Post Authorization Safety Study (PASS) Report - 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
Report version and date	V1.0, 19 December 2019
Study type / Study phase	Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☐ YES ☒ NO
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 was to gain more insights on patient-reported treatment satisfaction in patients with active cancer who changed from standard of care (SoC) anticoagulant to rivaroxaban for treatment of deep-vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE.

	MAIN OBJECTIVE The primary objective was to assess patient-reported treatment satisfaction regarding 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	54 investigational sites in 10 countries: Australia, Belgium, Canada, Denmark, France, Germany, Italy, Netherlands, Spain, and the United Kingdom
Author	PPD PPD PPD PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
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1. 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
Report version and date **Authors**	v1.0, 19 DEC 2019 PPD PPD PPD PPD
Keywords	Active cancer; health-related quality of life; patient preference; recurrent venous thromboembolism; rivaroxaban
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 about 1 to 2 cases per 1000 persons in the general population. Around 20% of VTE cases occur in patients with cancer. VTE is a leading cause of death in cancer patients. The guidelines valid at the time of study start recommended low molecular weight heparin (LMWH) as the preferred anticoagulant for VTE treatment. However, 2019 updates of the ITAC (International Initiative on Thrombosis and cancer) guidelines and ASCO (American Society of Clinical Oncology) guidelines as well as the ISTH (International Society of Thrombosis and Haemostasis) guidance statement published in 2018 included the use of rivaroxaban among other direct oral anticoagulants (DOACs) for the prevention and treatment of cancer-associated thrombosis. DOACs provide several benefits over LMWHs and vitamin K antagonists (VKAs), such as ease of use through oral administration, lower recurrent VTE rate and no monitoring, and may offer an opportunity to improve patient adherence, satisfaction and health-related quality of life (HrQoL). In previous clinical phase III studies with rivaroxaban, where patient treatment satisfaction was assessed by the anti-clot treatment scale (ACTS), results suggested an improvement in patients' treatment satisfaction with rivaroxaban versus the comparator treatment. However, such comprehensive information in cancer patients with VTE under routine clinical

	practice conditions was not readily available. Therefore, this study was designed to provide real-world information on anti-clot treatment preference, satisfaction and persistence in patients with VTE and active cancer who have switched from LMWH or VKA to rivaroxaban for the treatment of acute VTE or to prevent recurrent VTE.
Research question and objectives	The main goal of this study was to gain more insights on patient-reported treatment satisfaction in patients with active cancer who have changed from standard of care (SoC) anticoagulant to rivaroxaban for treatment of DVT and PE, and prevention of recurrent DVT and PE. **Primary objective:** To assess patient reported treatment satisfaction regarding 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. **Secondary objectives:** • 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 o clinical characteristics o patterns of use of anticoagulant treatment o 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 was 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. Patients with active cancer had to be treated for acute VTE for at least 4 weeks with SoC (LMWH or VKA) to be eligible for enrollment.

	Patient's treatment satisfaction with the previous standard of care (SoC) treatment (LMWH or VKA) at baseline was compared to prospective treatment with rivaroxaban using the ACTS questionnaire. The final scores were reported as two separate subscales (Benefit and Burden), For the primary endpoint, ACTS Burden score at Week 4 was compared to the ACTS Burden score at baseline. Information on patient treatment preferences were collected by means of a discrete choice experiment (DCE), in a semi-structured telephone interview. The telephone interview was conducted after a minimum of 4 weeks to a maximum of 12 weeks after enrollment of patients in the study or start of rivaroxaban. Information on quality of life by means of the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue self-administered questionnaire was also collected at baseline, as well as Week 4, Month 3, and Month 6 which were the time points of interest. The observation period for each patient started with enrollment and ended after 6 months (regardless of any treatment changes) or with withdrawal of consent, death or loss to follow-up. The study ended 6 months after end of enrollment. Cancer patients for whom the decision was made to change from SoC to rivaroxaban by the attending physician were invited to be a part of this study in a consecutive manner. The first visit had to be within the enrollment period for the respective country which means that there was no retrospective inclusion. The actual treatment duration was determined solely by the physician and was not dependent on the initial intended treatment duration.
Setting	Female and male patients with active cancer and a diagnosis of DVT/ and/or PE were enrolled after the decision to start treatment with rivaroxaban has been made by the investigator. The recommendations as per the local summary of product characteristics (SmPC) was followed. **Main 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 SoC 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 with Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2. **Main 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.
Subjects and study size, including dropouts	The sample size calculation was based on the primary endpoint, a change of the ACTS Burden score at Week 4 in comparison to baseline. The sample size was based on a 2-tailed paired t-test at the 0.05 level of significance. Planned number of patients: 500 Enrolled: 532 patients All-patients population: 509 patients Safety Analysis Set (SAF): 505 patients Efficacy sets: ACTS Analysis Set Week 4: 381 patients ACTS Analysis Set Month 3: 341 patients ACTS Analysis Set Month 6: 253 patients ACTS Analysis Set over time: 423 patients FACIT Analysis Set: 450 patients
Variables and data sources	PRIMARY ENDPOINT The primary endpoint of this study was the change in the ACTS Burden score from enrollment to Week 4, to assess changes in patient anticoagulation treatment satisfaction. SECONDARY ENDPOINTS • Preferences regarding the attributes of the anticoagulation medication options LMWH, VKA, rivaroxaban (DCE)

	• Change of ACTS (Burden score and Benefit score) over time (at Month 3 and Month 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. The investigator documented the study-relevant data for each patient (historic data from medical records and treatment related data during initial visit and follow-up visits) in the electronic case report form (eCRF). All variables were 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 were described by absolute value and as change from baseline per analysis time point, if applicable. The analyses for ACTS were performed for the population which included patients whose ACTS score at the time point for the target analysis, i.e. Week 4, or Month 3 and Month 6, was available. All details including calculated variables and proposed format and content of tables are described in the Statistical Analysis Plan (SAP). SAP was finalized on 05-SEP-2019, before study database lock.
Results	The mean (SD) age of the 505 study patients (SAF) was 64.0 (11.72) years, with 67.7 % (n=342/505) aged ≥ 60 years. More than half of the patients (55.4%, n=280/505) were female. Index VTE was defined as the VTE event leading to medical presentation before inclusion in the study. DVT was the index VTE for 45.3% (n=229/505), PE for 37.2% (n=188/505) and both DVT and PE for 9.7% of patients (n=49/505). The index VTE was symptomatic in most patients (72.1%, n=364/505). Of the SAF, 88.9% of patients (n=449) had a solid tumor and 11.1% (n=56) had hematological malignancy; 54.6% of patients with solid tumor (n=245/449) presented with metastatic cancer at enrollment. Of the solid tumors, a gastrointestinal malignancy was the primary cancer in 29.2% (n=131/449) of patients, breast cancer in 18.7% (n=84/449), gynecological cancer in 17.8% (n=80/449), lung cancer in 13.1% (n=59/449), and genitourinary cancer in 12.9% (n=58/449) of patients. According to the ECOG performance at baseline, physicians rated the patients as ECOG 1 (slightly

	restricted) in 54.7% (n=276/505) of patients and ECOG 0 (fully ambulatory) in 32.1% (n=162/505) of patients. Most frequent concomitant conditions were anemia (within the last 12 months) and hypertension in about 35% of patients, respectively. Furthermore, 11.1% of patients had records of diabetes mellitus. Before enrollment, 85.0% of patients (n=429/505) had received any systemic anti-cancer therapy, 31.7% (n=160/505) any radiotherapy and 6.1% (n=31/505) any local anti-cancer therapy. As to anti-coagulant treatment, the vast majority of patients (96.6%, n=488/505) had been treated with LMWH (initial anticoagulation treatment for index VTE event) before they changed to rivaroxaban in this study. The main reason for choosing rivaroxaban was related to 'physician decision' in 34.5% of patients (n=174/505), followed by 'burden of parenteral administration', 'quality of life' and 'patient decision' in 26.9%, 18.6% and 15.0% of patients, respectively. Most patients (78.6%, n=397/505) were prescribed once daily 20 mg rivaroxaban. There were 32 patients who had interruptions in their rivaroxaban treatment, i.e. they did not take rivaroxaban for at least 2 days - the reasons were most often not specified. Overall, 26.7% of patients (n=135/505) prematurely discontinued the treatment with rivaroxaban before 6 months of observation. Most frequently recorded reason was 'other adverse event' in 18.4% of patients (n=93/505). The median total treatment duration of anticoagulation treatment since the VTE index event was 272.0 days, corresponding to about 9 months. At the end of the observation, 59.8% of patients (n=302/505) continued treatment with rivaroxaban. The patient satisfaction scale ACTS was completed at least once by 423 patients at baseline (100.0%), by 381 patients (90.1%) at Week 4, by 341 patients (80.6%) at Month 3, and by 253 patients (59.8%) at Month 6. The mean (SD) ACTS Burden subscale (primary outcome variable) was 51.8 (7.28) at baseline, which increased by 3.9 (6.71) to 55.6 (5.46) at Week 4. The mean (SD) ACTS Benefit score was 11.2 (2.73) at baseline. Over time, the ACTS Benefit score increased, with a mean (SD) change from baseline at Month 3 of 0.4 (3.13), and at Month 6 of 0.5 (3.01). The quality of life (fatigue related) questionnaire FACIT was completed by 450 patients at baseline (100.0%), by 423 patients (94.0%) at Week 4, by 377 patients (83.8%) at Month 3, and by 323 patients (71.8%) at Month 6. The mean (SD) FACIT score was 34.4 (9.44) at baseline. Over time, the FACIT score increased, with a mean (SD) change from baseline at Month 3 of 1.4 (8.6), and at

	Month 6 of 2.1 (8.9). This indicates an improvement of fatigue-related quality of life over time, which was significant vs. baseline at Months 3 and 6. The increase in patient treatment satisfaction as assessed by the mean change in ACTS Burden score was larger in female than in male (4.4 vs. 3.3; median: 3.0 vs. 2.6) and larger in younger (< 60 years) than in older (≥ 60 years) patients (4.4 vs. 3.6; median: 9.0 vs. 6.0). Patients whose index VTE was symptomatic were more satisfied at Week 4 than those without symptoms (4.3 vs. 2.7; median: 3.0 vs. 2.0). Overall, 61.8% of patients (n=312/505) experienced any TEAE during the study (54.9% of patients had TEAEs excluding bleeding events, n=277/505); in 21.8% of patients (n=110/505) TEAEs were suspected to be drug-related. TEAEs were suspected to be cancer-related in 35.8% of patients (n=181/505) and related to cancer-therapy in 26.7% of patients (n=135/505). Serious TEAEs (as reported by the investigator) were documented in 29.3% of patients (n=148/505) and in 4.4% of patients (n=22/505) the serious TEAEs were suspected to be drug-related. In 0.4% of patients (n=2/505), the drug-related serious TEAEs led to death. Most frequently documented drug-related TEAEs on SOC-level were "Respiratory, thoracic and mediastinal disorders" (6.5% of patients, thereof the PT "epistaxis" in 5.3% of patients, n=27/505), "Gastrointestinal disorders" (5.5% of patients, n=28/505, thereof the PT "rectal haemorrhage" in 1.6%, n=8/505; the other events in this SOC occurred only once or twice), "Renal and urinary disorders" (3.6% of patients, all of them affected by the PT "haematuria"), and 'Skin and subcutaneous tissue disorders' (3.2%). The drug-related serious TEAEs were most often "Gastrointestinal disorders" (11 patients; 2.2%), "Respiratory, thoracic and mediastinal disorders" (4 patients; 0.8%), and "Vascular disorders" (3 patients; 0.6%). Overall (SAF), 47 patients died from start of rivaroxaban treatment until end of observation. The most frequently adjudicated cause of death was the underlying cancer in 30 patients (5.9%), followed by infectious disease in 6 patients (1.2%) and ischemic stroke in 5 patients (1.0%). Out of the 30 adjudicated fatal cases due to the underlying cancer, 5 cases were not treatment-emergent, i.e. the patients died at least 2 days after having stopped rivaroxaban treatment.
Discussion	The non-interventional, prospective COSIMO study generates new and additional information on the real-world use of rivaroxaban in a population with cancer and VTE, particularly from a patient-centered perspective. The primary results of the COSIMO study showed significant improvement (p<0.0001) in

