranial bleeding
    - gastrointestinal bleeding
    - urogenital bleeding
    - ischaemic heart disease
    - myocardial infarction

- heart failure
- stroke (ischaemic and haemorrhagic)
- transient ischaemic attack
- atrial fibrillation
- renal impairment
- renal failure
- depression
- hypertension
- hyperlipidaemia
- diabetes
- asthma
- COPD
- other cancers than PCa
- previous VTE events

- Co-medications at baseline (120 before the index event) and during follow-up (from index date)
  - Antiplatelets
  - Proton pump inhibitors
  - NSAIDs
  - SSRIs
  - Oral steroids
  - Antibiotics
  - Lipid-lowering medications
- PCa/specific parameters:
  - County
  - Hospital type (university, non-university)
  - Clinical TNM staging
  - PSA (at time of PCa diagnosis)
  - PCa risk categories (defined at diagnosis according to a modification of the National Comprehensive Cancer Network Guideline):
    a. Low-risk: T1-2, Gleason score of 2–6 and PSA < 10 n/ml
    b. Intermediate-risk: T1-2, Gleason score 7 and/or PSA 10–20 ng/ml
    c. High-risk: T3 and/or Gleason score 8–10 and/or PSA 20–50 ng/ml

d. Regionally metastatic T4 and/or N1 and/or PSA 50–100 ng/ml

e. Distant Metastatic disease: or M1 and/or PSA > 100 ng/ml; however PSA cutoff to be discussed

- Anti-cancer therapies that are delivered by a filled out-patient prescription

9.3.2 For patients in the VTE sub-population:

The outcome of interest is therapy with anticoagulants dispensed from pharmacies (no information is available on drugs delivered in- hospital), hence the analysis focuses on anticoagulant therapies for which an out-patient prescription has been filled, i.e. long-term therapy. A full list of the treatments with their relative ATC codes is found in Annex 3. The anticoagulation treatments that will be assessed include:

1. LMWH (after hospital discharge, long-term use)
2. VKAs
3. NOACs

9.3.3 Outcomes of interest

In men with PCa:

1. DVT or PE
2. Bleeding events leading to hospitalisation
3. Mortality

In PCa-free men:

4. DVT or PE

9.4 Follow up

9.4.1 Exposure to anticoagulants

The exposure to AC treatment will be defined in two ways:

- the first is by following the patients until the end of the follow-up time, regardless if they are still on the drug or not.
- the second way is to follow up the patients until the filled prescription for each respective drug expires ("on/treatment").

A grace period of 90 days will be used to define a new prescription of anticoagulant. The duration of a prescription will be derived from the median number of days between consecutive respective prescriptions after the grace period has passed.

The treatment exposure can then be used to study the switching of treatments and the discontinuation of treatments.

A start date will be defined as the date of the dispensed prescription for patients receiving anticoagulation.

Patients will be censored at earliest date of:

- Time of first occurrence of a recurrent VTE event or a bleeding event (major bleeding event i.e. intracranial, gastrointestinal, urogenital bleeding, or other bleeding leading to hospitalisation) or death
    - Patients will be followed until occurrence of one of the above mentioned outcomes of interest; similarly, the analysis is repeated in the same way for the other outcomes of interest. Therefore, the patients were not censored at the first outcome of interest and outcomes on treatment after the first is also taken in to account. Only first-time events of the same type are considered.
- End of observation time (data lock point for the database at 31st October 2017)
- Treatment discontinuation
- Treatment switching patients who switched will be censored at the time of the date of a filled prescription from a pharmacy of the new drug.

9.4.2 Switching

A therapeutic switch will be defined as a subsequent filling of a prescription for an alternative anticoagulant (LMWH, any NOAC, VKA).

9.4.3 Discontinuation

It will not possible to determine exactly when an anticoagulant drug was discontinued from dispensing data, except when a switch was made, where the date for dispensing of the other drug was considered to mark the end of the exposure to the study drug.

Therefore, two fundamentally different methods will be used to approximate the time when exposure to the anticoagulant drug ended: a dispensed quantity based-method and a method based on refill intervals, which have both been evaluated in a previous study (9).

