Post Authorization Safety Study Information

Acronym / Title	COSIMO Cancer associated thrombosis - patient reported outcomes with rivaroxaban. A non-interventional study on patients changing to Xarelto® for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in patients with active cancer.
Protocol version identifier	XA1502, version 1.2
Date of last version of protocol	01 Feb 2018
IMPACT study number	18137
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV, non-interventional
EU PAS register number	ENCEPP/SDPP/12608
Active substance	Antithrombotic agents/Direct factor Xa inhibitors /Rivaroxaban (B01AF01)
Medicinal product	Rivaroxaban, BAY 59-7939
Product reference	Xarelto® 15 mg: EU/1/08/472/011 to EU/1/08/472/016, EU/1/08/472/023, EU/1/08/472/036 Xarelto® 20 mg: EU/1/08/472/017 to EU/1/08/472/022, EU/1/08/472/024, EU/1/08/472/037
Procedure number	EMEA/H/C/000944
Study Initiator and Funder	Bayer AG, 51368 Leverkusen Please note that, effective as of 01 January 2017, Bayer Pharma AG has transferred its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Research question and objectives	The main goal of this study is to gain more insights on patient reported treatment satisfaction in patients with active cancer who are changing to rivaroxaban for treatment of DVT and PE, and prevention of recurrent DVT and PE. MAIN OBJECTIVE

	The primary objective is to assess patient reported treatment satisfaction with regard to the Anti-Clot Treatment Scale (ACTS) burden score for the use of rivaroxaban for treatment of acute DVT and PE, and prevention of recurrent DVT and PE in patients with active cancer changing to this therapy.
Country(-ies) of study	Approx. 10 countries in the region Europe, Canada, Australia. An updated list is available as stand-alone document (listed in Table 4: List of stand-alone documents, Annex 1).
Author	Miriam Bach miriam.bach@bayer.com

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	Sabine Frenzen sabine.frenzen@bayer.com

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.

1. Table of Contents

2. List of abbreviations

ACT	Anti-Clot Treatment
ACTS	Anti-Clot Treatment Scale
ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical (Classification System)
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DCE	Discrete Choice Experiment
DMP	Data Management Plan
DTI	Direct Thrombin Inhibitor
EC	European Commission
EDC	Electronic Data Capture
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FXa	Factor Xa
GCP	Good Clinical Practice
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
HEOR	Health Economics and Outcomes Research
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
IT	Information Technology
LMWH	Low Molecular Weight Heparin
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
N/A	Not Applicable
NOAC	Non-Vitamin K Oral Anticoagulant
OS	Observational Study
NNH	Number Needed to Harm
PAS	Post-Authorization Study
PBRER	Periodic Benefit-Risk Evaluation Report
PASS	Post-Authorization Safety Study
PSUR	Periodic Safety Update Report
QOL	Quality of Life
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
RIETE	Registro Informatizado de Enfermedad TromboEmbólica
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VKA	Vitamin K Antagonist
WHO DD	World Health Organization Drug Dictionary

3. Responsible parties

3.1 Study initiator and funder / MAH

Role: Study conduct responsible
Name: Khaled Abdelgawwad
E-mail: Khaled.abdelgawwad@bayer.com

Role: Qualified person responsible for pharmacovigilance (QPPV)
Name: Dr. Michael Kayser

Role: Study safety lead
Name: Dr. Frank Czekalla

Role: Study medical expert
Name: Dr. Miriam Bach

Role: Study statistician
Name: Yoriko de Sanctis

Role: Study data manager
Name: Dalila Lakbir

Role: Study epidemiologist
Name: Pareen Vora

Role: Study health economics and outcomes research (HEOR) responsible
Name: Kerstin Folkerts

3.2 Collaborators / Committees

Contact details on the investigators, co-investigators and other site personnel for each country and site participating in the study are listed in a stand-alone document (see Table 4: List of stand-alone documents, Annex 1) which is available upon request.

A Steering Committee of external experts will be asked to provide support for the development of the study protocol and CRF. The committee will also provide expertise and guidance regarding the study conduct, adjudication of events and the analysis and the interpretation and publication of results. Information on the Steering Committee and the members is kept as stand-alone document (see Table 4: List of stand-alone documents, Annex 1) and is available upon request.

Administrative changes of responsible persons and / or the composition of the committee will be documented by updating the respective lists, but do not require formal protocol amendments.

4. Abstract

Acronym / Title	COSIMO Cancer associated thrombosis - patient reported outcomes with rivaroxaban. A non-interventional study on patients changing to Xarelto® for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in patients with active cancer.
Protocol version identifier	XA1502, version 1.2, 01 Feb 2018
Date of last version of protocol	01 Feb 2018
IMPACT study number	18137
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV, non-interventional
Author	Miriam Bach
Rationale and background	Acute venous thromboembolism (VTE, i.e. deep-vein thrombosis [DVT] or pulmonary embolism [PE]) is a common disorder with an annual incidence of appr. 1 or 2 cases per 1000 persons in the general population; 15-20% of all VTE cases occur in patients with cancer. Patients living with cancer have an 4-7 fold increased risk for VTE and this is associated with complications such as an increased bleeding risk and reduced patient quality of life. Also, the VTE event might trigger a delay or discontinuation of their cancer treatment. For patients with active cancer, low molecular weight heparin (LMWH) is the recommended anticoagulant for initial and long-term therapy of VTE as per current guideline recommendation. The duration of treatment and secondary prophylaxis is recommended for at least 6 months, extended anticoagulation to prevent VTE recurrences in high-risk patients is encouraged. Vitamin K Antagonists (VKA) are used in patients where LMWH use is limited or not feasible, or as an alternative for long-term therapy if LMWH is not available. The inconvenience e.g. of parenteral application of LMWH or frequent international normalized ratio (INR) monitoring with VKA's are challenging in the care of the cancer patient with VTE. It is expected that gradually new oral anticoagulants such as rivaroxaban will be used for treatment of DVT and/ or PE and/ or prevention of recurrent DVT and PE in patients with active cancer. In previous clinical phase III studies with rivaroxaban patient satisfaction measured by the anti-clot treatment scale (ACTS) was assessed and an improvement of patients' treatment satisfaction with rivaroxaban in relation to the comparator treatment was suggested. However, we lack such comprehensive information in cancer patients with VTE under

	routine clinical practice conditions. Therefore, this study aims to collect patient reported outcomes and assess treatment satisfaction in active cancer patients treated with rivaroxaban for VTE. This will complement and add to existing data from the Phase III studies as in this regard there is still high unmet need among clinicians.
Research question and objectives	The main goal of this study is to gain more insights on patient reported treatment satisfaction in patients with active cancer who are changing to rivaroxaban for treatment of DVT and PE, and prevention of recurrent DVT and PE. PRIMARY OBJECTIVE To assess patient reported treatment satisfaction with regard to the ACTS burden score for the use of rivaroxaban for treatment of acute DVT and PE, and prevention of recurrent DVT and PE in patients with active cancer changing to this therapy. SECONDARY OBJECTIVES To assess patient reported outcomes on preferences regarding the attributes of anticoagulant treatment for VTE, on treatment satisfaction for rivaroxaban over time, and on quality of life and furthermore, to document comprehensive data on clinical characteristics, patterns of use of anticoagulant treatment and safety and effectiveness information of rivaroxaban for treatment of acute DVT and PE, and prevention of recurrent DVT and PE in patients with active cancer.
Study design	This is an international, prospective, non-interventional, multi-center, one-arm cohort study of cancer patients with DVT and PE changing to rivaroxaban for treatment of acute DVT and PE, and prevention of recurrent DVT and PE. The study is conducted in Europe, Canada and Australia. Patient's treatment satisfaction with the previous standard of care (SOC) treatment (LMWH or VKA) at baseline will be compared to prospective treatment with rivaroxaban using the ACTS questionnaire. The final scores are reported as two separate subscales (benefit and burden), thus it will be possible in this study to focus for the primary endpoint on the burden part of the ACTS questionnaire i.e. on the burden of treatment. The ACTS burden score at week 4 will be compared to the ACTS burden score at baseline. Patients with active cancer should have been treated for acute VTE for at least 4 weeks with SOC (LMWH or VKA) to be eligible for enrollment. Information on patient preferences will be collected by means of a discrete choice experiment (DCE), in a semi-structured telephone interview. The telephone interview should be conducted after a minimum of four weeks to a maximum of twelve weeks after enrollment of patients in the study/start of rivaroxaban. Information on quality of life by means of the FACIT-Fatigue self-administered questionnaire will also be collected at baseline, as well as week 4, months 3, and 6 which are the time points of interest. The observation period for each patient starts with enrollment