	patient-reported anti-clot treatment satisfaction 4 weeks after change from SOC to rivaroxaban for treatment of CAT, measured by the ACTS burden score. This reported improvement in treatment satisfaction persisted over 6 months of observation. Patient-reported improvement in treatment satisfaction was observed across the different components of treatment burden items that were measured, indicating improvement across several aspects of the patient's anti-clot treatment. The most substantial improvements were seen in the items addressing bruising, daily and occasional hassle of treatment, and the difficulty, time-consumption, frustration and burden of treatment. It is noteworthy that the overall improvement in patient-reported treatment satisfaction was observed despite ~35% of the patients changing to rivaroxaban treatment based on the physician's decision. The results of the COSIMO study were generally consistent with results of the randomized controlled trial EINSTEIN DVT of rivaroxaban vs. LMWH/VKA. Reported treatment satisfaction with rivaroxaban was slightly higher than in the XALIA study and in the EINSTEIN PE trial. While comparing the different studies, it should be considered that the proportion of cancer patients was not the same in the various populations. The incidence of adjudicated major bleeding events in the COSIMO study were lower than those previously reported in the randomized select-d trial (3.6% of patients at 6 months vs 6% of patients at 6 months). As to adjudicated recurrent symptomatic VTE events, the incidence rate amounted to 3.0%. The clinical outcomes from COSIMO were also within the range of results from database analyses and observational studies of rivaroxaban treatment or patients with CAT, with reports of VTE recurrence rates ranging from 1.2% to 13.2%, and major bleeding event rates of 1.9% to 8.2% at 6 months. Similarly, the all-cause mortality rate (adjudicated) in COSIMO (9.3%) is within the range reported in previous real-world studies with DOACs (4.8% to 17.8%). Data describing patient satisfaction with DOACs for the treatment of CAT are limited, and the present study is the first dedicated evaluation of DOAC treatment satisfaction in patients with VTE and active cancer. The patients recruited in the COSIMO study were representative of patients with CAT who are likely to be selected for rivaroxaban therapy in routine clinical practice, particularly with the minimal inclusion and exclusion criteria. Similar to the select-d trial, approximately

	half of patients enrolled in the current study had metastases and ~90% had solid tumors The results of the COSIMO study demonstrate that patients with CAT who change their VTE treatment from LMWH, fondaparinux or VKA therapy to rivaroxaban in routine clinical practice experience an improvement in treatment satisfaction, particularly in reducing patient-reported anticoagulation burden. Analyses suggest that rivaroxaban provides a more convenient, easy-to-follow treatment regimen that is less time-consuming and less likely to cause frustration, worry and bruising than SOC therapy (predominately LMWH). Improved treatment satisfaction following a change to rivaroxaban for the treatment of CAT has conceivable positive implications for long-term persistence with therapy and improved clinical outcomes.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen
Names and affiliations of principal investigators	Contact details of the principal and/or coordinating investigators for each country and site participating in the study are listed in a stand-alone document (see Annex 1: List of stand-alone documents which is available upon request).

2. List of abbreviations

ACT	Anti-Clot Treatment
ACTS	Anti-Clot Treatment Scale
AE	Adverse Event
aPTT	activated Partial Thromboplastin Time
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
CAT	Cancer-associated thrombosis
CFR	Code of Federal Regulations
CRF	Case Report Form
CrCl	Creatinine Clearance
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events Discrete
DCE	Choice Experiment
DMP	Data Management Plan
DOAC	Direct Oral Anticoagulant
DVT	Deep-Vein Thrombosis
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines 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
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practice
Hb	Hemoglobin
HCT	Hematocrit
HrQoL	Health-related Quality of Life
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee

INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
LMWH	Low Molecular Weight Heparin
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
N/A	Not Applicable
PASS	Post-Authorization Safety Study
PE	Pulmonary Embolism
P-gp	P-Glycoprotein
PT	Preferred Term
QoL	Quality of Life
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOC	System Organ Class
ULN	Upper Limit of Normal
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
WHO DD	World Health Organization Drug Dictionary

3. Investigators

The study was conducted at 54 study centers in 10 countries (Australia, Belgium, Canada, Denmark, France, Germany, Italy, Netherlands, Spain. and the United Kingdom).

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

4. Other responsible parties

A Steering Committee of external experts provided input for the development of the study protocol and case report form (CRF). The committee also provided 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 Members and the respective Charters are kept as stand-alone documents (see Annex 1 of the study protocol, Annex 1) and are available upon request.

Project Implementation, quality review, data management, and statistical analysis were performed by Institute Dr. Schauerte, Finkenstrasse 7, 80333 Munich, Germany.

Discrete Choice Experiment (DCE) analyses, as described in the DCE charter (Annex 1 of the study protocol, Annex 1), were performed independently by Ingress GmbH, Alter Holzhafen 19, 23966 Wismar, Germany.

5. Milestones

Table 5.1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection / observation	15 Sep 2016	11 Oct 2016	
End of data collection / observation	15 Dec 2018	07 Dec 2018	
Registration in the EU PAS register	n.a.	19 Apr 2016	
IEC or IRB approval - Study protocol version 1.0	n.a.	First approval: *25 Jul 2016* Last approval: *26 Sep 2017*	
IEC or IRB approval -Study protocol version 1.1	n.a.	First approval: *19 Dec 2016* Last approval: *22 Nov 2017*	

IEC or IRB approval -Study protocol version 1.2	n.a.	First approval: *09 Feb 2018* Last approval: *24 Apr 2018*	
Database Clean	15 Mar 2019	28 Mar 2019	
Final report of study results	15 Oct 2019	*19 Dec 2019*	

6. 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; 15-20% of all VTE cases occur in patients with cancer. Patients living with cancer have a 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 [Heit 2015]. Also, the VTE event might trigger a delay or discontinuation of their cancer treatment [Lee and Carrier 2014, Wharin and Tagalakis 2014]. 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 [Lyman 2007, Lyman 2014, Mandala 2011]. 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 [Lyman 2007, Lyman 2014, Mandala 2011]. 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 [Wharin and Tagalakis 2014]. A simple, effective and affordable alternative for the prevention and treatment of venous thromboembolism in patients with cancer is an unmet clinical need.

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 [Bamber 2013, Prins 2015]. However, such comprehensive information in cancer patients with VTE under routine clinical practice conditions is lacking. Therefore, this study was designed to collect patient reported outcomes and to assess treatment satisfaction in active cancer patients treated with rivaroxaban for VTE. The aim of the study was to complement and add to existing data from the Phase III studies as in this regard there is still high unmet need among clinicians.

7. Research question and objectives

The main goal of this study was 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.

7.1 Primary objective

The primary objective in this study was 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.

7.2 Secondary objectives

The secondary objectives in this study were:

- 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.

8. Amendments and updates

There were 2 updates to the final protocol v1.0 introduced after start of the study, as summarized in Table 8.1.

Table 8.1: Amendments

No.	Date	New version number	Reason for Amendment
Update 01	15 November 2016	v1.1	Update of PASS register number, timelines and list of stand-alone documents
Update 02	09 November 2016	V1.1_BE	Belgium reimbursement information for patients switched from VKA to rivaroxaban was added
Update 03	01 February 2018	v1.2	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.

OS = observational study, PASS = Post-Authorization Safety Study

9. Research methods

The study was conducted according to the original protocol, version 1.2, dated 01 February 2018. The protocol and a sample blank CRF (amended version 1.7, dated 05 September 2017) can be found in Annex 1. The statistical analyses performed for this study are defined in the statistical analysis plan (SAP), version 1.2, dated 05 SEP 2019 (Annex 1).

9.1 Study design

This was 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 was conducted in Europe, Canada and Australia.

The study design is illustrated in Figure 9-1.

Patients with active cancer who had been treated for acute VTE for at least 4 weeks with standard of care (SoC; LMWH or VKA) were eligible for enrollment.

Patient's treatment satisfaction with the previous SoC treatment (LMWH or VKA) at baseline was compared to prospective treatment with rivaroxaban using the ACTS questionnaire (for more details see Section 9.4.1). The ACTS was measured at baseline for the previous SoC treatment and at follow-up visits for the rivaroxaban treatment (Week 4, Month 3 and Month 6; time points of interest for data collection). The ACTS Burden score at Week 4 was compared to the ACTS Burden score at baseline.

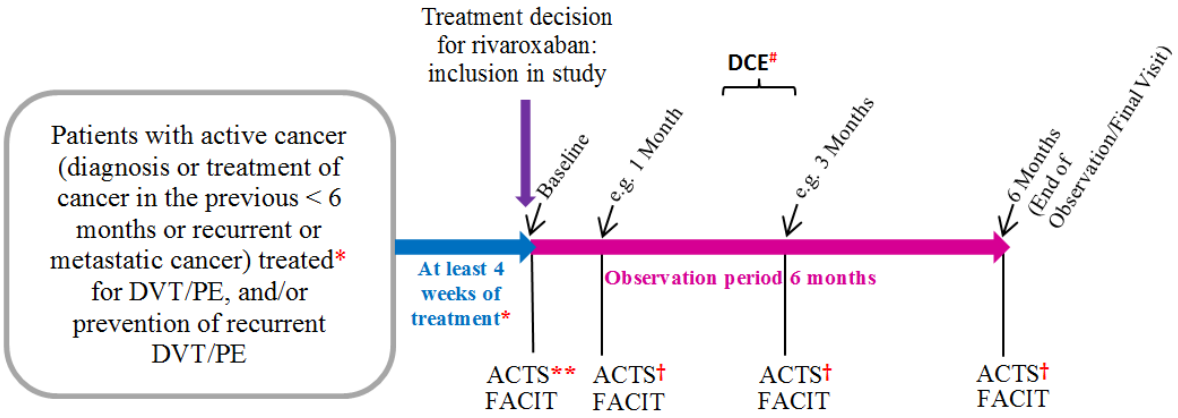
Information on patient preferences was collected by means of a discrete choice experiment (DCE). In a semi-structured telephone interview (aided by a corresponding online tool which was used by trained interviewers during the interview), patients that consented to participate in the DCE were surveyed once regarding preference for the different convenience properties of LMWH, VKA or rivaroxaban. The telephone interview was to be conducted after a minimum of 4 weeks to a maximum of 12 weeks after enrollment of patients in the study/start of rivaroxaban.

Information on quality of life by means of the self-administered Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire was also collected at baseline, as well as Week 4, Month 3 and Month 6 (time points of interest for data collection).

The observation period for each patient started with enrollment and ended after 6 months (regardless of any treatment changes) or with withdrawal of consent, death or lost to follow-up. The study ended 6 months after end of enrollment. Follow-up visits of the patients were regular visits to their physicians, but data of interest was collected at above mentioned time points. All the available patient and treatment information (see Section 9.4) was collected at inclusion and at follow-up visits (Week 4, Month 3 and Month 6). Results from laboratory or diagnostic procedures were documented at the visits as far as they were 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 were 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 was documented in the eCRF to document real-world practical management of VTE in patients with cancer. The first visit had to be within the enrollment period for the respective country so that no retrospective inclusion was possible. The actual treatment duration was determined solely by the physician and was not dependent on the initial intended treatment duration.

As per the guidelines valid at the time of study start, a high percentage of cancer patients with VTE was expected to be treated with SoC, i.e. LMWH. In a non-interventional setting for this study, a one-arm design would avoid differences due to selection or inclusion of patients receiving either SoC treatment or rivaroxaban and included patients who were treated according to the guidelines but switched to rivaroxaban due to several possible reasons. This design was chosen to reduce differences caused by patient perceptions (e.g. pain, satisfaction, improvement etc.) which can differ for every individual patient and might cause between patient variations in a comparative setting. Also, the patients could 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

Figure 9-1: COSIMO study design and data collection

9.2 Setting

9.2.1 Regulatory setting

This was a non-interventional study, carried out within an approved indication in accordance with guidelines and regulations of European Medicines Agency (EMA), Food and Drug Administration (FDA) and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012). Recommendations given by other organizations were followed as well (e.g. EFPIA, ENCePP). International Conference of Harmonization (ICH)-Good Clinical Practice (GCP) guidelines were followed whenever possible.