The dispensed quantity method counts the number of days the dispensed quantity of the drug would last if taken as prescribed and without missed doses. As the dosing of SOC varies greatly over time and between individuals, and the dosage is not recorded in the registers, this method could only be used for NOACs.

The refill interval method counts all days between two dispensings as days on treatment. If there is a gap exceeding six months, a single prescription or no more refills, treatment will be considered to have ceased three months after the last recorded dispensing. If there is another refill after more than six months, another treatment period will be considered to have started.

For both methods, the number of days on treatment days will be added up and a medicine possession ratio (MPR) calculated as the proportion of days on treatment out of the total number of days at risk (time to end of follow up, death or emigration). As a further sensitivity analysis, both methods will be assessed assuming that all patients were fully compliant to treatment (MPR 100%) and allowing

for patient´s forgetfulness that every tenth dose is missed (on average). In this case a dispensed quantity would last approximately 11% longer than with full compliance.

9.5 Data sources

The National Prostate Cancer Register (NPCR) of Sweden captures 98% of all newly diagnosed prostate cancer cases since 1998 (8). By use of the unique Swedish Person Identity Number (PIN), the NPCR has been linked with a number of other health care registries to create PCBaSe. These include the National Cancer Registry, the National Patient Registry (with hospital and outpatient hospital clinic diagnoses), the Cause of Death Registry, the Prescribed Drug Registry with dispensed prescriptions since July 2005, and the Swedish longitudinal integration database for health insurance and labour market studies (LISA), which is a socioeconomic database with information on the educational level, income, and marital status of patients (8).

PCBaSe contains more than 180,000 Pca cases diagnosed between 1998 to 2016. The linkage of registries means PCBaSe contains comprehensive data on tumour characteristics, patients demographic, clinical and socioeconomic characteristics as well as treatment delivered or decided upon up to six months after date of diagnosis. In addition, there over 900,000 Pca-free control men (five for each PCa case matched on birth year and county of residence) derived from the general population of men in Sweden.

From PCBaSe, it is possible to extract data on the patients' dispensed drug prescriptions for anticoagulants and partially for anti-cancer therapies (since July 2005 when the Prescribed Drug Registry started). We are also able to use the in- and outpatients registries to detect any diagnosis of VTE events experienced by the patients (defined as pulmonary embolism or deep vein thrombosis). The ATC codes for the anticoagulant and anti-cancer drugs, as well as the ICD-10 codes for the VTE diagnosis are described in annex 3.

9.6 Study size

The full PCBaSe database contains data on 185 729 men diagnosed with PCa since 1998 and more than 900 000 Pca-free men. This study will utilize the period from 2007 and contain approximately 98 000 men with PCa and about 500 000 men free of PCa from the population. More than 20% of patients with cancer will experience VTE (1). If the cumulative incidence within 5 years of follow-up is between 1% and 30%, the width of a 95% CI for the cumulative incidence of VTE will be approximately 0.12-0.58%. Although the corresponding cumulative estimate in PCa free men most likely is lower but on the other hand the sample size is larger, thus the resulting confidence interval is expected to be tight.

Table 1 shows the width of 95% CI for the cumulative incidence of VTE (based on binomial distribution) for different observed number of VTE among 98 000 patients.

Table 1. Estimated cumulative incidence (%) and two-sided 95% Binomial Confidence Intervals for 98 000 patients

Number of cases	Observed Cum Incidence (%)	Lower CI	Upper CI	Width (%)
980	1	0.94	1.06	0.12
1960	2	1.91	2.09	0.18
2940	3	2.89	3.11	0.22
3920	4	3.88	4.12	0.24
4900	5	4.86	5.14	0.28
9800	10	9.81	10.19	0.38
14700	15	14.78	15.23	0.45
19600	**20**	**19.75**	**20.25**	**0.50**
24500	25	24.73	25.27	0.54
29400	30	29.71	30.29	0.58

9.7 Data management

Data will be extracted from PCBaSe by members of the PCBaSe team according to routine procedures by the database owners.