	and ends after 6 months (regardless of any treatment changes) or with withdrawal of consent, death or lost to follow-up. The study ends 6 months after end of enrollment. Cancer patients for whom the decision was made to switch from SOC to rivaroxaban by the attending physician will be invited to be a part of this study in a consecutive manner. The first visit must be within the enrollment period for the respective country which means that there should be no retrospective inclusion. The actual treatment duration will be determined solely by the physician and is not dependent on the initial intended treatment duration.
Population	INCLUSION CRITERIA • Adult female and male patients with active cancer other than fully treated basal-cell or squamous-cell carcinoma of the skin (active cancer defined as the diagnosis or treatment of cancer in the previous < 6 months or recurrent or metastatic cancer) • Patients that have been treated with standard of care anticoagulation (LMWH/VKA) for treatment of DVT and/ or PE (index VTE event) and/ or prevention of recurrent DVT and PE for at least 4 weeks prior to inclusion in the study • Patients for whom the decision was made to start rivaroxaban for treatment of DVT and/ or PE and/ or prevention of recurrent DVT and PE • Patients with Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2 • Patients who are willing to participate in this study (signed informed consent) • Patients who are available for follow-up with a life expectancy > 6 months EXCLUSION CRITERIA • The contra-indications according to the local marketing authorization must be considered • Patients who developed an index VTE event despite chronic anticoagulant therapy • Patients receiving apixaban, edoxaban or dabigatran or any investigational drug as the initial therapy for the index VTE event • Patients participating in an investigational program with interventions outside of routine clinical practice with exception of oncology investigational trials
Variables	PRIMARY ENDPOINT • Treatment satisfaction burden score (ACTS) SECONDARY ENDPOINTS • Attributes and their levels with regard to the DCE choice sets • Treatment satisfaction burden and benefit scores (ACTS) • Patient quality of life measured by the FACIT-Fatigue questionnaire • Clinical characteristics of cancer disease

	• Type and date of index VTE event • Type and duration of initial anticoagulation • Reason for drug switch to rivaroxaban • Planned and actual duration of anticoagulation with rivaroxaban • Dosage of rivaroxaban; reason for any potential dose adjustments during course of treatment with rivaroxaban at baseline and at 6 months if still on treatment • Reasons for any switch from rivaroxaban treatment and type and modus of switch to or bridging with other anticoagulant if applicable • Persistence with rivaroxaban treatment • Reasons for permanent cessation of rivaroxaban treatment • Bleeding events and thromboembolic events
Data sources	The investigator collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data during visits that take place in routine practice. In addition data will be collected from patient questionnaires and patient interviews
Study size	The sample size calculation is based on the primary endpoint, a change of the ACTS burden score at week 4 in comparison to baseline. The sample size is based on a 2-tailed paired t-test at the 0.05 level of significance. Data from active cancer patients in the XALIA study was used for source data. XALIA Visit 1 ACTS burden score for SOC is assumed as baseline, and for rivaroxaban is assumed as week 4 data. The mean (standard deviation; SD) of ACTS burden score for SOC and rivaroxaban is 52.9 (8.06) and 54.2 (6.11), respectively. From this result, a difference between baseline and week 4 is assumed to be 1.3. The standard deviation of the difference is 10, however, considering within-patient correlation, SD of 8.0 is considered as reasonable. Based on these assumptions, 300 patients will be needed to reach power of 80%. Considering 20% drop-out rate, 375 patients have to be included. Due to the heterogeneous population of patients with cancer and assumed high drop-out rates after week 4, 500 patients will be enrolled in the COSIMO study to have sufficient numbers for secondary analyses.
Data analysis	STATISTICAL CONSIDERATIONS All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable. The analyses for ACTS will be performed for the population which includes patients whose ACTS score at the time point for the target analysis, i.e. week 4, or months 3 and 6, is available. Other analyses will be performed for the population which includes patients receiving at least one dose of rivaroxaban. All details including calculated variables

	and proposed format and content of tables will be described in the Statistical Analysis Plan (SAP). SAP will be finalized before study database lock. ANALYSIS OF PRIMARY OUTCOME VARIABLE The primary efficacy outcome is a change of the ACTS burden score at week 4 (-2 to + 4 weeks) in comparison to baseline. The null hypothesis H_0 and the alternative hypothesis H_A are H_0: $\Delta = 0$ and H_A: $\Delta \neq 0$, where Δ is the change in the ACTS burden score. The change is assumed to be normally distributed and will be tested using paired t-test at a $\alpha = 5\%$ significant level.
Milestones	FPFV: 11-Oct-2016 (actual) LPLV: 15-Nov-2018 End of study: 15-Mar-2019

5. Amendments

Table 1: Amendments

Amendment Number	Reason for Amendment	New version number	Effective Date
Update 01	Update of PASS register number, timelines and list of stand-alone documents	v 1.1	15 Nov 2016
Update 02	Administrative Update to: • Study timelines for extension of enrollment period by 3 months • Study team responsibility 3.1: change of OS Conduct Responsible Person and OS Safety Lead • Market Authorization Holder: for the change from Bayer Pharma AG to Bayer AG • Annex.1: List of Standalone Documents • Correction of typing errors in sections 10.1 and 11.1	V1.2	01 Feb 2018

6. Milestones

Definitions:

- Start of study: first center initiated
- Start of data collection: FPFV

- End of data collection: date of last data entry in database (after LPLV)
- End of study: date of clean database
- Observation period: time-window for data collection (FPFV until LPLV)
- Final report: final report of study results 12 months after clean database

Table 2 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrollment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document (Table 4: List of stand-alone documents, Annex 1) that is available upon request.Table 2: Milestones

Milestone	Planned date
Registration in the EU PAS register	19-Apr-2016 (actual)
Start of data collection	15-Sep-2016
End of data collection	15-Dec-2018
End of study	15-Mar-2019
Final report of study results	15-October-2019

7. Rationale and background

Acute venous thromboembolism (VTE, i.e. deep-vein thrombosis [DVT] or pulmonary embolism [PE]) is a common disorder with an annual incidence of approximately 1 or 2 cases per 1000 persons in the general population and is the third most common cause of vascular death after myocardial infarction and stroke. Approximately 15-20% of all VTE cases occur in patients with cancer. Patients living with cancer have an 4-7 fold increased risk for VTE as compared to patients not suffering from cancer [1]. Oncology patients who develop thrombosis have an annual 21-27% risk of VTE recurrence and a 2-6 fold higher risk of death. Furthermore, VTE in patients with cancer is associated with complications such as an increased bleeding risk which was shown to be related to cancer severity [2] and reduced patient quality of life. Additionally, the thrombotic event might trigger a delay or discontinuation of their cancer treatment such as surgery or chemotherapy [3] [4].

For patients with active cancer, low molecular weight heparin (LMWH) is the recommended anticoagulant for initial and long-term therapy of VTE as per current guideline recommendation [5] [6] [7]. LMWH injections have certain limitations that include among others painful injections and high costs. The duration of treatment and secondary prophylaxis is recommended for at least 6 months. Vitamin K Antagonists (VKA) are used in patients where LMWH use is limited or not feasible, or as an alternative for long-term therapy if LMWH is not available [5] [7] [6]. In high-risk patients with active malignancy continuing on chemotherapy, extended anticoagulation to prevent VTE recurrences is encouraged.