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

The present report presents the results of the final analysis. Summary results of the DCE analyses are included in Section 10.5.4. Detailed results are contained in the final report provided by Ingress (Annex 2). No interim analyses were conducted.

9.2.2 Locations and observation periods

Recruitment period: In total, 532 patients were enrolled in 54 sites (academic or private health care providers, hospitals etc.) in 10 countries (in Europe, Canada and Australia) in a time period of 20 months (October 2016 to May 2018). For details on patient enrollment refer to Section 9.3.

Enrollment / initial visit: Once a patient was found eligible for inclusion, and after the patient signed the informed consent (for data collection and to take part in the additional phone interviews for the DCE), the patient could be enrolled. It was also possible to participate only in the study, but not in the DCE. Baseline information was recorded with the status at initial visit. For details on documentation procedures please refer to Section 9.4.

Follow-up documentation: The observation period covered 6 months regardless of any treatment changes. Follow-up visits of the patients were regular visits to their physicians and were not mandated on them. During that time frame, two follow-up visits of interest, e.g. after 4 weeks and 3 months, were documented. For details on documentation procedures please refer to Section 9.4.

End of observation / final visit: The observation period for a patient ended after 6 months regardless of any treatment changes after enrollment. Possible reasons for premature end of observation were consent withdrawal, lost to follow-up or death of patient.

9.3 Subjects

Female and male adult patients with active cancer and a diagnosis of DVT/ and/or PE were 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 Summary or Product Characteristics (SmPC) was to be followed.

9.3.1 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 has been 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 (details for the ECOG score can be found in Annex 3 of the study protocol, Annex 1)
- Patients who were willing to participate in this study (signed informed consent)
- Patients who were available for follow-up with a life expectancy > 6 months.

9.3.2 Exclusion criteria:

- Patients with contraindications to rivaroxaban
- 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.

9.4 Variables

The investigator collected historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collected treatment related data during initial visit and follow-up visits. The investigator documented the study-relevant data for each patient in the electronic case report form (eCRF). A blank sample CRF can be found in Annex 1.

Table 9.1 lists with an X all tests and assessments recordable at the various time points, if performed. The procedures are described in more detail in the Study Protocol, which is provided in Annex 1 of this report.

Table 9.1: Documentation schedule

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 was 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 had a recall period of 4 weeks, it was to be collected between -2 to + 4 weeks around each visit.
* If a patient reported an SAE/AE during the telephone interview this was adequately followed-up
** Serious Adverse Events were reported to the MAH within 1 business day. AEs and SAEs were collected up to 30 days after stop of treatment with rivaroxaban
§ Only documented if information was available from regular practice. No additional diagnostics were required for the study.

9.4.1 Variables to determine the primary endpoint

The primary outcome of this study was treatment satisfaction, assessed as change in the ACTS Burden score [Bamber et al. 2013] from enrollment to Week 4. The current ACTS questionnaire is an adaptation of the Duke Anti-Coagulation Satisfaction Scale (DASS) (Samsa et al., 2004), which has undergone a rigorous development process to ensure that the scale is appropriate for use with atrial fibrillation (AF) and venous thromboembolism (VTE) patients internationally. The ACTS charter is provided in Annex 1.

Treatment satisfaction was measured using the self-administered ACTS questionnaire. The aim of the ACTS is to assess patient views associated with anti-coagulant therapies. The ACTS scale is a 17-item patient-reported measure of satisfaction with anticoagulant treatment. It includes 13 items about the burdens of ACT (including a 12-item Burden scale and one global question about burdens) and 4 items about the benefits of ACT (including a 3-item Benefit scale and one global question about benefits). The final scores are reported as two separate burden and benefit subscales. The use of separate subscales for ACTS burdens and benefits means that it was possible to focus specifically on the burdens of anticoagulant therapy as the primary outcome.

ACTS scores were calculated where rivaroxaban was taken at least 2 weeks before assessing ACTS score at the respective visit (Week 4, Month 3, Month 6).

Each item is scored on a 5-response Likert scale. Items 13 and 17 are questions about the overall satisfaction with the same five possible answers. For the present analysis, items 13 and 17 were excluded from the subscale calculation. The calculation of the Burden and Benefit subscales is shown in Table 9.2.

Table 9.2: ACTS Benefit and Burden subscale

Subscale	Questions included	Coding	Calculation of Subscale Score
Burden	1-12	Reverse Coding	Sum of item score 1 to 12
Benefit	14, 15, 16	Normal Coding	Sum of item score 14 to 16

Reverse coding was adopted for the calculation of the Burden subscale score in order that higher scores indicate higher satisfaction (from 1=not at all to 5=extremely). Items for which more than one response was given for one question could not be included in the summation and were treated as missing. The Burden subscale score could take values between 12 and 60 and the Benefit subscale (normal coding, i.e. item score = item response) score ranged from 3 to 15.

Imputation to the mean was used for the Burden and Benefit scales when at least 50% of the questions were completed (6 items for Burden scale and 2 items for Benefit scale). For details about the imputation methods refer to Section 4.6 the SAP (Annex 1).

9.4.2 Variables to determine the secondary endpoints

Patient preferences (Discrete Choice Experiment)

Information on convenience-related patient preferences in anticoagulation treatment was collected by means of a DCE conducted by telephone at 4–12 weeks after enrollment.

A DCE is an attribute-based measure of benefit. During the DCE, participants were asked to make a choice between options 'A' and 'B' across nine treatment scenarios (plus a control scenario) on pictorial charts, considering differing combinations of utility-increasing and utility-decreasing

attribute levels (trade-off type of choice) [Böttger et al. 2015]. The aim of the DCE was to define the ideal anticoagulant treatment from the perspective of patients with cancer-associated thrombosis.

The report with results of the DCE assessments provided by Ingress is annexed (Annex 2). Summary results are described in Section 10.5.4.

Patient Quality of life (FACIT)

FACIT Fatigue is a 13-item questionnaire that assesses feelings of tiredness, weakness, listlessness, frustration, energy levels, ability to perform daily tasks (including eating) and need for help to complete tasks. The items are scored on a five-point (0 to 4) scale; a higher score indicates better health-related quality of life (HRQoL).

If more than 50% of the items had a response, values for missing responses could be calculated via prorating: the sum of the scores for the completed items (i.e. those with responses) was multiplied by 13 and then divided by the number of completed items. Patients completed this instrument at enrollment and, for example, at Week 4 and Month 3 and Month 6.

Demographic data and disease history

Demographic data and the disease history were evaluated. Data regarding current indication and VTE event included the type of index event (DVT, PE, catheter-associated DVT), date, method of diagnosis, location of VTE (incl. catheter-associated VTE), type of indication, details about initial anticoagulation, details about planned and actual 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, and other individual risk factors.

Data regarding the underlying cancer was also assessed, including date of diagnosis, ECOG performance status at enrollment, disease status at study start, 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, and, if applicable, number and location of metastases and extent of disease and/or related surgeries.

Previous and concomitant diseases and medication

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

- Thrombophilia
- Hypertension

Other co-morbidities judged as relevant by the physician could be documented by the physician. For any co-morbidity, the diagnosis, the start and the stop date/ongoing was documented.

All medication taken as well as cancer-specific treatments before study start (initiated and stopped before study start) was classified as ‘prior medication and treatments’. All medication taken and cancer-specific treatments that overlaps with rivaroxaban treatment for any indication (either initiated before study start or during the study) was termed ‘concomitant medication and treatments’. Information collected for medication included trade name or International Nonproprietary Name (INN), start date, stop date/ongoing, dose/dosing schedule, unit, and indication.

Initial anticoagulation treatment for index VTE event was defined as the last treatment before switch to rivaroxaban.

All therapies documented were coded using the World Health Organization – Drug Dictionary (WHO DD). Medical history, any diseases and adverse events were coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

Exposure / treatment

The dosage and frequency of rivaroxaban use, reason for any potential dose adjustments during course of treatment with rivaroxaban at baseline and at 6 months (if still on treatment), the reasons for any switch from rivaroxaban treatment and type and modus of switch to or bridging with other anticoagulant(s) were documented. The reasons for any permanent cessation of rivaroxaban treatment, if applicable, was also documented.

9.4.3 Safety variables

Adverse events

An adverse event (AE) was considered as treatment-emergent when it started on or after the day of the first dose of rivaroxaban and up to 2 days after the last dose.

AEs and serious AEs (SAEs) were documented up to the completion of the 6-month observation period or up to 30 days after rivaroxaban discontinuation, whichever occurred earlier (with exception of the post-observational period: AEs could then be documented within 30 days and under the condition that rivaroxaban was not discontinued).

Adverse events were coded using the MedDRA coding dictionary, version 21.1. The severity of AEs was coded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Bleeding events, thromboembolic events, major adverse cardiovascular events

A bleeding adverse event was considered as treatment-emergent when it started on or after the day of the first dose of rivaroxaban and up to 2 days after the last dose.

Details about bleeding events included the bleeding type (major or non-major), bleeding site, provocation of bleeding, diagnosis test, effects of the bleeding on patients (medical or surgical intervention, associated discomfort, collection of any hematology labs, transfusions including unit). Bleeding events (collected as serious AEs or non-serious AEs) were adjudicated and categorized as major or non-major bleeding.

A thromboembolic event was considered as treatment-emergent when it started on or after the day of the first dose of rivaroxaban and up to 2 days after the last dose.

Details for thromboembolic adverse events included clinical presentation, time of onset since start of rivaroxaban, diagnosis test, and clot location.

Thromboembolic events, including incidental thromboembolic events documented in routine imaging (e.g. incidental PE from staging computed tomography; collected as serious AEs or non-serious AEs) were adjudicated and categorized (symptomatic or incidental).

Major adverse cardiovascular events (MACE) were defined as occurrence of stroke, myocardial infarction, unstable angina, acute coronary syndrome, or cardiovascular death. MACE included events detected during medical review and adjudicated as such.

A Central Adjudication Committee (Steering Committee, see Section 4) adjudicated major bleeding and thromboembolic events (major bleeding, recurrent VTE (symptomatic or incidental), other thromboembolic events (symptomatic or incidental), major adverse cardiovascular events). All death events (as reported by the investigator) were adjudicated. Causes of death were categorized as being related to cancer, thrombosis, bleeding, infectious diseases or other.

Laboratory data

The following laboratory parameters were documented: D-dimer, Platelets, Hemoglobin (Hb), Hematocrit (HCT), White blood cells, Lymphocytes, Creatinine, Creatinine clearance (CrCl), Bilirubin, ALT, AST (the latter two liver parameters in the categories 'below normal limits', 'within normal limits', 'within 1-3 × upper limit of normal (ULN)', 'within >3-5 × ULN', 'within >5-20 × ULN' and 'above 20 × ULN'), Sodium, Calcium, Hemoccult test ('negative', 'positive'), C-reactive protein (CRP) level, Activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR).

As this is a non-interventional study, the study initiator could not influence if, and when laboratory tests were performed. No central laboratory was used.

9.5 Data sources and measurement

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

A Contract Research Organization (CRO) was selected and assigned for EDC system development. The CRF was part of the EDC system which allowed documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request.

9.6 Bias

Due to the observational, non-interventional design of the study, the results were prone to bias and confounding. Potential sources of bias were:

- a potential overestimation of patient satisfaction on rivaroxaban due to selection bias, as the eligible patients for this study were likely dissatisfied with their previous SoC treatment
- the absence of a reasonable control cohort
- high discontinuation rates due to the potential worsening of the patient's condition under treatment with progressive chemotherapy and/or dissatisfied patients
- carry-over effects from previous treatment
- follow-up visits took place under routine care, i.e. a patient might have come back to his/her physician only after 2 or 3 or 5 months after enrollment
- Impact of other treatments, where patients might have temporarily switched to another treatment during the observation period

- Likelihood of patient giving false answers during the DCE survey

To address these potential biases, a time-window of -2 to +4 weeks for ACTS data collection was considered to take such variations into account for this study. Furthermore, potential bias due to high discontinuation rate should have a minimal impact on the primary outcome (treatment satisfaction), which was measured at Week 4 after the initiation of the rivaroxaban treatment. Patients who switched to another treatment during the study were followed up until the end of the study so that safety related data could still be documented. The lack of a control patient cohort might make it difficult to put the results in perspective but finding a matched comparator group of cancer patients treated with cancer-associated thrombosis would have been a major challenge.