Internal Bayer data analyst will have access to the anonymized data via a secure remote server to carry out the analysis. No individual data will be exported from secured server and only outputs in the form of figures and tables will be exported from the server.

9.8 Data analysis

Descriptive statistics will be used to define the socio-demographic and clinical characteristics (including main types of cancer therapies) of all PCa patients at the time of PCa diagnosis (Objective 1 and 3) and PCa-free men at the time of inclusion in PCBaSe (Objective 8) and include variables of interest listed above.

All categorical variables will presented by counts and proportions and continuous variables by mean, standard deviation, range, median, and first and third quartiles.

The occurrence will be estimated by calculating an incidence rate (accompanied by 95% CI) of cancer-related VTE events, split into PE and DVT events, in men with PCa (Objective 2) and in PCa-free men (Objective 10). The incidence rate is defined as the number of events of interest divided by the total number of person-years at risk. In men with PCa, the person-time at risk will be calculated from date of incident PCa diagnosis up until an outcome of interest, death or end of follow-up, whichever came first. The occurrence will be also described by Kaplan-Meier curves in different strata within different time-periods.

The AC treatment received by the PCa patients after a first cancer-related VTE event on an out-patient long-term basis will be reported by type of anticoagulation (LMWH, VKAs and NOACs) and its estimated duration (from the time-point of a hospital discharge up to 3 months, 3-6 months, more than 6 months) (Objective 4).

Time at risk for Objectives 5, 6 and 7 (recurrent VTE, bleeding leading to hospitalisation or death) will be calculated from first cancer-related VTE (the time-frame of defining cancer-relatedness will be specified later) for each events of interest up until event, death or end of follow-up.

The 95% CI for the incidence rate will be calculated using the Poisson distribution.

Incidence rates of recurrent VTE, bleedings and death will be calculated by the type and duration of AC treatment (stratification variables); however no comparative analysis of outcomes in three sub-groups of AC treatments, is planned.

9.9 Quality control

The PCBaSe investigators participating in the study are required to archive documents and data sets, statistical programs, and study-relevant documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended that documents be stored for a retention period of at least 15 years, unless local regulations define otherwise.

9.10 Limitations of the research methods

The main limitation of this study is that only drugs dispensed to patients via a pharmacy are recorded. This means that anti-coagulation treatments and anti-cancer treatments delivered in-hospital are not recorded in the database. Therefore, as these patients with VTE events and cancer are at high risk of being hospitalized, we will likely be missing data on their prescribed anti-coagulation treatments during their in-hospital period. However, given that treatment for VTE is usually a minimum of three months will be captured by the ensuing out-patient treatment that includes filling of prescriptions.

Another limitation is that there are no data on height and weight or lifestyle factors such as smoking status, alcohol use.

No information on adherence to the drug treatment is available directly. Therefore, dates of starting and stopping exposure to anticoagulation medications may not be fully accurate, hence we have applied two ways of defining drug exposure to account for this.

9.11 Other aspects

N/A

10. Protection of human subjects

This study is an observational study where treatment is prescribed in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

All data collected in the study will be stripped of all personal identifiers and data will be uploaded on a remote server where all data traffic is logged. The Bayer epidemiologist/data analyst will

perform the statistical analyses on the server with access by use of a VPN account. Only aggregated data in the form of tables and figures can be exported from the server, whereas no 'raw' individual data can be exported. Thus breach of confidentiality with regard to personal identifiers or health information is minimized. Country-specific data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

An approval from the Research Ethics Board in Uppsala (Sweden) has been granted.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products [Revision 2]), individual reporting of adverse reactions is not required for non-interventional study designs that are based on secondary use of data. Reports of adverse events/reactions will be summarised in the study report (10)

12. Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov" and in in the EU PAS register at "http://www.encepp.eu/encepp_studies/indexRegister.shtml". Results will be disclosed in a publicly available database within the standard timelines.

Progress reports will be sent to the competent authorities on regular basis; the content and frequency will be agreed upon.

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. Current guidelines and recommendation on good publication practice will be followed (GPP2 Guidelines(11), STROBE(12)). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the MAH.