Data from real world clinical practice, RIETE (Registro Informatizado de Enfermedad TromboEmbólica) a European registry, showed, that 92% of patients with cancer and VTE are initially treated with LMWH; 5,63%, of patients receive unfractionated heparin, 4,72% an inferior vena cava filter, 0,32% thrombolytics and 1,65% other anticoagulation treatments. For long-term treatment, LMWH are prescribed in 58% of these patients, in comparison to VKA (34%) or other anticoagulants (7,87%) indicating a switch after initial treatment with LMWH in a considerable amount of patients [8]. Mean overall anticoagulation treatment length is 284±383 days; interestingly, 43% of patients with cancer are anticoagulated for > 12 months [8]. In the US, 50% of patients with cancer receive VKA [9] despite guideline recommendation for initial treatment with LMWH [7]. Furthermore, US patients with cancer and VTE initially receiving LMWH are switched more frequently and earlier to another anticoagulant [9]. However, so far, comprehensive data is lacking on when and why a switch from LMWH to an alternative anticoagulation occurs.

The inconvenience of daily injections, weight-adjustment of dose, and risk of heparin induced thrombocytopenia with LMWH or frequent international normalized ratio (INR) monitoring and numerous food and drug interactions with VKAs impose significant challenges in the care of the cancer patient with VTE [4]. A simple, effective and affordable alternative for the prevention and treatment of venous thromboembolism in patients with cancer is an unmet clinical need.

New oral anticoagulants are thus discussed as a simpler and effective alternative for the prevention and treatment of venous thromboembolism in patients with cancer. Rivaroxaban is a potent and selective direct Factor Xa (FXa) inhibitor and can be given as fixed oral dosing without need for routine coagulation monitoring. Rivaroxaban is currently the only NOAC with a robust set of data in patients with PE and DVT and active cancer, as the EINSTEIN programme did not exclude patients with active cancer or withdraw patients who developed cancer during the study period [10] [11]. Subgroup analyses from the EINSTEIN studies showed similar efficacy of a single drug approach with oral, fixed-dose rivaroxaban compared to the combination of subcutaneous enoxaparin and INR-titrated therapy with VKA in patients with cancer [10]. In the EINSTEIN studies, in patients with cancer (history of cancer, active cancer and cancer diagnosed during the study), recurrent venous thromboembolism occurred in 5% of patients allocated to rivaroxaban and 7% of patients allocated to enoxaparin and VKA (HR 0,67; 95% CI 0,35-1,30). Rivaroxaban had a significant advantage compared to enoxaparin and VKA in patients with active cancer with regard to major bleeding (rivaroxaban 2% vs. enoxaparin/VKA 5% (HR 0,42; CI 0,18-0,99; p=0, 047) and net clinical benefit (rivaroxaban 7% vs. enoxaparin/VKA 13% (HR 0,54; CI 0,33-0,90; p = 0·018) [10], consistent with the overall result of the pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies [11] .

As part of the ongoing review process for the FXa inhibitors or direct thrombin inhibitor (DTI), the EMA has been looking to harmonize the labelling with regard to the treatment of PE and DVT in patients with active cancer. Except rivaroxaban, all other NOAC labels currently include a standard statement that efficacy and safety of the respective NOAC has not been established in the treatment of DVT/PE, and prevention of recurrent DVT and PE (VTEs) in patients with active cancer. After its approval and marketing for treatment of DVT and/ or PE, and/ or prevention of recurrent DVT and PE, rivaroxaban use is therefore expected to gradually increase in patient populations with high disease burden, including

cancer patients. In this setting a careful benefit-risk assessment of the anticoagulation treatment and its associated burden requires consideration.

Factors such as cancer or cancer therapy related comorbidities, e.g. cachexia, and the need for multiple concurrent antineoplastic and supportive therapies itself, have a strong influence on quality of life, as may have the need for daily self-injections. Treatment satisfaction, patient preferences and quality of life play an important role in cancer patients, as they are known to have an impact on treatment length and adherence, therewith on potential recurrence of VTE.

Treatment satisfaction with anticoagulants can be assessed by the anti-clot treatment scale (ACTS) questionnaire (See ACTS charter Annex 1.) [12]. By means of this self-administered questionnaire, which includes 13 items about the burdens of anti-clot treatment (ACT) (including a 12-item burdens scale and one global question about burdens) and 4 items about the benefits of ACT (including a 3-item benefits scale and one global question about benefits), the patients' opinions on their anticoagulant treatment can be evaluated.

Besides treatment satisfaction, also patient perception in regard to preferences of their treatment might differ. This is of particular importance because, inherently, treatment should be centered on the patient. Data about cancer patient preferences with regard to so called "convenience attributes" could support the choice of oral anticoagulation treatments for both physicians and patients. To generate this, a technique like a discrete choice experiment (DCE) needs to be applied, since by simply asking patients to rate treatment-related attributes will generally yield no substantial information, as generally it can be expected that patients would state to want all the benefits and none of the indirect/direct costs of a treatment. Instead, a choice experiment like a DCE requires that patients be forced to make a trade-off between two or more options, and choosing (as it is the case in reality) between treatment options that may be associated with utility-increasing and utility-decreasing attribute levels [13]. Through a semi structured telephone interview the preferences of patients with cancer and DVT/PE with regard to the attributes of the medication options LMWH, VKA and rivaroxaban can be documented (See DCE charter Annex 1.).

A plethora of questionnaires exist to assess quality of life (QOL) in different patient populations. The FACIT (Functional Assessment of Chronic Illness Therapy) Measurement System is a collection of quality of life questionnaires targeted to the management of chronic illness. Since fatigue is one of the most common side effects in patients with cancer and under cancer-therapy, affecting all areas of life, the 'FACIT-Fatigue' questionnaire (See FACIT-Fatigue Charter Annex 1.), a 13 item self-administered questionnaire, of the FACIT scales will be used to assess quality of life in the COSIMO study.

In previous clinical phase III studies with rivaroxaban patient satisfaction measured by the anti-clot treatment scale (ACTS) was assessed and an improvement of patients' treatment satisfaction with rivaroxaban in relation to the comparator treatment was suggested [14] [15]. However, we lack such comprehensive information in cancer patients with VTE under routine clinical practice conditions. Therefore, this study aims to collect patient reported outcomes and assess treatment satisfaction in active cancer patients treated with rivaroxaban for VTE. This will complement and add to existing data from the Phase III studies as in this regard there is still high unmet need among clinicians.

8. Research questions and objectives

The main goal of this study is to gain more insights on patient reported treatment satisfaction in patients with active cancer who are changing to rivaroxaban for treatment of DVT and PE, and prevention of recurrent DVT and PE.

8.1 Primary objective

The primary objective in this study is:

to assess patient reported treatment satisfaction with regard to the Anti-Clot Treatment Scale (ACTS) burden score for the use of rivaroxaban for treatment of acute DVT and PE, and prevention of recurrent DVT and PE in patients with active cancer changing to this therapy.

8.2 Secondary objectives

The secondary objectives in this study are:

- to assess patient reported outcomes on preferences regarding the attributes of anticoagulant treatment for VTE
- to assess patient reported outcomes on treatment satisfaction for rivaroxaban over time
- to assess patient reported outcomes on quality of life
- to document comprehensive data on
    - clinical characteristics
    - patterns of use of anticoagulant treatment
    - safety and effectiveness information of rivaroxaban for treatment of acute DVT and PE, and prevention of recurrent DVT and PE in patients with active cancer

9. Research methods

9.1 Study design

This is an international, prospective, non-interventional, multi-center, one-arm cohort study of cancer patients with DVT and PE changing to rivaroxaban for treatment of acute DVT and PE, and prevention of recurrent DVT and PE. The study is conducted in Europe, Canada and Australia.

Patient's treatment satisfaction with the previous standard of care (SOC) treatment (LMWH or VKA) at baseline will be compared to prospective treatment with rivaroxaban using the ACTS questionnaire. The score of each of the 13 items of the questionnaire is obtained through a 5-point Likert scale responses. The final scores are reported as two separate subscales (benefits and burden), thus it will be possible in this study to focus for the primary endpoint on the burden part of the ACTS questionnaire i.e. on the burden of treatment [14].

Patients with active cancer should have been treated for acute VTE for at least 4 weeks with SOC (LMWH or VKA) to be eligible for enrollment. The ACTS will be measured at baseline for the previous SOC treatment and at follow-up visits for the rivaroxaban treatment (e.g. week 4, months 3, and 6 which are the time points of interest). The ACTS burden score at week 4 will be compared to the ACTS burden score at baseline.