9.7 Study sample size calculation

The sample size calculation was based on the primary endpoint, a change in the ACTS Burden score at Week 4 in comparison to baseline. The sample size was based on a 2-tailed paired t-test at the 0.05 level of significance.

Data from active cancer patients in the XALIA study [Cano S et al. 2018; Ageno W et al. 2017] was used as source data. XALIA Visit 1 ACTS Burden score for SoC was assumed as baseline, and for rivaroxaban was assumed as Week 4 data. The mean (standard deviation; SD) of ACTS Burden score for SoC was 52.9 (8.06) and for rivaroxaban 54.2 (6.11). From this result, a mean of difference between baseline and Week 4 was assumed to be 1.3. The standard deviation of the difference was 10.0. However, considering within-patient correlation, SD of 8.0 was considered as reasonable. Based on these assumptions, 300 patients were needed for a power of 80%. Considering a 20% drop-out rate based on data from the CLOT-study [Lee A et al. 2003] and the SAFARI non-interventional study [Hanon O et al. 2016], 375 patients had to be included.

Calculations were performed with nQuery 7.

Due to the heterogeneous population of patients with cancer and expected high dropout rates after Week 4, 500 patients were planned to be enrolled in the COSIMO study to have a sufficient number of patients for secondary analyses.

9.8 Data transformation

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.

In order to achieve the goal of a well conducted, non-interventional, post-authorization study according to EudraLex Volume 9A (Pharmacovigilance for Medicinal Products for Human Use), every effort was made to collect all available data. However, despite all possible efforts, it was inevitable that missing or incomplete data were collected.

Missing or partial information were implemented so as not to exclude data from subjects for analyses due to missing or partially complete data. Rules for handling missing or partial information are given in detail in Section 4.3 of the SAP (Annex 1) and summarized in Section 9.9.3 **Error! Reference source not found.**.

9.9 Statistical methods

The analysis of the preferences regarding the attributes of the anticoagulation medication options (LMWH, VKA, rivaroxaban) by means of the DCE survey was performed by Ingress GmbH,

Germany. Summary results are provided in Section 10.5.4, the detailed report is included in Annex 2.

All other statistical analyses were performed by Institute Dr. Schauerte, Germany. Statistical issues including calculated variables and proposed format and content of tables were detailed in the Statistical Analysis Plan (SAP) Version 1.2, dated 05 SEP 2019. (Annex 1).

The statistical evaluation was performed by using the software package SAS release 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

9.9.1 Main summary measures

Statistical analyses were explorative and descriptive 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 were described by absolute value and as change from baseline per analysis time point, if applicable. Subgroup analyses were planned to be performed for subgroups containing more than 5 patients.

All background data such as patient demographics, history / risk factors for VTE, active cancer classification, cancer specific treatments, and concomitant medication were described by presenting frequency distributions and/or basic summary statistics.

9.9.2 Main statistical methods

9.9.2.1 Treatment information

Initial treatment (before rivaroxaban), rivaroxaban treatment and anticoagulation treatment after stop of rivaroxaban as described in Section 6.1.4 of the SAP.

Initial treatment (before rivaroxaban)

Total duration of anticoagulation treatment for index VTE, before rivaroxaban, was calculated from first dose of initial anticoagulation treatment to last dose of initial anticoagulation treatment, including interruption of medication.

Anticoagulation treatments before initial anticoagulation treatment for index VTE event were provided by category (LMWH, VKA, Fondaparinux or Other).

Every change from one anticoagulation treatment to another was classified into one of the two groups ‘change within category’ and ‘change across category’ (0, 1, 2, 3, or >3 changes).

Rivaroxaban treatment

Reasons for choosing rivaroxaban, planned and actual treatment duration, dosage and dose changes/interruption including reasons for dose changes/interruptions, and treatment discontinuation were summarized.

Treatment interruption was defined as no rivaroxaban taken for at least 2 days. It did not include patients who were on rivaroxaban and had a treatment interruption which was bridged with LMWH or fondaparinux (these were counted as ‘bridging’). Treatment interruptions were calculated from actual treatment data, not using ‘Intent’ from the CRF.

Treatment duration in days was calculated for each patient individually from first dose of rivaroxaban treatment to last dose of rivaroxaban treatment, including interruption of medication.

For patients with an interruption / bridging period > 14 days, a listing for treatment-emergent adverse events (TEAEs) occurring during interruption /bridging period was provided with preferred term, reported term, start/stop date of the event, days from interruption, rivaroxaban dose before the event and concomitant medication.

A Kaplan-Meier plot of time to the first interruption (start of rivaroxaban to the first interruption) was provided. Patients who did not have interruption were right-censored. Kaplan-Meier plots were shown restricted to the period in which at least approximately 10% of patients were at risk.

Anticoagulation treatment (after stop of rivaroxaban)

The type of anticoagulation treatment after stop of rivaroxaban, including the number of patients who took anticoagulation treatment after stop of rivaroxaban, number of patients with ongoing anticoagulation treatment at the end of the study and actual treatment duration was summarized.

Antiplatelet treatment (after stop of rivaroxaban)

Antiplatelet therapy was defined as single or multiple ingredient drugs containing a drug which defined as ATC group B01AC (Patelet aggregation inhibitors excluding heparin). The number of patients with antiplatelet therapy (after stop of rivaroxaban, without taking any other anticoagulant treatment) was summarized.

9.9.2.2 Analysis of primary variable

The primary efficacy outcome was the change of the ACTS Burden score at Week 4 (14 – 56 days) in comparison to baseline. The ACTS Analysis Set Week 4, which defined as a patient whose baseline ACTS Burden score and a valid Week 4 ACTS Burden score were available (treatment with rivaroxaban within 2 weeks before ACTS assessment) was used for this analysis.

The null hypothesis H0 and the alternative hypothesis HA were

$H_0: \Delta = 0$

$H_A: \Delta \neq 0,$

where Δ was the change in the ACTS Burden score. The hypothesis was tested at a $\alpha = 5\%$ significance level.

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

9.9.2.3 Analysis of secondary variables (efficacy)

ACTS questionnaire

For the ACTS Burden score, Benefit score and individual items, the trend and shape of the scores were examined over time. ACTS Analysis Set (Secondary outcome over time analyses) which included the patients whose baseline ACTS Burden score and at least one valid post-baseline ACTS Burden score were available, was used for this analysis.

Since the questionnaire responses were multiple measurements on the patient satisfaction of treatment over a period of time, a mixed model repeated measures analyses was used to analyze the questionnaire data. If more than one questionnaire per time window was present, the average result was taken.

Visits are defined as follows:

Week 4: from week 2 to week 8, (i.e. day 14-56)

Month 3: from week 8 to week 18, (i.e. day 57 to 126)

Month 6: from week 18 to week 30 and greater, (i.e. day 127 to day 210 and greater)

For the mixed model, the valid (treatment with rivaroxaban within 2 weeks before ACTS assessment) repeated ACTS Burden scores were used as dependent variable. 'Subject' was included as a random effect.

Baseline ACTS scores, time point as well as stratification variable (refer to Section 6.2 of the SAP, Annex 1) were included in the model as independent factors. A further model additionally included the time by stratification variable interaction.

A model of fit analysis was done to find an appropriate covariance structure, i.e. various types of covariance structure (unstructured, compound symmetry and Toeplitz) were fitted and compared by their Akaike information criterion (AIC).

FACIT-Fatigue

The FACIT-Fatigue total score was analyzed by visit using summary statistics for FACIT Analysis Set which included the patients whose baseline score and at least one valid post-baseline score were available, was used for this analysis.

9.9.2.4 Safety analysis

Adverse events

The number of patients with event and incidence proportion was presented for the safety analysis set by NCI CTC by the worst CTCAE grade and in addition by MedDRA primary SOC and PT for

- TEAEs
- cancer-related TEAEs
- cancer-therapy-related TEAEs
- TEAEs excluding bleeding events, TEAEs leading to discontinuation, to (prolonged) hospitalization or to death, and
- AEs > 2 days after stop of study medication,

each drug-related or not related, and any or serious.

The MedDRA presentations displayed system organ class and the PTs within the system organ class alphabetically.

In addition, a Kaplan-Meier plot of time to treatment-emergent death (start of rivaroxaban to death due to any cause) was provided. Patients who did not die until up to 2 days after the last dose were right-censored (Figure 14.3.1.22 ➔ Figure 10-5).

All Kaplan-Meier plots were shown restricted to the period in which at least approximately 10% of patients were at risk (Tables 14.1.2.3, 14.1.6.17, 14.3.4.1.3, 14.3.4.2.3, 14.3.4.3.3).

Bleeding and thromboembolic events (adjudicated events)

For bleeding and thromboembolic events, the incidence proportion and incidence rates were calculated as described below:

$$\text{Incidence proportion} = \frac{\text{Number of patients with events}}{\text{Number of treated patients}}$$

$$\text{Incidence rates} = \frac{\text{Number of patients with events}}{\text{Cumulative person-time at risk (in 100 patient-years)}}$$

Cumulative person-time at risk = time from start of study drug until the censoring date or occurrence of first event

They were provided for overall and by the categories for bleeding types defined in Section 9.4.3.

Thromboembolic adverse events by type of VTE event (DVT, PE, catheter associated DVT) were summarized for clinical presentation, time of onset since start of rivaroxaban, diagnosis test, and clot location.

MACE were adjudicated and summarized for time of onset since start of rivaroxaban, age, cancer category and type, cancer therapy, type of index VTE, concomitant antiplatelet therapy, concomitant CYP3A4 use, concomitant CYP3A4 or P-gp inhibitor use, concomitant steroid use, creatinine clearance and fragility (see Section 10.6.5.3).

Details for this analysis can be found in Section 6.4.1 and 6.4.2 of the SAP (Annex 1).

9.9.3 Missing values

ACTS

Imputation rules for the ACTS questionnaire can be found in Section 9.4.1 and Section 4.6 of the SAP (Annex 1).

VTE Treatment

If at least one study medication record was available for a patient, VTE treatment for the respective patient was valid, even if parts of the start and/or stop dates were missing. In this case, the missing parts were imputed as described in Section 4.3.1 of the SAP (Annex 1).

Initial treatment of VTE

The patient was required to have been treated with SoC anticoagulation (LMWH/VKA) for treatment of VTE for at least 4 weeks prior to inclusion in the study. If some (parts) of the start and/or stop dates were missing, they were imputed as described in Section 4.3.2 of the SAP (Annex 1).

Concomitant medication

When it was not clear whether a medication was ongoing at study entry, the medication was considered as concomitant.

Imputation rules for missing dates are described in Section 4.3.3 of the SAP (Annex 1).

Comorbidities

When it was not clear whether a comorbidity was ongoing at study entry, the comorbidity was considered as concomitant disease.

Date of diagnosis and start of AEs

Imputation rules for missing dates are described in Section 4.3.5 and 4.3.6 of the SAP (Annex 1).

Other missing values

Other missing values were not imputed. Frequency tables for categorical data included the number of missing values as additional categories. Percentages were calculated as proportion of each category including the category of missing values.

9.9.4 Sensitivity analyses

A sensitivity analysis for the primary endpoint was conducted to investigate potential impact of patients who dropped out from the study earlier than Week 4 due to other reasons than death of cancer (adjudicated event) as outcome. The SAF was used for this analysis. Patients who dropped out from the study due to death due to cancer were not included into the sensitivity analysis because their score was not relevant to treatment satisfaction. Where a patient withdrew due to other reasons than death due to cancer before Week 4 assessments, the worst possible value of ACTS Burden score (=12) was imputed.

For a second sensitivity analysis visits were defined as follows:

Week 4: 28 days after initial visit ± 7 days

The ACTS Analysis Set Week 4 was used for this analysis.