13. References

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Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). European Medicines Agency; 28 July 2017. Available at: website: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232767.pdf. Accessed 5 September 2018.

11. Graf C, Battisti WP, Bridges D, Bruce-Winkler V, Conaty JM, Ellison JM, et al. International Society for Medical Publication Professionals. Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines. BMJ. 2009.

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Annex 1: List of stand-alone documents

None

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

ENCePP Checklist for Study Protocols (Revision 4)

ENCePP Checklist for Study Protocols (Revision 4)

Study title: PRostAte Cancer vTe In SwEden: epidemiology and anticoagulation treatment of VTE PRACTISE

EU PAS Register® number: not available yet
Study reference number (if applicable): 20653

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

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)	☒	☐	☐	7,8
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Comments:

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)	☐	☐	☒	
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))	☒	☐	☐	9.8
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?	☒	☐	☐	9.1, 9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1, 9.2
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3, 9.2.4

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)	☒	☐	☐	9.4.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.4
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	9.4
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

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?	☒	☐	☐	9.3.1,9.3.2
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
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)	☐	☐	☒	

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
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.10

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**

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)	☐	☐	☒	

Comments:

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)	☒	☐	☐	9.5
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.5
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.2.3,9.3,9.5
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)	☒	☐	☐	9.4.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.1, 9.3.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Annex 3
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?	☒	☐	☐	9.3.1
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.2.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.8
10.3 Are descriptive analyses included?	☒	☐	☐	9.8

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Are stratified analyses included?	☒	☐	☐	9.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.8

Comments:

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)	☒	☐	☐	9.7
11.2 Are methods of quality assurance described?	☒	☐	☐	9.9
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

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?	☒	☐	☐	9.10
12.1.2 Information bias?	☒	☐	☐	
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).	☒	☐	☐	
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)	☐	☐	☒	

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

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

Comments:

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: CCI

Date: 09/May/2019

Signature: _____

Annex 3: Additional information

Table 1. ATC codes for anticoagulant drugs

Class	Drug name	ATC code
1. Parenteral anticoagulants	Heparin	B01AB01
	Enoxaparin	B01AB05
	Dalteparin	B01AB04
	Nadroparin	B01AB06
	Tinzaparin	B01AB10
	Reviparin	B01AB08
	Parnaparin	B01AB07
	Bemiparin	B01AB12
	Fondaparinux	B01AX05
	Danaparoid	B01AB09
	Bivalirudin	B01AE06
	Argatroban	B01AE03
2. Vitamin K antagonists	Warfarin	B01AA03
	Phenprocoumon	B01AA04
	Acenocoumarol	B01AA07
	Dicoumarol	B01AA01
	Tioclomarol	B01AA11
	Ethyl biscoumacetate	B01AA08
	Fluindione	B01AA12
	Phenindione	B01AA02
	Chlorindione	B01AA09
	Diphenadione	B01AA10
3. Non-vitamin K oral anticoagulants (NOACs)	Rivaroxaban (Xarelto)	B01AF01
	Dabigatran (Pradaxa)	B01AE07
	Apixaban (Eliquis)	B01AF02
	Edoxaban (Savaysa/Lixiana)	B01AF03

Tabel 2. ICD-10 codes used to define disease conditions

Condition	**ICD-10 or Swedish procedure code beginning with**
Intracranial bleeding	I60-62, S064, S065, S066
Gastrointestinal bleeding	I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922
Urogenital bleeding	N02, R319, N95
Other bleeding	H431, R04, R58, D629, procedure code DR029
Anaemia	D50-64
Coagulation or platelet defect	D65-69
Ischaemic stroke	I63
Heart failure	I50,I110,I130,I132,I255,K761,I42-43
Unspecified stroke	I64
TIA	G45
Peripheral systemic emboli	I74
Thromboembolism (composite)	I63-64, G45, I74
Pulmonary embolism	I26
Deep venous thrombosis	I801-802
Venous thromboembolism (composite)	I26, I801-802
Myocardial infarction	I21,I252
Ischaemic heart disease	I20-25

“Swedish alcohol index" : will be used with ICD-10 codes: E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z71