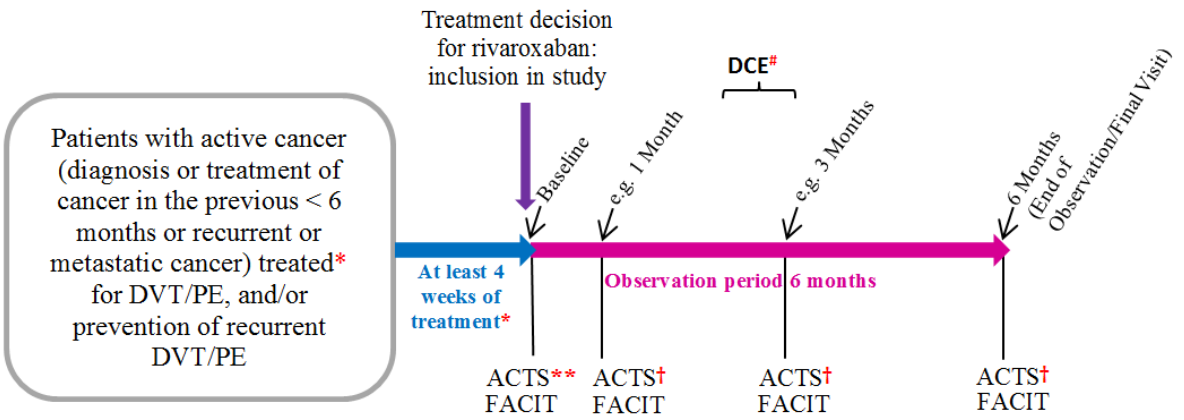
Information on patient preferences will be collected by means of the DCE. In a semi-structured telephone interview (aided by a corresponding online tool which is used by trained interviewers during the interview), patients that consented to participate in the DCE will be surveyed once with regard to preference for the different convenience properties of LMWH, VKA or rivaroxaban. The telephone interview shall be conducted after a minimum of four weeks to a maximum of twelve weeks after enrollment of patients in the study/start of rivaroxaban.

Information on quality of life by means of the FACIT-Fatigue self-administered questionnaire will also be collected at baseline, as well as week 4, months 3, and 6 which are the time points of interest.

The observation period for each patient starts with enrollment and ends after 6 months (regardless of any treatment changes) or with withdrawal of consent, death or lost to follow-up. The study ends 6 months after end of enrollment. Follow-up visits of the patients will be regular visits to their physicians but data of interest will be collected at above mentioned time points. All the available patient and treatment information specified in section 9.3 will be collected at inclusion and at follow-up visits (e.g. week 4, months 3, and 6). Results from laboratory or diagnostic procedures will be documented at the visits as far as they are available for the patient (i.e. no additional diagnostics outside routine practice).

Cancer patients for whom the decision was made to switch from SOC to rivaroxaban by the attending physician will be invited to be a part of this study in a consecutive manner. The exact reasons for the switch in anticoagulation, as length of prior treatment with SOC will be documented in the eCRF to document real-world practical management of VTE in patients with cancer. The first visit must be within the enrollment period for the respective country which means that there should be no retrospective inclusion. The actual treatment duration will be determined solely by the physician and is not dependent on the initial intended treatment duration.

As per the current guidelines, high percentage of cancer patients with VTE is treated with SOC which is LMWH (92%). In a non-interventional setting for this study, a one-arm design will avoid differences due to selection or inclusion of patients receiving either SOC treatment or rivaroxaban and will include patients who were treated according to the guidelines but switch to rivaroxaban due to several possible reasons. This design will also reduce differences caused by patient perceptions (e.g. pain, satisfaction, improvement etc.) which differs for every individual patient and might cause between patient variations in a comparative setting. Also, the patients can evaluate their experiences on previous treatment as well as for the new treatment.



* Patients treated for at least 4 weeks with standard of care anticoagulation (LMWH or VKA)
** For previous anticoagulation treatment
† For rivaroxaban treatment
# Discrete Choice Experiment (DCE): per telephone interview 4 – 12 weeks after starting rivaroxaban treatment

ACTS – Anti-Clot Treatment Scale
FACIT – FACIT-Fatigue questionnaire

9.1.1 Primary endpoint

The primary endpoint is:

Change of ACTS burden score between baseline and week 4

9.1.2 Secondary endpoints

The secondary endpoints are:

- Preferences regarding the attributes of the anticoagulation medication options LMWH, VKA, rivaroxaban (DCE)
- Change of ACTS (burden score and benefit score) over time (at months 3 and 6)
- Patient's quality of life using the FACIT-Fatigue questionnaire
- Clinical characteristics of cancer patients with VTE
- Patterns of use of anticoagulation treatment
- Bleeding and thromboembolic events

9.1.3 Strengths of study design

This one-arm cohort study will evaluate patient reported treatment satisfaction for previous SOC anticoagulant treatment and Rivaroxaban treatment in cancer patients with VTE using the ACTS. The ACTS is a treatment-specific patient-report experience instrument, specific for anticoagulation; therefore, we should not expect it to be affected by the different stages of

cancer and cancer treatment. The number of subjects required tends to be smaller in a one-arm design compared to a conventional approach, which should be taken into account as recruiting cancer patients for this study setting might be challenging. Also, enrolling (inviting) eligible patients to be a part of this study in a consecutive manner will reduce selection bias. As patients are switched to rivaroxaban from previous anticoagulant therapy, it will allow patients to evaluate the change experienced with the rivaroxaban treatment in contrast to previous anticoagulant therapy, furthermore information on the reasons for switch will be collected.

The prospective aspect of the study will not only permit us to a priori implement common definitions of covariates and outcomes but also to collect information regarding necessary covariates and potential confounders (e.g. time-varying factors).

Patient reported outcomes in the controlled trials may not be representative of patients treated under routine clinical practice conditions. A non-interventional real-world setting is thus appropriate to gain information on patient reported outcomes as well as on the characteristics and patterns of use of anticoagulation treatment in cancer patients with VTE. A one-arm design is appropriate to collect patient reported outcomes and also to describe the characteristics of a heterogeneous patient population, such as the cancer population which includes patients with different cancer types, sites, and treatments. A comparative setting might not work well to evaluate treatment satisfaction because patient perception (e.g. pain, satisfaction, improvement etc.) differs for every patient and might cause between patient variations. However, in a one-arm design patients can rate their experiences on previous treatment and can evaluate the change with the new treatment. Also, in such a design, patients can indicate preferences for recent treatment versus previous treatment. Therefore, using such a design would be favorable to eliminate inter-patient variations. The DCE will allow patients to make a trade-off between two options and choose a favorable treatment based on the treatment-related attributes.

9.2 Setting

9.2.1 Eligibility

Female and male patients with active cancer and a diagnosis of DVT/ and/or PE will be enrolled after the decision to start treatment with rivaroxaban has been made by the investigator.
For conversion from parenteral anticoagulation (LMWH) or from VKA to Xarelto the recommendations as per the local SmPC should be followed.

9.2.2 Inclusion criteria

- Adult female and male patients with active cancer other than fully treated basal-cell or squamous-cell carcinoma of the skin (active cancer defined as the diagnosis or treatment of cancer in the previous < 6 months or recurrent or metastatic cancer)
- Patients that have been treated with standard of care anticoagulation (LMWH/VKA) for treatment of DVT and/ or PE (index VTE event), and/ or prevention of recurrent DVT and PE for at least 4 weeks prior to inclusion in the study

- Patients for whom the decision was made to start rivaroxaban for treatment of DVT and/ or PE, and/ or prevention of recurrent DVT and PE
- Patients with Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2 (See Annex 3. For ECOG score details)
- Patients who are willing to participate in this study (signed informed consent)
- Patients who are available for follow-up with a life expectancy > 6 months

9.2.3 Exclusion criteria

- The contraindications according to the local marketing authorization must be considered
- Patients who developed an index VTE event despite chronic anticoagulant therapy
- Patients receiving apixaban, edoxaban or dabigatran or any investigational drug as the initial therapy for the index VTE event
- Patients participating in an investigational program with interventions outside of routine clinical practice with exception of oncology investigational trials

9.2.4 Withdrawal

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the patient's medical care. Each patient can refuse to further participate or may withdraw from the study at any time and without giving a reason. If a patient wants to terminate the study participation, no further data will be collected. However, the patient will be asked whether s/he agrees that the data collected so far can be used. In case the patient does not agree, these data will not be used for any patient level analysis of study data.
This includes safety data with the exception that data already captured in the company's safety database will be kept. However, data which are relevant for primary outcomes might be displayed on an aggregated level to assess a potential bias. In case a patient would like to withdraw the consent given earlier, s/he should inform his/her doctor and the site should document the withdrawal in the Case Report Form as well as in the patient medical records.