In addition, subgroup analyses of the primary outcome were performed. Stratification variables are provided in Section 6.2 of the SAP (Annex 1).

9.9.5 Amendments to the statistical analysis plan

There were no amendments to the SAP. After database lock, two supplements were added to the SAP (version 1.1 and 1.2).

9.10 Quality control

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

The CRO Schauerte GbR was 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 were recorded in a standardized CRF. After data entry, missing or implausible data were queried and the data was validated. A check for multiple documented patients was done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the DMP. The same plan specifies measures for handling of missing data and permissible clarifications. The DMP is available upon request.

Medical Review of the data was performed according to the Medical Review Plan (MRP). The purpose of the Medical Review was to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could have affected 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.

National and international data protection laws as well as regulations on observational studies were followed. Electronic records used for capturing patient documentation (eCRF) were validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) [FDA 2012]. The documentation is available upon request.

In a subset of patients (at least 10% of all patients) source data verification was conducted. The purpose was to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors accessed medical records on site for data verification. Detailed measures for quality reviews are described in the Quality Review Plan (QRP). The QRP is available upon request.

10. Results

10.1 Participants

A total of 532 patients were screened for this study which was conducted between October 2016 and March 2019 in 10 countries; 16 patients were screening failures, 4 patients were never included, and 3 patients withdrew after screening. Thus, 509 patients were included into the study.

Four patients did not receive any rivaroxaban treatment, leaving 505 patients in the SAF.

A total of 381 patients comprised the ACTS Analysis Set (Week 4), which was used for the primary endpoint analysis. A patient was included in this set if the patient's baseline ACTS Burden score and a valid Week 4 (+/- 2 weeks) ACTS Burden score were available. Most frequently documented reason for exclusion from the ACTS Analysis Set (Week 4) was 'missing ACTS assessment at Week 4' (Table 10.1).

The other analysis sets comprised 341 patients for the ACTS Analysis Set (Month 3) and 253 patients for the ACTS Analysis Set (Month 6), i.e. for these patients, a baseline ACTS Burden score and a valid Month 3 / Month 6 (+/- 2 weeks) ACTS Burden score were available. Moreover, 423 patients were in the ACTS Analysis Set (over time), and 450 patients in the FACIT Analysis Set (Table 10.1). A patient was included in the ACTS Analysis Set (over time) if the patient's baseline ACTS Burden score and at least one valid post-baseline ACTS Burden score were available, which explains why it comprised more patients than the ACTS Analysis Set (Week 4). Concerning the FACIT Analysis Set, patients were included who took at least one dose of rivaroxaban during the observation period and who provided baseline and any follow-up FACIT questionnaire.

Primary reasons for exclusion from the respective analysis sets can be found in Table 14.1.1.1. Most frequently documented primary reason for exclusion from the analysis sets was 'missing follow-up ACTS assessment' at the time point of interest. Note that patients could have had more than one reason documented for exclusion from the analysis set.

Table 10.1: Patient validity from analysis (patients enrolled)

	Included patients N=509 (100%)
Patients enrolled	**532**
Complete withdrawal	3
Never included	4
Early screening failures	16
Total patients included in the study	**509 (100.0)**
Patients valid for safety analysis (SAF)	**505 (99.2)**
Patients valid for ACTS Week 4 analysis	**381 (74.9)**
Patients valid for ACTS Month 3 analysis	**341 (67.0)**
Patients valid for ACTS Month 6 analysis	**253 (49.7)**
Patients valid for ACTS over time analysis	**423 (83.1)**
Patients valid for FACIT analysis	**450 (88.4)**

Source: Table 14.1.1.1

Of the 505 patients enrolled (SAF), 76.8% (n=388/505) completed the study as it had been planned and 23.2% (n=117/505) discontinued the study prematurely (Table 10.2). Most frequently

documented reasons for premature study discontinuation were 'patient died' (11.7%, n=59/505), 'withdrawal of consent' (4.2%, n=21/505), 'other reasons' (4.0%, n=20/505), and 'lost to follow-up' (3.4%, n=17/505). The reason "patient not eligible for the study" concerns 7 patients (1.4%) who were already included in the study, but revealed to fail the inclusion and/or exclusion criteria and were thus not eligible anymore (late screening failure, i.e. reason could not be found before documentation of the first follow-up visit).

For 3 patients, an AE was documented as reason for study discontinuation. For more details about AEs leading to study discontinuation see Section 10.6.1.4.

Table 10.2: Patient disposition (Safety Analysis Set)

	Rivaroxaban N=505 (100%)
Regular end of observation	388 (76.8)
Discontinued prematurely	117 (23.2)
Patient died*	59 (11.7)
Patient lost to follow-up	17 (3.4)
Patient withdrew consent (but agreed to further use data collected so far)	21 (4.2)
Other	20 (4.0)
Adverse event	3 (0.6)
Costs of treatment	1 (0.2)
End of treatment	4 (0.8)
Patient not eligible for the study	7 (1.4)
Physician decision	1 (0.2)
Progressive disease – clinical progression	1 (0.2)
Therapeutic procedure required	1 (0.2)
Missing	2 (0.4)

Source: Table 14.1.2.1
* Patient died includes patients who died 30 days after stop of treatment

The mean (SD) duration of observation was 5.71 (1.64) months, ranging between 0.03 and 12.0 months (median 6.0 months, IQR 5.6 to 6.3 months), as provided in Table 14.1.2.2.

According to Kaplan-Meier analysis, 117 patients had an event of study discontinuation and 388 were censored (up to 360 days). The cumulative proportion of patients who did not discontinue until an observation period of 180 days was 81.8% of all patients (95% CI [78.0;84.9]). The median time [95% CI] until study discontinuation was 260.0 days [246.0;356.0], as visualized in Figure 10-1.

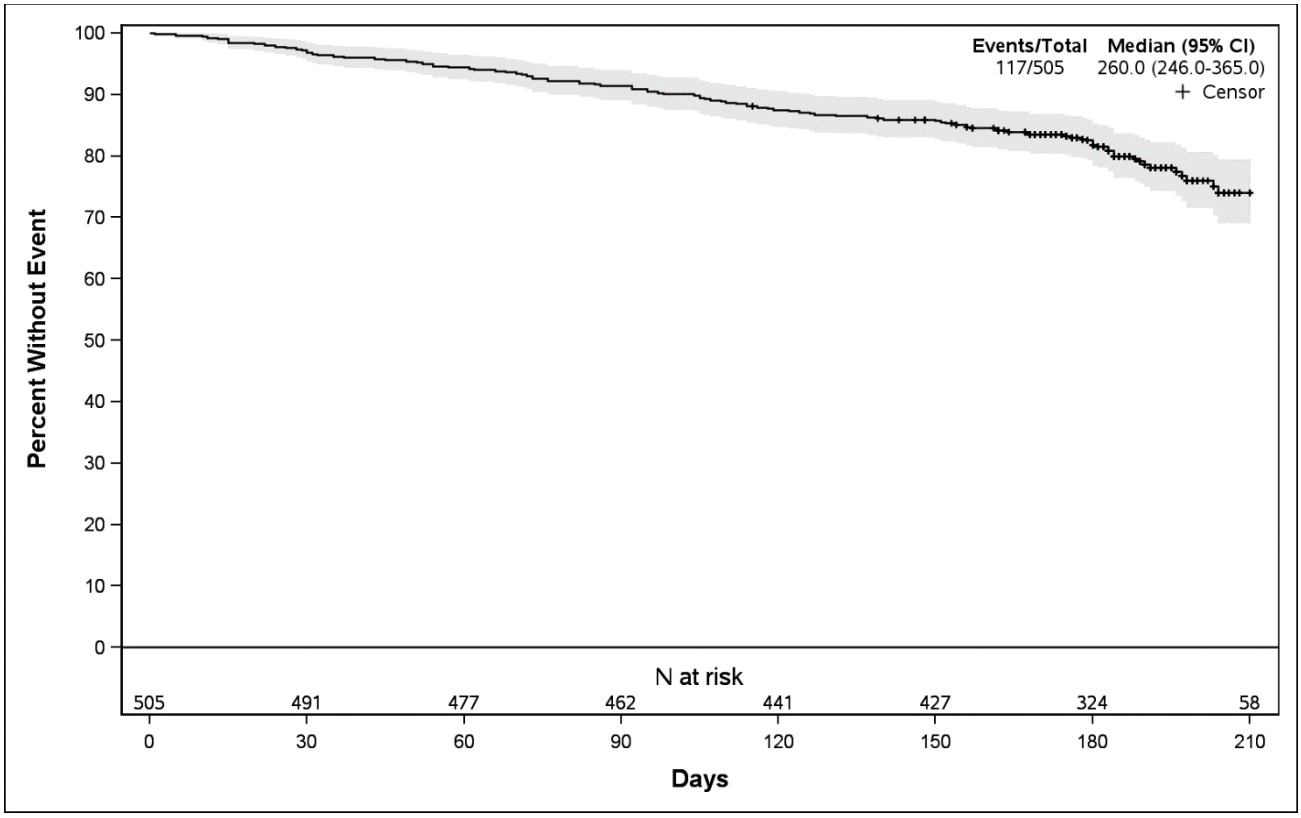


Figure 10-1: Kaplan-Meier analysis of time to study discontinuation (Safety Analysis Set)

Source: Figure 14.1.2.3
Note: time at risk restricted to the period in which at least approximately 10% of patients were at risk
Patients with regular end of observation where censored at date of end of observation

10.2 Descriptive data

10.2.1 Demographic and baseline data

Demographic data for the SAF are summarized in Table 10.3.

The mean (SD) age of the 505 study patients (SAF) was 64.0 (11.72) years (range 23.0 to 89.0 years), with 67.7% (n=342/505) aged ≥ 60 years. More than half of the patients (55.4%, n=280/505) were female; most patients were white (86.7%, n=438/505) and most were married (68.9%, n=348/505).

Participating patients mostly resided in Canada (25.3%, n=128/505), Belgium (16.8%, n=85/505), the United Kingdom (13.7%, n=69/505), and Spain (10.1%, n=51/505).

Demographics and baseline data were similar for the patients in the ACTS Analysis Set Week 4 (Table 14.1.2.3.2).

Table 10.3: Demographic data (Safety analysis Set)

	Rivaroxaban N=505 (100%)
Age (years)*	
n (missing)	505 (0)
Mean (SD)	64.0 (11.72)
Median	65.0
Minimum – Maximum	23.0 – 89.0
Age categories, n (%)*	
< 60 years	163 (32.3)
≥ 60 years	342 (67.7)
Gender, n (%)	
Male	225 (44.6)
Female	280 (55.4)
Race, n (%)	
White	438 (86.7)
Asian	12 (2.4)
Black	6 (1.2)
not reported	49 (9.7)
Country, n (%)	
Australia	7 (1.4)
Belgium	85 (16.8)
Canada	128 (25.3)
Denmark	27 (5.3)
France	31 (6.1)
Germany	48 (9.5)
Italy	30 (5.9)
Netherlands	29 (5.7)
Spain	51 (10.1)
United Kingdom	69 (13.7)

Source: Table 14.1.2.3.1
* Age at time of informed consent

Baseline characteristics for the SAF are summarized in Table 10.4.

Most patients were of normal weight, as shown by the mean (SD) BMI of 27.0 (5.56) kg/m^2. Renal function was normal (≥ 80 ml/min) in 46.3% (n=234/505), and showed mild impairment (50-< 80 ml/min) in 29.3% (n=148/505), moderate impairment (30 -< 50 ml/min) in 8.3% n=42/505, and severe impairment (15-< 30 ml/min) in 0.8% (n=4/505) of patients. Most patients (61.8%, n=312/505) were not in a fragile health status at baseline (i.e. > 75 years of age or weight ≤ 50 kg or first available CrCl < 50 ml/min). More than half of the patients never smoked (52.7%, n=266/505) and about one third were former smokers (37.4%, n=189/505); most patients were documented with no (42.4%, n=214/505) or light alcohol consumption (39.4%, n=199/505).

Results were similar for the ACTS Analysis Set Week 4 (Table 14.1.2.4.2).