9.2.5 Replacement

Patients will not be replaced after drop out.

9.2.6 Representativeness

A minimal set of inclusion and exclusion criteria at baseline will allow the accrual of a representative population with a broad range of individual risk groups (e.g. patients with co-morbidities, etc.) increasing the generalizability of the study results. The exclusion criteria applied in this study will increase homogeneity in the baseline risk of the study population by excluding patients pretreated with anticoagulants other than standard of care (LMWH/VKA) and by excluding patients that developed an index VTE event despite chronic anticoagulation therapy. This homogeneity will increase the robustness of the study results given the diversity (cancer types and treatments) of the study population. This study will not exclude patients on oncology investigational trials which reflects the real-life situation where most of the cancer patients are involved in such trials. Hence, no specific patient groups will be excluded from the study maintaining the external validity. Detailed information regarding cancer and

chemotherapy will be captured in the study which will allow valid interpretation of the results. Using ECOG performance status (ECOG < 3) will only exclude frail/debilitated patients who are not able to self-care, mostly bedridden, or completely disabled. This study is intended to assess the use of rivaroxaban in routine, real-world clinical practice hence study procedures will not interfere with the clinical management of patients, prescribing behaviors of attending physicians or with the individual needs of the cohort members to assure data collection of standardized, reliable clinical data from baseline until the end of the follow-up documentation.

The representativeness of the study population, with regard to the range of characteristics that are reflective of the broader target population, is addressed by the fact that the study will include typical cancer patients, which constitute more heterogeneous populations than those participating in randomized clinical trials (e.g., wide range of age, ethnicity, and comorbidities). In addition, the inclusion of a representative sample of study sites (i.e. health care providers, hospitals, etc.) in terms of geography, practice size, and academic or private practice type is aimed for as a measure to enhance the generalizability of study results. The sample of study sites should, ideally, reflect the distribution of VTE treatment settings in each participating country for cancer patients. Nevertheless, the final sample of study sites will strongly depend on the willingness of investigators to participate in the study. Different combinations of chemotherapy, differing patient management, and monitoring plans in cancer care in different countries might affect the generalizability however, this gives an opportunity to observe and establish the results of this study to the population of different countries.

Sites will be selected under the governance of the country Medical Affairs function in the participating countries. The site selection process shall ensure that sites are representative with respect to treatment routines for each country. However, the potential ability to fulfill the study specific documentation requirements, that rivaroxaban is actually available/prescribed at this site, and the quality of the sites must be observed as well.

9.2.7 Visits

Study participants can be enrolled immediately after the choice of rivaroxaban for treatment has been made by the attending physician, e.g. first step is treatment decision by attending physician, second step is inclusion in study (non-randomized, observational study). Prior anticoagulation therapy for the index VTE is a prerequisite for inclusion in the study (as per inclusion criterion) and will be recorded in the eCRF. The investigator will document the initial visit, the follow-up visits and a final visit for each patient in the case report form (CRF). Follow-up visits occur during routine practice, the study protocol does not define exact referral dates for those visits. The final visit should be performed and documented after 6 months.

The observation period for each patient is 6 months.

Enrollment / Initial Visit

Once a patient is found eligible for inclusion, the investigator will inform the patient about the study. This will include discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent. The consent will have two parts. The first part will refer to data collection within the COSIMO study, the second part will refer to the

additional phone interviews for the DCE. It will be possible to participate only in the study, but not in the DCE.

Baseline information is recorded with the status at initial visit.

Follow-up Visits during treatment

The observation period will cover 6 months regardless of any treatment changes. Follow-up visits of the patients should be regular visits to their physicians and would not be mandated on them. During that timeframe two follow-up visits of interest, e.g. after 4 weeks and 3 months should be documented.

End of Observation / Final Visit

The observation period for a patient will end after 6 months regardless of any treatment changes after enrollment. Possible reasons for premature end of observation are consent withdrawal, lost to follow-up or death of patient.

9.3 Variables

The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during initial visit and follow-up visits. The investigator documents the study-relevant data for each patient in the electronic case report form (eCRF). The CRF is available upon request (see Table 4: List of stand-alone documents, Annex 1).

Table 3: Tabulated overview on variables collected during the study

Schedule / Variables	Initial Visit	Follow-up Visits (e.g. week 4 and month 3)[1]	DCE Telephone Interview (4-12 weeks after start of rivaroxaban)	End of Observation Visit/Final Visit[1]
Visit date	X	X	X	X
- Inclusion criteria - Sign informed consent form (ICF) - Demography - VTE risk factors including previous VTE	X			
Cancer related information: - Staging/ grading at VTE diagnosis and/ or inclusion in study - Medical/ surgical history	X			
Cancer related concomitant medication / treatment	X	X[§]		X[§]
Relevant, non-cancer related medical/ surgical history	X			
Relevant, non-cancer related concomitant diseases and medication	X	X[§]		X[§]
Laboratory results (if available)	X[§]	X[§]		X[§]
Index diagnosis of DVT/ PE	X			
Initial anticoagulation: drug, dosage, planned and actual duration	X			
Reason for change of initial anticoagulant therapy	X			
Planned duration of anticoagulation with rivaroxaban (changes if applicable)	X	X		X
Current rivaroxaban regimen	X	X		X
Any temporary or permanent interruption or drug switch regarding rivaroxaban		X		X
Anticoagulation regimen other than rivaroxaban incl. interruptions and switches and their reason (if applicable, e.g. after stop of rivaroxaban)		X		X
Patient satisfaction (ACTS)[2]	X	X[2]		X[2]
Patient quality of life (FACIT-Fatigue)	X	X		X
DCE survey			X	
Adverse events**		X	X*	X
Assessment of therapy				X

[1] It is recommended that patients should be followed-up regularly (e.g. after 4 weeks, and at months 3 and 6 (end of observation visit))

[2] Since the ACTS has a recall period of 4 weeks, it should be collected between -2 to + 4 weeks around each visit.

[*] If a patient reports a SAE/AE during the telephone interview this will be adequately followed-up

[**] Serious Adverse Events must be reported to the MAH within 1 business day. AEs and SAEs should be collected up to 30 days after stop of treatment with rivaroxaban.

[§] Only documented if information is available from regular practice. No additional diagnostics are required for the study.

9.3.1 Variables to determine the primary endpoint

- Treatment satisfaction burden score (ACTS)

(Details of the Questionnaire will be described in the ACTS charter)

9.3.2 Variables to determine the secondary endpoints

- Attributes and their levels with regard to the DCE choice sets (*Details of the DCE will be described in the DCE charter*)
- Treatment satisfaction burden and benefit scores (ACTS)
- Patient quality of life measured by the FACIT-Fatigue questionnaire *(Details of the Questionnaire will be described in the FACIT-Fatigue charter)*
- Clinical characteristics of cancer disease
- Type and date of index VTE event
- Type and duration of initial anticoagulation
- Reason for drug switch to rivaroxaban
- Planned and actual duration of anticoagulation with rivaroxaban
- Dosage of rivaroxaban; reason for any potential dose adjustments during course of treatment with rivaroxaban at baseline and at 6 months if still on treatment
- Reasons for any switch from rivaroxaban treatment and type and modus of switch to or bridging with other anticoagulant if applicable
- Persistence with rivaroxaban treatment. Reasons for permanent cessation of rivaroxaban treatment
- Bleeding events and thromboembolic events

9.3.3 Demography

For demographic / socio-demographic assessment, the following data will be recorded:

- Year of birth
- Sex
- Race (e.g. White, Black or African American, Asian, not reported)) (Note: Race will only be recorded where legally permitted)
- Weight
- Height
- Alcohol, tobacco, drug use
- Insurance (private/public)

9.3.4 Disease history

Disease history describes any medical findings that are relevant to the underlying disease and were present before inclusion into the study. Findings and diagnosis meeting the criteria listed below have to be documented:

Data regarding current indication and VTE event

- Type of index event (DVT, PE, catheter-associated DVT)
- Date, method of diagnosis, location of VTE (incl. catheter-associated VTE)
- Type of indication, e.g. treatment of VTE or prevention of recurrent events
- Start date, dosage, planned and actual duration of initial anticoagulation
- If applicable dose and reason for prior dose adjusting of initial anticoagulation (e.g. due to platelet reduction)
- Start date, dosage, planned duration of anticoagulation with rivaroxaban
- Reason for switch from initial anticoagulation to rivaroxaban
- Bleeding diathesis/history of prior bleedings
- Abnormal kidney function (e.g. also due to cancer treatment)
- History of VTE
- Other individual risk factors

Data regarding underlying cancer

- Date of diagnosis
- ECOG performance status at enrollment
- Disease status at study start
- Date of last response milestone assessment and result
- Risk factors for cancer
- Tumor Classification/Primary Site of Cancer at enrollment
- Histological class of cancer
- TNM staging at enrollment for solid tumors or type of hematological malignancy
- If applicable: number and location of metastases and extent of disease and/or related surgeries

9.3.5 Co-morbidities (medical history, concomitant diseases)

Co-morbidities are any medical findings, whether or not they pertain to the study indication, that were present before start of therapy with rivaroxaban independent on whether or not they are still present. They have to be documented in the Medical History / Concomitant Diseases section.

Findings meeting the criteria listed below are considered to be relevant to the study indication and have to be documented:

- Thrombophilia
- Hypertension

Other co-morbidities judged as relevant by the physician should be documented by the physician.

For any co-morbidity, the diagnosis, the start and the stop date/ongoing have to be documented.

9.3.6 Prior and concomitant medication and cancer specific treatments

All medication taken as well as cancer specific treatments obtained before study start (initiated and stopped before study start) is termed prior medication and treatments. All medication taken and cancer specific treatments obtained in addition to rivaroxaban for any indication (either initiated before study start or during the study) is termed concomitant medication and treatments and has to be documented.

Information to be collected for medication includes: trade name or INN, start date, stop date/ongoing, dose, unit, and indication.

Prior and concomitant medication and treatments meeting the criteria listed below are considered to be relevant to the study indication have to be documented:

- Prior /concomitant systemic anticancer treatment for the active cancer
- Prior /concomitant local anticancer treatment
- Prior /concomitant radiotherapy
- Prior /concomitant VTE or anticoagulation/antithrombotic treatment
- Prior /concomitant diagnostic and therapeutic procedures (e.g. Billroth's operation I, Billroth's operation II, Roux-en-Y, pancreaticoduodenectomy/Whipple procedure, bladder pouch, other)
- Prior /concomitant other/supportive therapies/medication for the active cancer
- Planned future cancer specific treatment (e.g. surgery, other)

9.3.7 Exposure / treatment

Information on rivaroxaban treatment during the observation period to be documented includes:

- Actual start and stop date
- Planned treatment duration on start of rivaroxaban

- Dosage
- Frequency
- If applicable: reasons for change of rivaroxaban dosage
- If applicable: reason for interruption of treatment with rivaroxaban; bridging therapy

9.3.8 Visits

Typical data to be collected during follow-up visits include:

- Date of visit
- Assessment of VTE
- Tumor status evaluation
    - Extent of disease and/or related surgeries
    - Status of cancer response (date last assessed)
    - ECOG performance status
- Change in concomitant cancer specific treatment/medication (including supportive medication) or additional medication
- Change in anticoagulant/antithrombotic therapy
- Change in concomitant other medication
- Treatment satisfaction ACTS questionnaire
- FACIT-Fatigue questionnaire
- Adverse events and serious adverse events
- Bleeding and thromboembolic events (including additional event forms)

Typical data to be collected during end of observation visit:

- Ongoing treatment or stop of rivaroxaban (if ongoing planned duration of rivaroxaban and reasons if planned duration has changed from initially planned duration)
- Treatment satisfaction ACTS questionnaire
- FACIT-Fatigue questionnaire
- Assessment of therapy
- Adverse events and serious adverse events (up to 30 days after stop of treatment with rivaroxaban)
- Primary reason for end of observation, i.e., regular end of observation after 6 months, patient lost to follow-up, consent withdrawn by patient, investigator decision, patient died

9.3.9 Regular Lab Tests

The documentation of laboratory tests will strictly follow clinical practice. Only routinely performed laboratory tests can be documented in this non-interventional study. The following lab tests will be recorded in the CRF if available from routine practice.

- Hemoglobin (Hb)
- Hematocrit (HCT)
- White blood cells
- Hemoccult test
- Platelets
- Electrolytes (Sodium and Calcium levels)
- C-reactive protein (CRP) levels
- Serum Creatinine
- Creatinine Clearance
- Liver enzymes: ALT, AST

9.4 Data sources

The investigator collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data during visits that take place in routine practice. In addition data will be collected from patient questionnaires and patient interviews. Each patient is identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel is able to identify the patient based on the patient identification code.

9.5 Study size

The sample size calculation is based on the primary endpoint, a change of the ACTS burden score at week 4 in comparison to baseline. The sample size is based on a 2-tailed paired t-test at the 0.05 level of significance.
Data from active cancer patients in the XALIA study [16] was used for source data. XALIA Visit 1 ACTS burden score for SOC is assumed as baseline, and for rivaroxaban is assumed as week 4 data. The mean (standard deviation; SD) of ACTS burden score for SOC and rivaroxaban is 52.9 (8.06) and 54.2 (6.11), respectively. From this result, a mean of difference between baseline and week 4 is assumed to be 1.3. The standard deviation of the difference is 10.0, however, considering within-patient correlation, SD of 8.0 is considered as reasonable. Based on these assumptions, 300 patients will be needed to reach power of 80%. Considering 20% drop-out rate based on data from the CLOT-study [17] and the SAFARI non-interventional study [18], 375 patients have to be included.

Calculations were performed with nQuery 7.

Due to the heterogeneous population of patients with cancer and assumed high drop-out rates after week 4, 500 patients will be enrolled in the COSIMO study to have sufficient numbers for secondary analyses.

9.6 Data management

A Contract Research Organization (CRO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request (Table 4: List of stand-alone documents, Annex 1). Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP), which is available upon request (see Table 4: List of stand-alone documents, Annex 1).

For information on quality control, refer to section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

The analyses for ACTS will be performed for the population which includes patients whose ACTS score at the time point for the target analysis, e.g. week 4, or months 3 and 6, is available.

Other analyses will be performed for the population which includes patients receiving at least one dose of rivaroxaban.

All analyses will be performed for the total study population (overall analysis) and separately for each participating country if patient numbers are sufficient and if required for local reasons. Whenever reasonable, data will be stratified by subgroups (e.g. age, gender, baseline characteristics, type and duration of SOC, reason for switch from SOC, type of cancer (high risk vs low risk for VTE) [19], type of cancer treatment (active vs no active treatment / change vs no change of treatment).

Sample size and disposition information by analysis time point will be displayed in a frequency table.

All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version. In addition, Adverse Events will be coded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock. The SAP is available upon request (see Table 4: List of stand-alone documents, Annex 1).

No interim analyses are planned. The study status and ongoing safety information (unadjusted, safety listings) will be reported to the EMA on a regular basis together with the Periodic Safety Update Reports (PSURs)/ Periodic Benefit-Risk Evaluation Reports (PBRERs).

The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.

9.7.2 Analysis of demography, disease details, prior and concomitant medication and other baseline data

All background data such as patient demographics, cancer related information, VTE risk factors, medical / surgical history, concomitant medication / treatment will be described by summary tables.

9.7.3 Analysis of treatment data

All treatment data analyses are indicated as secondary outcomes.