Table 10.4: Baseline characteristics (Safety Analysis Set)

	Rivaroxaban N=505 (100%)
BMI (kg/m^2)	
n (missing)	417 (88)
Mean (SD)	27.0 (5.56)
Median	26.4
Minimum – Maximum	15.8 – 66.6
Creatinine clearance, first available value (ml/min), n (%)	
< 15	0 (0.0)
15 - < 30	4 (0.8)
30 - < 50	42 (8.3)
50 - < 80	148 (29.3)
≥ 80	234 (46.3)
Missing	77 (15.2)
Creatinine clearance, baseline (ml/min), n (%)	
< 15	0 (0.0)
15 - < 30	2 (0.4)
30 - < 50	29 (5.7)
50 - < 80	107 (21.2)
≥ 80	167 (33.1)
Missing	200 (39.6)
Fragile, n (%)	
Yes	116 (23.0)
No	312 (61.8)
Missing	77 (15.2)
Alcohol consumption, n (%)	
Abstinent	214 (42.4)
Light	199 (39.4)
Moderate	41 (8.1)
Heavy	2 (0.4)
Unknown	48 (9.5)
Missing	1 (0.2)
Cigarette smoking, n (%)	
Never	266 (52.7)
Former	189 (37.4)
Current	37 (7.3)
Missing	13 (2.6)
Drug abuse, n (%)	
No	455 (90.1)
Yes	6 (1.2)
Missing	44 (8.7)

Source: Table 14.1.2.4.1

Creatinine Clearance was calculated via Cockcroft-Gault formula. The first available Creatinine value was used in this analysis
Fragile was defined as age > 75 years or weight ≤ 50 kg or first available CrCl < 50 ml/min. If any variables were not available, they were categorized as missing
BMI = weight in kg / height^2 in m^2

10.2.2 Medical history

10.2.2.1 VTE-related medical history

Most patients (91.3%, n=461/505) had not experienced a previous VTE event within the last 5 years (SAF), as shown in Table 14.1.2.8.1, similarly with the patients included in the Week-4 ACTS Analysis Set (Table 14.1.2.7.2 and Table 14.1.2.8.2).

At baseline, a majority of patients (73.5%, n=371/505) did not have any known risk factors for VTE (other than the underlying cancer disease). Most frequently recorded risk factors were recent (< 3 months) surgery or trauma (10.5%, n=53/505), prolonged immobilization with at least 2 days bed rest (6.1%, n=31/505), and other (6.9%, n=35/505), as summarized in Table 10.5.

History of VTE risk factors were similar for patients included in the ACTS Analysis Set Week 4 (Table 14.1.2.5.2).

Table 10.5: Risk factors for venous thromboembolism (Safety Analysis Set)

Risk factor*	Rivaroxaban N=505 (100%) n (%)
No known risk factor for VTE (other than cancer disease)	371 (73.5)
Thrombophilia	6 (1.2)
Recent surgery or trauma < 3 months	53 (10.5)
Prolonged immobilization with at least two days bed rest	31 (6.1)
Use of estrogen containing drugs	15 (3.0)
Recent long-haul travelling < 4 weeks	3 (0.6)
Venous insufficiency	10 (2.0)
Leg paresis	0 (0.0)
Puerperium	0 (0.0)
Other	35 (6.9)

Source: Table 14.1.2.5.1
* Patients could report more than one risk factor

Index VTE was defined as the VTE event leading to medical presentation before inclusion in the study. DVT was the index VTE for 45.3% (n=229/505), PE for 37.2% (n=188/505) and both DVT and PE for 9.7% of patients (n=49/505) (SAF), as provided in Table 10.6. The index VTE was symptomatic in most patients (72.1%, n=364/505).

At time of commencing rivaroxaban treatment, median time since index VTE diagnosis was 100 (IQR 46 to 183) days, ranging from 1 to 3427 days. Most frequently used diagnostic tests for index VTE were ultrasound (54.5%, n=275/505) and computer tomography (CT) scan (50.9%, n=257/505) (Table 14.1.2.9.1).

For the index VTE, location of the clot in patients with any DVT is provided in Table 14.1.2.9.2.

Clot location were similar for patients included in the ACTS Analysis Set Week 4 (Table 14.1.2.9.3).

Table 10.6: Index venous thromboembolism (Safety Analysis Set)

	Rivaroxaban N=505 (100%) n (%)
Type of index event	
DVT	229 (45.3)
PE	188 (37.2)
DVT + PE	49 (9.7)
Catheter associated DVT	38 (7.5)
Missing	1 (0.2)
VTE symptomatic	
No	140 (27.7)
Yes	364 (72.1)
Missing	1 (0.2)
Type of non-symptomatic index event	
Incidental DVT	48 (9.5)
Incidental PE	72 (14.3)
Incidental DVT + PE	15 (3.0)
Missing	5 (1.0)
Type of symptomatic index event	
DVT	181 (35.8)
PE	116 (23.0)
DVT + PE	34 (6.7)
Missing	33 (6.5)

Source: Table 14.1.2.9.1
DVT = deep-vein thrombosis, PE = pulmonary embolism

10.2.2.2 Cancer-related medical history

43.6% (n=220/505) of patients had a known family history of cancer (Table 14.1.3.1.1), most frequently (70.4%, n=178/220) in first-degree relatives (Table 14.1.3.1.2) (SAF). 28.4% of patients (n=73/220) had a history of same type of cancer as their relative (Table 14.1.3.1.3).

Of the SAF, 88.9% of patients (n=449) had a solid tumor and 11.1% (n=56) had hematological malignancy; 54.6% of patients (n=245/505) presented with metastatic cancer at enrollment (Table 10.7 and Table 10.8).

Of the hematological malignancies (n=56), non-Hodgkin lymphoma (39.3%, n=22/56) and myeloma (33.9%, n=19/56) were documented most frequently (Table 10.7). Of the solid tumors, a gastrointestinal malignancy was the primary cancer in 29.2% (n=131/449) of patients (most frequently in the colon; 55/131 patients; Table 14.1.3.3.1), breast cancer in 18.7% (n=84/449), gynecological cancer in 17.8% (n=80/449), lung cancer in 13.1% (n=59/449), and genitourinary cancer in 12.9% (n=58/449) of patients (Table 10.8). The median time since diagnosis of both the

hematological malignancy and the solid tumor was 1.0 year. About half of the patients had stage IV cancer and the primary tumor was unresected in 35.4% (n=159/449) of patients at study entry.

According to the ECOG performance at baseline, physicians rated the patients as ECOG 1 (slightly restricted) in 54.7% (n=276/505) of patients and ECOG 0 (fully ambulatory) in 32.1% (n=162/505) of patients (Table 10.9). Cancer status was assessed as 'stable disease' in 28.9% (n=146/505) and as 'relapsed/progressive' in 17.6% (n=89/505) of patients at baseline. Note: The cancer response status was not available (i.e. not assessed) at baseline in 29.7% (n=150/505) of patients and not evaluable in 6.9% (n=35/505) of patients (Table 10.9).

Table 10.7: Cancer type: hematological malignancies present at the time of enrollment (Safety Analyis Set)

	Rivaroxaban (N=56, 100%)
Hematological malignancy, n (%)	
Leukemia	7 (12.5)
Hodgkin lymphoma	6 (10.7)
Non-Hodgkin lymphoma	22 (39.3)
Myeloma	19 (33.9)
Myelodysplastic syndrome (MDS)	1 (1.8)
Missing	
Time since diagnosis of hematological malignancy (years)	
n (missing)	45 (11)
Mean (SD)	2.3 (2.56)
Median	1.0
Minimum – Maximum	0.0 – 10.0

Source: Table 14.1.3.2.1
SD = standard deviation
Time since initial diagnosis was calculated as year of informed consent - year of first cancer diagnosis

Table 10.8: Cancer type: solid tumor present at the time of enrollment (Safety Analysis Set)

	Rivaroxaban (N=449, 100%)
Solid tumors (primary tumor), n (%)	
Gastrointestinal malignancies	131 (29.2)
Breast cancer	84 (18.7)
Gynecological cancer	80 (17.8)
Lung	59 (13.1)
Genitourinary cancer	58 (12.9)
CNS-glioblastoma	11 (2.4)
Head and neck	8 (1.8)
Sarcoma	5 (1.1)
Malignant melanoma	3 (0.7)
Other	10 (2.2)
Time since diagnosis of solid tumor (years)	
n (missing)	398 (51)
Mean (SD)	2.0 (2.96)
Median	1.0
Minimum – Maximum	0.0 – 20.0
Metastases at enrollment, n (%)	
No	204 (45.4)
Yes	245 (54.6)
Status of primary tumor at study entry, n (%)	
Unresected	159 (35.4)
R0 complete tumor resection with all margins histologically negative	113 (25.2)
R1 incomplete tumor resection with microscopic surgical resection margin involvement (margins grossly uninvolved)	26 (5.8)
R2 incomplete tumor resection with gross residual tumor that was not resected (primary tumor, regional nodes, macroscopic margin involvement	28 (6.2)
Resected. Status of residual tumor unknown	123 (27.4%)
Stage of solid tumor, n (%)	
I	40 (8.9)
II	64 (14.3)
III	89 (19.8)
IV	214 (47.7)
Missing	42 (9.4)

Source: Table 14.1.3.3.1, Table 14.1.3.3.2
SD = standard deviation

Table 10.9: Cancer response at baseline (Safety Analysis Set)

	Rivaroxaban (N=505) n (%)
ECOG performance status	
0 (fully active, able to carry on all pre-disease performance without restriction)	162 (32.1)
1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature)	276 (54.7)
2 (ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% waking hours)	63 (12.5)
Missing	4 (0.8)
Status of cancer response	
Complete remission	47 (9.3)
Partial remission	38 (7.5)
Stable disease	146 (28.9)
Relapsed disease/progressive disease	89 (17.6)
Not evaluable	35 (6.9)
Not done	150 (29.7)

Source: Table 14.1.3.4
Cancer response = 'Not done" refers to status of cancer response either not applicable or not done

10.2.2.3 Other relevant medical history

Relevant medical conditions, especially in view of the underlying risk for bleeding, are summarized in Table 10.10 (SAF).

Only a minority of patients had records of gastric ulcer (4.2%, n=21/505), abnormal kidney function (5.5%, n=28/505), abnormal kidney function, which was ongoing at study start (4.6%, n=23/505), abnormal liver function (4.2%, n=21/505) (ongoing at study start in 3.6% of patients), stroke (3.0%, n=15/505), and major bleeding event (according to the International Society on Thrombosis and Hemostasis [ISTH] criteria) (2.2%, n=11/505).

Medical conditions that were recorded more often were anemia (within the last 12 months) in 35.4% (n=179/505) - ongoing at study entry in 28.1% patients (n=142/505) - and hypertension in 35.2% (n=178/505).

Table 10.10: Relevant medical conditions (Safety Analysis Set)

	Rivaroxaban N=505 (100%) n (%)
Gastric ulcer	
No	484 (95.8)
Yes	21 (4.2)
ongoing at study entry	4 (0.8)
Abnormal kidney function	
No	477 (94.5)
Yes	28 (5.5)
ongoing at study entry	23 (4.6)
Abnormal liver function	
No	484 (95.8)
Yes	21 (4.2)
ongoing at study entry	18 (3.6)
Anemia (within the last 12 months)	
No	326 (64.6)
Yes	179 (35.4)
ongoing at study entry	142 (28.1)
Hypertension	
No	327 (64.8)
Yes	178 (35.2)
Stroke	
No	490 (97.0)
Yes	15 (3.0)
Major bleeding according to ISTH	
No	494 (97.8)
Yes	11 (2.2)

Source: Table 14.1.2.7.1
ISTH = International Society on Thrombosis and Hemostasis

Furthermore, 11.1% (n=56/505) of patients had records of diabetes mellitus. Other medical history included hypertension (3.4%, n=17/505), hypothyroidism (2.8%, n=14/505), asthma (2.6%, n=13/505), and depression (1.6%, n=8/505).

A manual reconciliation of the general medical history with risk factors for VTE and bleeding performed at the patient level did not find relevant omissions or sources of bias.