9.7.4 Analysis of primary outcomes

The primary efficacy outcome is a change of the ACTS burden score at week 4 (-2 to +4 weeks) in comparison to baseline.

As mentioned previously, the ACTS includes 13 items about the burden of ACT and 4 items about the benefit of ACT, with the global questions 13 and 17 being excluded from the scoring of the burden and benefit scales, respectively.

The score of each item is obtained through a 5-point Likert scale responses. The final scores are reported as two separate subscales (benefit and burden). The ACTS benefit scale is analyzed as a secondary outcome.

The null hypothesis H_0 and the alternative hypothesis H_A are

$$H_0: \Delta = 0$$

and

$$H_A: \Delta \neq 0,$$

where Δ is the change in the ACTS burden score. The hypothesis will be tested at a $\alpha = 5\%$ significant level.

The change in the ACTS burden score is assumed to be normally distributed and will be analyzed using paired t-test. The assumption of normality will be tested using the Shapiro-Wilk test at the 0.10 level of significance. In case the test shows significant, Wilcoxon signed rank test will be used.

For missing items, imputation to the mean is used where there are greater than 50% of the questions (> 6 items for burden) completed. Otherwise the item should be regarded as a missing value.

Subgroup analyses, by type and duration of SOC, and by reason for switch from SOC will be provided.

Sensitivity analyses will be conducted to investigate potential impact of patients who dropped out from the study earlier than week 4 on the outcome.

Further details will be given in the SAP.

9.7.5 Analysis of secondary outcomes

- Discrete Choice Experiment (DCE) based preference of patients for rivaroxaban vs. other anticoagulants

  DCE analyses will be performed by a third party, independently, as described in the DCE charter (see Table 4: List of stand-alone documents, Annex 1). Further details will be given in the separate SAP.

- ACTS Questionnaire

  ACTS burden score, benefit scale and items, boxplots by time will be created to examine the trend and shape of the score over time. In addition, descriptive statistics like average scores and frequencies of the number of patients who finished at least one questionnaire will be provided.

  Since the questionnaire responses are multiple measurements on the patient satisfaction of treatment over a period of time, a mixed model repeated measures analyses will be used to analyze the questionnaire data. Further details will be given in the SAP.

- FACIT-Fatigue

  Summary statistics will be provided for the FACIT-Fatigue total score by visit.

- Summary statistics will also be provided for bleeding events and thromboembolic events (refer to 9.7.6)

Descriptive statistics will be provided for the following outcomes:

- Information on the type of index event
- Type and duration of initial anticoagulation
- Reason for drug switch to rivaroxaban
- Planned and actual duration of anticoagulation with rivaroxaban
- Dosage of rivaroxaban; reason for any potential dose adjustments during course of treatment with rivaroxaban
- Reasons for any switch from rivaroxaban treatment, type and modus of switch to other anticoagulant
- Persistence with rivaroxaban treatment. Reasons for permanent cessation of rivaroxaban treatment

9.7.6 Analysis of safety data

Summary statistics (frequency and percentage of patients) will be presented by NCI CTC by the worst CTCAE grade for the following:

- Incidence proportion of AEs
- Incidence proportion of AEs leading to discontinuation of treatment
- Incidence proportion of serious adverse events

In addition, treatment emergent events will be presented; this will be specified in the SAP.

An adverse event is considered as treatment emergent when it starts on or after the day of the first dose of study medication and up to 2 days after the last dose.

These summary statistics will also be presented by MedDRA by the worst CTCAE grade.

Bleeding events and Thromboembolic events will be summarized separately as the secondary outcome.

Other safety parameters will be summarized descriptively.

9.7.7 Analysis of other data

Not applicable.

9.7.8 Interim analysis

No interim analyses are planned.

9.8 Quality control

9.8.1 Data quality

Before study start at the sites, all investigators will be sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators will have the chance to discuss and develop a common understanding of the study protocol and the CRF.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer.

All outcome variables and covariates will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request (see Table 4: List of stand-alone documents, Annex 1).

Medical Review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the Medical Review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on

the Medical review will be described in the MRP, which is available upon request (Table 4: List of stand-alone documents, Annex 1).

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing patient documentation (eCRF) will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) [20]. The documentation is available upon request (Table 4: List of stand-alone documents, Annex 1).

9.8.2 Quality review

In a subset of patients (at least 10% of all patients) source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors will access medical records on site for data verification. Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request (see Table 4: List of stand-alone documents, Annex 1).

9.8.3 Storage of records and archiving

The MAH will make sure that all relevant documents of this study including CRFs and other patient records will be stored after end or discontinuation of the study at least for 15 years. Further authority requirements for storage of medical records will remain unaffected.

The investigators participating in the study have to archive documents at their sites according to local requirements, considering possible audits and inspections from the MAH and/or local authorities. It is recommended to also store documents for a retention period of at least 15 years.

Statistical programming performed to generate results will be stored in the productive area of the programming system for at least 15 years at MAH's site.

9.8.4 Certification/qualification of external parties

The study responsible parties will ensure that any external supplier involved in the study will be appropriately qualified and, if applicable, certificated.

9.9 Limitations of the research methods

One of the major limitations of the design of this study is that it is not robust towards confounders/variables that vary over time. Another limitation of this study is that dissatisfied patients on rivaroxaban might drop-out from the study at any point of the study, however treatment satisfaction for the primary endpoint is measured at week 4 after the initiation of the rivaroxaban treatment. As this study includes all patients with cancer, their condition might worsen over time and with progressive chemotherapy. Therefore, there is a potential of high drop-out rate. Also, lack of a second cohort might make it difficult to put the results in perspective. On the other hand finding a matched comparator group of cancer patients treated for VTE would have been a major challenge and would have required a larger sample size to power the study. There might be a problem of carryover effects from the treatment administered before the intervention of interest hence baseline measurement becomes crucial to mitigate it. Another limitation of this study is that patient follow-up is based on routine care and there might be instances where a patient might come back to his physician only after 2 or 3 or 5 months after enrollment. However, a time-window of -2 to +4 weeks is considered to

take such variations in to account for this study. Also, patients might switch to another treatment during the observation period. However, those patients would still be followed until the end of the study. Also, there might be a potential overestimation of satisfaction on rivaroxaban, considering that patients were dissatisfied with the previous SOC treatment. Patients will be surveyed in writing and by telephone and therefore the possibility of false answers cannot be excluded.

9.10 Other aspects

Not applicable

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is an observational study where rivaroxaban 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.

10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, FDA and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012 [21]). Recommendations given by other organizations will be followed as well (e.g. EFPIA [22], ENCePP [23]). ICH-GCP guidelines will be followed whenever possible.

In addition, the guidelines on good pharmacovigilance practices (GVP module VI [24], and since the study qualifies as a PASS, GVP module VIII [25]) will be followed.

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

In all countries where reference to an IEC / IRB is required, documented approval from appropriate IECs / IRBs will be obtained for all participating centers prior to study start. When necessary, an extension, amendment or renewal of the IEC / IRB approval must be obtained and also forwarded to the MAH. The IEC / IRB must supply to the MAH, upon request, a list of the IEC / IRB members involved in the vote and a statement to confirm that the IEC / IRB is organized and operates according to applicable laws and regulations.

10.4 Patient information and consent

Before documentation of any data, informed consent is obtained by the patient in writing. In countries where required by law or regulation, the investigator must have the IECs / IRB written approval / favorable opinion of the written informed consent form and any other written information to be provided to patients prior to the beginning of the observation.

10.5 Patient insurance

In this study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and

monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both patient and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.6 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to the MAH. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the MAH. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

11. Management and reporting of adverse events/adverse reactions

11.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [26].

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- Off label use, occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event

- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)
- Product exposure via mother/father (exposure during conception, pregnancy, childbirth and breastfeeding)

As mentioned above no causal relationship with a product is implied by the use of the term "adverse event".

An Adverse Reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to rivaroxaban.

Causal relationship: The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are "yes" or "no".

An assessment of "no" would include:

The existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site)

Non-plausibility (e.g. the subject is struck by an automobile when there is no indication that the product caused disorientation that may have caused the event; cancer developing a few days after the first product administration)

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment. Factors to be considered in assessing the relationship of the AE to study treatment include:

The temporal sequence from product administration: The event should occur after the product is given. The length of time from product exposure to event should be evaluated in the clinical context of the event.

Recovery on product discontinuation (de-challenge), recurrence on product re-introduction (re-challenge): Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.

Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

Concomitant medication or treatment: The other products the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

An AE is serious (SAE) if it:

- Results in death
- Is life-threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is 'sudden death' where no cause has been established. In this instance, 'sudden death' should be regarded as the AE and 'fatal' as its reason for being 'serious'.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious, unless the admission is:

- planned before patient's inclusion in the study (i.e. elective or scheduled surgery) or
- ambulant (shorter than 12 hours) or
- part of the normal treatment or monitoring of the studied disease (cancer as well as VTE), e.g. chemotherapy/radiotherapy (i.e. not due to a worsening of the disease)

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Other medically important serious event: any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

11.2 Collection

Starting with the first application of rivaroxaban after enrollment into the study, all non-serious adverse events (AE) must be documented on the AE Report Form or in the CRF / EDC system and forwarded to the MAH within 7 calendar days of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within 1 business day of awareness). For each AE, the investigator must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event. Furthermore the investigator

has to assess whether the documented SAE/AE is related to either cancer or cancer-therapy or anticoagulation treatment.

If a pregnancy occurs during the study, although it is not a serious adverse event itself, it should be documented and forwarded to the MAH within the same time limits as a serious adverse event. The result of a pregnancy will be followed-up according to applicable Bayer SOPs. Any data on abnormal findings concerning either the mother or the baby will be collected as adverse events.

The documentation of any AE / SAE ends with the completion of the observation period of the patient. However, any AE / SAE - regardless of the relationship and the seriousness - occurring up to 30 days after the last dose of rivaroxaban within the study period has to be documented and forwarded to the MAH within the given timelines, even if this period goes beyond the end of observation.

As long as the patient has not received any rivaroxaban within the frame of the study AEs /SAEs do not need to be documented as such in this observational study. However, they are part of the patient's medical history.

For any serious product-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

Bleeding events (collected as SAEs or non-serious AEs) will be adjudicated and categorized (major vs non-major).

Thromboembolic events (collected as SAEs or non-serious AEs) (including asymptomatic thromboembolic events documented in routine imaging e.g. incidental PE from staging CT) will be adjudicated and categorized (recurrent vs new location, symptomatic vs asymptomatic) (as defined by standardized MedDRA Query 'Embolic and thrombotic events').

Adjudications will be performed by the steering committee as described in the steering committee charter (see Table 4: List of stand-alone documents, Annex 1).

11.3 Management and reporting

Non-serious AEs

The outcome of all reported AEs will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with rivaroxaban that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Module VI [24]) and according to national regulations by the MAH; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the CRF / EDC system will be forwarded immediately (within 1 business day of awareness) to the pharmacovigilance country person being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by the MAH for SAEs related rivaroxaban treatment; however, all investigators must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

11.4 Evaluation

Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case reports, refer to section 11.2 and 11.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

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.

The results of this 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 (e.g. GPP2 Guidelines [27], STROBE [28]). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the MAH.

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Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Number	Document Name / Reference number	Date*	Title
1	*<Name / Reference>*	*will be available after start of study*	Investigator list
2	*COSIMO_CRF_V1.0.pdf*	*29 Sep 2016*	CRF
3	*ClinDoc Version 4.1.0*	*03 Oct 2016*	EDC System
4	*18137_COSIMO_Data Management Plan_V1.0_2016-11-17_signed.pdf*	*17 Nov 2016*	DMP
5	*<Name / Reference>*	*tbd*	SAP
6	*19137_COSIMO UAT Approval_2016-10-03*	*03 Oct 2016*	EDC System Validation
7	*18137_COSIMO_QRP V 1.1_2017-05-12.docx*	*12 May 2017*	QRP
8	*18137_COSIMO_Medical Review Plan_Version 1.1_2017-07-13.docx*	*13 Jul 2017*	MRP
9	*18137_COSIMO_Steering Committee Charter_2017-01-26_v1.0 final_signed*	*26 Jan 2017*	Steering Committee Charter and members
10	*2016-05-30_18137_COSIMO_ACTS Charter v1.0.docx*	*30 May 2016*	ACTS Charter
11	*2016-10-05_DCE Charter for COSIMO Protocol_final v.1.1.docx*	*05 Oct 2016*	DCE Charter
12	*18137_COSIMO_Fatigue Charter v1.0_final.docx*	*12 May 2016*	FACIT-Fatigue Charter
13	18137_COSIMO_Protocol_Amend_BE_track1.1_2016-11-09_Sign.pdf	11 Nov 2016	Local amendment BE

***** Draft versions are indicated by date and <draft> in brackets. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

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

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.
For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.
This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
COSIMO Cancer associated thrombosis - patient reported outcomes with rivaroxaban.

Study reference number:
18137

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	13
1.1.2 End of data collection[2]	☒	☐	☐	13
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	13
1.1.6 Final report of study results.	☒	☐	☐	13

Comments:

Progress reports are not needed as the study is not included in RMP.

[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.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	13
2.1.2 The objective(s) of the study?	☒	☐	☐	16
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15-17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	30
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	18

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	19
4.2 Is the planned study population defined in terms of:	☒	☐	☐	16-17
4.2.1 Study time period?	☒	☐	☐	19-20
4.2.2 Age and sex?	☒	☐	☐	16, 20
4.2.3 Country of origin?	☒	☐	☐	19-20
4.2.4 Disease/indication?	☒	☐	☐	19-20
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19-20

Comments:

Seasonality does not apply for VTE/cancer.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	26-27
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	22-28
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	16-18
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Rivaroxaban is a direct acting Factor Xa inhibitor with little interaction potential, as is known from available clinical data. Furthermore 5.4, 5.5 not applicable as this is an NIS.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	24
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	29

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	22-32
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

There are no known effect modifiers.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face	☒	☐	☐	28

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
interview, etc.) 8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.) 8.1.3 Covariates?	☒ ☒	☐ ☐	☐ ☐	28 22
8.2 Does the protocol describe the information available from the data source(s) on: 8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) 8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event) 8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒ ☒ ☒	☐ ☐ ☐	☐ ☐ ☐	26 27 22
8.3 Is a coding system described for: 8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) 8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒ ☒ ☒	☐ ☐ ☐	☐ ☐ ☐	29 29 29
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	28

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	29
10.3 Are descriptive analyses included?	☒	☐	☐	31
10.4 Are stratified analyses included?	☒	☐	☐	29
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

This is a NIS, in an in label indication, excess risks are not expected. Medical Review of SAE/AE will occur regularly.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	32
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	33
11.3 Are methods of quality assurance described?	☒	☐	☐	32
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	32-33
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

No independent review of study results is planned, however results will be discussed and reviewed by a steering committee, and also published.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	18/33
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	18/33
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	13, 18
12.3 Does the protocol address other limitations?	☒	☐	☐	33

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	34
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	34
13.3 Have data protection requirements been described?	☒	☐	☐	35

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	34, 39
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	39

Comments:

Name of the main author of the protocol: Dr. Miriam Bach

Date: 29/2/2016

Signature: _____

Annex 3: Additional information

Performance Status (PS) (Eastern Cooperative Oncology Group [ECOG])

Table 5: ECOG PS

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

Annex 4: Description of amendments

None

Annex 5: Signature pages

Signature Page - Study medical expert

Title	COSIMO Cancer associated thrombosis - patient reported outcomes with rivaroxaban. A non-interventional study on patients changing to Xarelto® for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in patients with active cancer.
Protocol version identifier	XA1502, version 1.2
Date of last version of protocol	01 Feb 2018
IMPACT study number	18137
Study type / Study phase	☒ PASS ☐ non PASS Phase IV, observational
EU PAS register number	ENCEPP/SDPP/12608
Active substance (medicinal product)	Antithrombotic agents/Direct factor Xa inhibitors /Rivaroxaban (B01AF01)
Marketing authorization holder(s)	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: Dr. Miriam Bach

Date, Signature: _____, _____