Table 10.11: General medical history (incidence ≥ 1%) (Safety Analysis Set)

Condition Preferred Term	Rivaroxaban N=505 (100%) n (%)
Patients with at least one medical history finding	**248 (49.1)**
Diabetes mellitus (type 1/2)	56 (11.1)
COPD	21 (4.2)
Atrial fibrillation	15 (3.0)
Acute coronary syndrome	10 (2.0)
Chronic inflammatory disease	6 (1.2)
Hypertension	17 (3.4)
Hypothyroidism	14 (2.8)
Asthma	13 (2.6)
Depression	8 (1.6)
Breast cancer	6 (1.2)
Cholecystectomy	6 (1.2)
Dyslipidaemia	6 (1.2)
Gastrooesophageal reflux disease	6 (1.2)
Osteoarthritis	6 (1.2)
Appendicectomy	5 (1.0)
Hysterosalpingo-oophorectomy	5 (1.0)
Osteoporosis	5 (1.0)

Source: Table 14.1.2.6.1
MedDRA version 21.1

10.2.3 Prior and concomitant medication and procedures

10.2.3.1 General medications

Almost all patients (95.6%, n=483/505) had records of prior medication, with antineoplastic and immuno-modulating agents reported most often in 85.0% of patients (n=429/505), followed by alimentary tract and metabolism drugs (56.2%, n=284/505) and cardiovascular system drugs (55.0%, n=278/505), as provided in Table 14.1.4.1.1 (SAF).

At the initial visit, 91.7% of patients (n=463/505) were on at least one concomitant medication (ongoing or stop after study enrollment), with alimentary tract and metabolism drugs (71.7%, n=362/505), cardiovascular system drugs (62.2%, n=314/505) and nervous system drugs (56.4%, n=285/505) recorded most often (Table 14.1.4.1.2) (SAF).

10.2.3.2 Cancer-specific treatments

Before enrollment, 85.0% of patients (n=429/505) had received any systemic anti-cancer therapy (chemotherapy in 74.3%; Table 14.1.4.2.11.1), 31.7% (n=160/505) any radiotherapy and 6.1% (n=31/505) any local anti-cancer therapy, such as radio frequency ablation or cryo-therapy ablation (Table 10.12) (SAF). About half of the patients (54.7%, n=276/505) received systemic anti-cancer therapy only and 25.7% (n=130/505) a combination of systemic and radiotherapy (Table 14.1.4.2.3.1.2).

During the study, 35.2% of patients (n=178/505) were concomitantly receiving any systemic cancer therapy (chemotherapy in 29.7% of patients; Table 14.1.4.2.12.1), 15.6% any radiotherapy (n=79/505) and 1.8% any local anti-cancer therapy (n=9/505) (Table 10.12) (SAF).

Other concomitant medications, such as antiplatelet therapy, Cyp3A4 inhibitors, Cyp3A4 or P-gp inhibitors, or steroids were not documented in the majority (i.e. > 85%) of patients (Table 14.1.4.2.22.1.1, Table 14.1.4.2.22.2.1, Table 14.1.4.2.22.3.1, Table 14.1.4.2.22.4.1).

Table 10.12: Prior and concomitant procedures and anti-cancer therapy (Safety Analysis Set)

	Rivaroxaban (N=505) n (%)
Prior procedures and anti-cancer therapy*	
Any local anti-cancer therapy	31 (6.1)
Any systemic anti-cancer therapy	429 (85.0)
Any radiotherapy	160 (31.7)
Concomitant procedures and anti-cancer therapy*	
Any local anti-cancer therapy	9 (1.8)
Any systemic anti-cancer therapy	178 (35.2)
Any radiotherapy	79 (15.6)

Source: Table 14.1.4.2.3.1.1, Table 14.1.4.2.4.1.1
* a patient could have multiple treatments

10.2.4 Treatments

10.2.4.1 Initial anti-coagulation treatment for index VTE event

Table 10.13 summarizes details of the index VTE treatment which may have occurred at any time in the patient's history. The vast majority of patients (96.6%, n=488/505) had been treated with LMWH (initial anticoagulation treatment for index VTE event) before they changed to rivaroxaban in this study; some patients had received Fondaparinux (1.8%, n=9/505) and VKA (1.6%, n=8/505) (SAF). Before this initial treatment, most patients (74.7%, n=381/505) had not received any anticoagulation treatment (SAF).

The duration of the gap between stop of initial treatment with LMWH and start of rivaroxaban was 2-3 days in most patients (74.0%, n=361/505) (Table 14.1.5.7).

Only a minority of patients changed their initial treatments before start of rivaroxaban treatment (4.6% switched between the different drug classes LMWH, Fondaparinux and VKA, and 12.5% switched to products with different substances but within the same drug class), as shown in Table 14.1.5.10.

Before start of rivaroxaban treatment, the median total duration of anticoagulation treatment (i.e. initial anticoagulation plus all previous treatments) for the index VTE was 100 days, ranging from 25 to 3173 days (SAF) (Table 10.13).

Table 10.13: Details about initial anticoagulation treatment for index event before switch to rivaroxaban (Safety Analysis Set)

	Rivaroxaban (N=505)
Anticoagulation treatment before initial treatment for index VTE, n (%)	
None	381 (74.7)
LMWH	115 (22.5)
VKA	7 (1.4)
Fondaparinux	2 (0.4)
Other	5 (1.0)
Initial anticoagulation treatment for index VTE, n (%)	
LMWH	488 (96.6)
VKA	8 (1.6)
Fondaparinux	9 (1.8)
Actual duration of initial anticoagulation treatment for index VTE (days)	
n (missing)	505 (0)
Mean (SD)	171.9 (295.12)
Median	100.0
Minimum - Maximum	25.0 - 3173

Source: Table 14.1.5.1.1, Table 14.1.5.1.2, Table 14.1.5.11
SD = standard deviation, VTE = venous thromboembolism
LMWH: defined by ATC code B01AB; VKA: defined by ATC code B01AA; Fondaparinux: defined by ATC code B01AX05 and DRECNO 015512
A patient could have more than one treatment;
Initial treatment for index event was defined as the last treatment before switch to rivaroxaban
Total duration was calculated as stop of initial anticoagulation treatment - start of first treatment +1

10.2.4.2 Rivaroxaban treatment

10.2.4.2.1 Start of rivaroxaban treatment

The main reason for choosing rivaroxaban was related to ‘physician decision’ in 34.5% of patients (n=174/505), followed by ‘burden of parenteral administration’, ‘quality of life’ and ‘patient decision’ in 26.9%, 18.6% and 15.0% of patients, respectively (SAF) (Table 10.14).

The planned duration of rivaroxaban treatment was between > 90 and 180 days in 28.3% (n=143/505) and > 180 days in 57.4% of patients (n=290/505) (SAF) (Table 10.14), irrespective of the underlying type of index VTE (DVT, PE, DVT+PE or catheter associated DVT) (Table 14.1.6.3). The actual treatment duration largely corresponded to the planned treatment duration; most patients received rivaroxaban for between 90 and 180 days (36.0%, n=182/505) or > 180 days (44.2%, n=223/505). The median actual treatment duration was 176.0 (IQR 105.0 to 189.0) days, with little influence of the underlying type of index VTE (Table 10.14).

Table 10.14: Main reason for choosing rivaroxaban and planned treatment duration (Safety Analysis Set)

	Rivaroxaban (N=505)
Main reason for choosing rivaroxaban, n (%) –	
Physician decision	174 (34.5)
Burden of parenteral administration	136 (26.9)
Quality of life	94 (18.6)
Patient decision	76 (15.0)
Distance to treating physician	4 (0.8)
Adverse event or invasive procedure*	6 (1.2)
Interaction of oral anticoagulation with anti-cancer treatment	1 (0.2)
Instable INR	3 (0.6)
Medical/hospital guidelines	4 (0.8)
Price of drug	0 (0.0)
Other	4 (0.8)
Missing	3 (0.6)
Planned treatment duration, n (%)	
≤ 30 days	29 (5.7)
> 30 to ≤ 90 days	40 (7.9)
> 90 to ≤ 180 days	143 (28.3)
> 180 days	290 (57.4)
Actual treatment duration, n (%)	
≤ 30 days	48 (9.5)
> 30 to ≤ 90 days	52 (10.3)
> 90 to ≤ 180 days	182 (36.0)
> 180 days	223 (44.2)
Actual treatment duration (days)	
n (missing)	505 (0)
Mean (SD)	148.5 (65.43)
Median (IQR)	176.0
Minimum – Maximum	1.0 – 362.0
Median actual treatment duration by type of index VTE (days)	
DVT (n=229)	176.0
PE (n=188)	179.0
DVT + PE (n=49)	177.0
Catheter associated DVT (n=38)	169.5

Source: Table 14.1.6.1.1, Table 14.1.6.1.2, Table 14.1.6.2, Table 14.1.6.6, Table 14.1.6.7
QoL = quality of life, SD = standard deviation
* Previous Adverse Event or Invasive Procedure = major bleeding event or other adverse event or invasive procedures / surgeries
Planned treatment duration at first start of rivaroxaban
Treatment duration = stop date of the last dose - start day of the first dose +1. Interruptions ignored.

Most patients (78.6%, n=397/505) were prescribed once daily 20 mg rivaroxaban (SAF). The majority of patients (89.3%, n=451/505) did not change the rivaroxaban dose during the study. However, 54 patients (10.7%) did, most frequently due to 'adverse event' (21 patients) or 'other reason' (26 patients) (Table 10.15, Table 10.16).

Out of the 43 patients who started with 15 mg rivaroxaban twice daily, 28 patients switched to the recommended dose of 20 mg once daily after 3 weeks (Table 14.1.6.8).

Furthermore, most patients (93.7%, n=473/505) did not interrupt the rivaroxaban treatment. There were 32 patients who interrupted the rivaroxaban treatment (i.e. did not take rivaroxaban for at least 2 days), the reasons were most often not specified ('other reason' in 17 patients) (Table 10.16).

At the end of the observation, 59.8% of patients (n=302/505) continued treatment with rivaroxaban (Table 14.1.6.15).

Table 10.15: Initial dose and frequency of rivaroxaban (Safety Analysis Set)

Dosage Dosing frequency	Rivaroxaban (N=505) n (%)
10 mg	
Once daily	23 (4.6)
Twice per day	1 (0.2)
15 mg	
Once daily	39 (7.7)
Twice per day	43 (8.5)
Missing	1 (0.2)
20 mg	
Once daily	397 (78.6)
Other	
Once daily	1 (0.2)

Source: Table 14.1.6.4

Table 10.16: Number of patients with at least one rivaroxaban dose change and reason for dose change (Safety Analysis Set)

	Rivaroxaban (N=505) n (%)
Number of dose changes [a]	
None	451 (89.3)
1	46 (9.1)
2	5 (1.0)
3	2 (0.4)
> 3	1 (0.2)
Patients with at least one dose change	54 (10.7)
Reason [b]	
Adverse event (excl. certain conditions that were asked for separately)[c]	21 (4.2)
Regular stop of therapy	10 (2.0)
Decreased renal function	2 (0.4)
Other reason	26 (5.1)
Missing	1 (0.2)
Number of treatment interruptions	
None	473 (93.7)
1	30 (5.9)
2	0 (0.0)
3	2 (0.4)
> 3	0 (0.0)
Patients with at least one treatment interruption	32 (6.3)
Reason [b]	
Other reason	17 (3.4)
Adverse event (excl. certain conditions that were asked for separately)[c]	12 (2.4)
Low platelet count	3 (0.6)
Decreased renal function	1 (0.2)

Source: Table 14.1.6.9, Table 14.1.6.10, Table 14.1.6.12, Table 14.1.6.14
[a] Planned dose changes were excluded from the table
[b] A patient could have more than one reason
[c] These certain conditions were the following: low platelet count, decreased renal function, episode of nausea/vomiting, diarrhea and potential drug-drug interaction with anti-cancer treatment
Dose change with reason = regular end of therapy not included in the analysis.
Treatment interruption was defined as no rivaroxaban taken for at least 2 days. A patient could have more than one interruption

10.2.4.2.2 Stop of rivaroxaban treatment

Overall (SAF), 26.7% of patients (n=135/505) prematurely discontinued the treatment with rivaroxaban before 6 months of observation. Most frequently recorded reason was ‘other adverse event’ in 18.4% of patients (n=93/505) (Table 10.17).

Table 10.17: Documented reason for patients who discontinued rivaroxaban before 6 months of observation

	Rivaroxaban (N=505) n (%)
Number of patients with premature termination	135 (26.7)
Reason for premature termination*	
Low platelet count	2 (0.4)
Decreased renal function	1 (0.2)
Episode of nausea/vomiting	2 (0.4)
Diarrhea	1 (0.2)
Potential drug-drug interaction with anti-cancer treatment	3 (0.6)
Other adverse event	93 (18.4)
Other reason	32 (6.3)
Missing	1 (0.2)

Source: Table 14.1.6.16
* A patient could have more than one reason

Kaplan-Meier analysis of the time to first interruption shows that up to 6 months of observation (180 days) the estimate of the proportion of patients who have not experienced an interruption in their rivaroxaban treatment was 92.5% (95% CI [89.5,94.7]) (Table 14.1.6.17). The Kaplan-Meier curve is visualized in Figure 10-2.

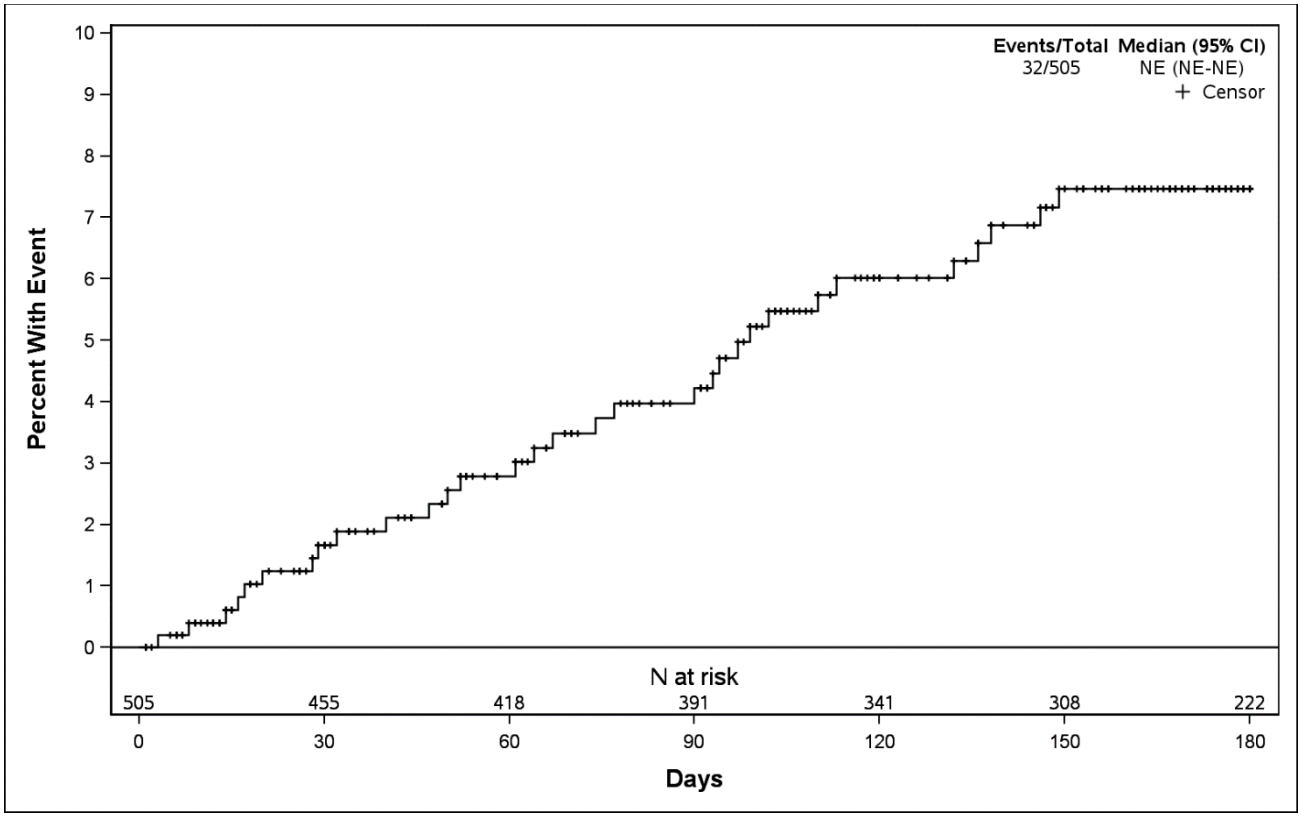


Figure 10-2: Kaplan-Meier estimates of time to first interruption of rivaroxaban treatment (Safety Analysis Set)

Source: Table 14.1.6.17
Time at risk restricted to the period in which at least approximately 10% of patients were at risk

10.2.4.3 Bridging treatment

During observation, a bridging period (defined as an interruption with treatment, bridged with LMWH or Fondaparinux) was recorded for 28 patients (5.5%; 27 patients with 1 bridging period and 1 patient with 2 bridging periods) (Table 10.18); 28 patients received LMWH as bridging treatment and 1 patient 'other treatment' (Table 14.1.7.4). Reason for bridging was 'other reason' (15 patients, 3.0%), 'other adverse event' (12 patients, 2.4%), 'potential drug-drug interaction with anti-cancer treatment' (1 patient, 0.2%), and 'regular stop of therapy' (1 patient, 0.2%) (Table 14.1.7.3).

Table 10.18: Bridging treatment – Safety Analysis Set

	Rivaroxaban (N=505)
Number of bridging periods, n (%)	
None	477 (94.5)
1 bridging period	27 (5.3)
2 bridging periods	1 (0.2)
Duration of bridging period (days)*	
n	29
Mean (SD)	16.8 (28.2)
Median	7.0
Minimum - Maximum	1.0 – 136.0

Source: Table 14.1.7.1, Table 14.1.7.2
n = number of bridging periods, SD = standard deviation
* A patient could have more than 1 bridging treatment
A bridging period was defined as an interruption with rivaroxaban which is bridged with LWMH or Fondaparinux
Duration (in days) was calculated as stop date - start date of bridging period +1.

10.2.4.4 Anticoagulation treatment after stop of rivaroxaban treatment

After permanent stop of rivaroxaban treatment, 64 (12.7%) patients continued treatment with another anticoagulation drug, with LMWH reported most often (11.1%). Of these patients (n=64), 49 (76.6% continued anticoagulation treatment (excluding rivaroxaban) at the end of the study (Table 10.19).

Table 10.19: Anticoagulation treatment after stop of rivaroxaban treatment and at the end of oservation (Safety Analyis Set)

	Rivaroxaban (N=505) n (%)
Anticoagulation treatment after permanent stop of rivaroxaban	64 (12.7)
Treatment, category*	
LMWH	56 (11.1)
Fondaparinux	1 (0.2)
Other (DOAC)	11 (2.2)
Anticoagulation treatment after permanent stop of rivaroxaban	**N=64 (100%)**
Number of patients with ongoing anticoagulation treatment at the end of observation	49 (76.6%)

Source: Table 14.1.8.1, Table 14.1.8.4
DOAC = Direct Oral Anticoagulant
* A patient could have more than one treatment

10.2.4.5 Total duration of anticoagulation treatment

The median total treatment duration of anticoagulation treatment since the VTE index event was 272.0 days, corresponding to about 9 months. Most frequently (61.2%, n=309/505), patients were treated for between >180 and ≤ 360 days (SAF) (Table 10.20).

The total duration was similar for the different types of index VTE (Table 14.1.9.2).

Table 10.20: Total duration of anticoagulation treatment since index event (Safety Analysis Set)

	Rivaroxaban (N=505)
Total treatment duration (days)	
n (missing)	505 (0)
Mean (SD)	332.0 (301.01)
Median	272.0
Minimum - Maximum	34.0 – 3349.0
Total treatment duration, n (%)	
≤ 30 days	0 (0.0)
> 30 to ≤ 90 days	8 (1.6)
> 90 to ≤ 180 days	60 (11.9)
> 180 to ≤ 360 days	309 (61.2)
> 360 days	128 (25.3)

Source: Table 14.1.9.1
SD = standard deviation
Total treatment duration = last day of intake of any anticoagulation treatment – first day of intake of any anticoagulation treatment + 1.
A patient could take more than one category of drugs.

10.3 Outcome data

The primary outcome (change of the ACTS Burden score at Week 4 in comparison to baseline) was based on the ACTS Analysis Set (Week 4), comprising 381 patients.

The analysis of the ACTS Burden score, Benefit score and individual items (secondary outcomes) was based on the ACTS Analysis Set Month 3 (341 patients), ACTS Analysis Set Month 6 (253 patients), and ACTS Analysis Set over time (423 patients).

The analysis of the patient reported outcomes on quality of life (secondary outcome) was based on the FACIT (fatigue) Analysis Set (450 patients).

Patterns of use of anticoagulant treatment and the evaluation of safety and efficacy of rivaroxaban for treatment of acute DVT and PE, and prevention of recurrent DVT and PE in patients with active cancer was based on the Safety Analysis Set, comprising 505 patients.

The secondary outcome of patient preferences (DCE) are reported in Section 10.5.4.

10.4 Main results

10.4.1 Primary outcome

The patient satisfaction scale ACTS was completed at least once by 423 patients at baseline (100.0%), by 381 patients (90.1%) at Week 4, by 341 patients (80.6%) at Month 3, and by 253 patients (59.8%) at Month 6 (Table 14.2.1.1).

The mean (SD) ACTS Burden subscale (primary outcome variable) was 51.8 (7.28) at baseline, which increased by 3.9 (6.71) to 55.6 (5.46) at Week 4. The median increased from 54.0 by 3.0 to 57.0 points, indicating a significant increase of satisfaction at Week 4, as provided in Table 10.21 (ACTS Analysis Set Week 4).

Sensitivity and subgroup analyses of the primary outcome are reported in Section 10.5.

Table 10.21: Primary outcome: change of ACTS Burden score from baseline at Week 4 (ACTS Analysis Set Week 4)

ACTS Burden score	Rivaroxaban (N=381)
Baseline	
n (missing)	381 (0)
Mean (SD)	51.8 (7.28)
Median	54.0
Minimum - Maximum	16.0 – 60.0
Week 4	
n (missing)	381 (0)
Mean (SD)	55.6 (5.46)
Median	57.0
Minimum - Maximum	26.0 – 60.0
Change from baseline	
n (missing)	381 (0)
Mean (SD)	3.9 (6.71)
Median	3.0
Minimum - Maximum	-27.3 – 41.0
p-value*	< 0.0001

Source: Table 14.2.1.1.1
SD = standard deviation
* Wilcoxon signed-rank test, as data were not normally distributed; higher scores indicate higher satisfaction

10.4.2 Secondary outcomes

10.4.2.1 ACTS Burden score at Month 3, Month 6 and over time

The mean (SD) ACTS Burden scale, analyzed for the Analysis Sets at the respective time points (ACTS Analysis Set Month 3 and Month 6), increased by 4.2 (7.16) at Month 3 and by 4.8 (7.33) at Month 6. The median score increased by 3.0 and 4.0 points, respectively, indicating that the increase of satisfaction was maintained or even improved over time. Data are provided in Table 10.22 and Table 10.23.

A box plot of the ACTS Burden score at baseline, Week 4, Month 3 and Month 6 is additionally provided in Figure 10-3.

Table 10.22: Secondary outcome: change of ACTS Burden score from baseline at Month 3 (ACTS Analysis Set Month 3)

ACTS Burden score	Rivaroxaban (N=341)
Baseline	
n (missing)	341 (0)
Mean (SD)	52.1 (7.33)
Median	54.0
Minimum - Maximum	16.0 – 60.0
Month 3	
n (missing)	341 (0)
Mean (SD)	56.2 (4.85)
Median	58.0
Minimum - Maximum	31.0 – 60.0
Change from baseline	
n (missing)	341 (0)
Mean (SD)	4.2 (7.16)
Median	3.0
Minimum - Maximum	-16.5 – 44.0
p-value*	< 0.0001

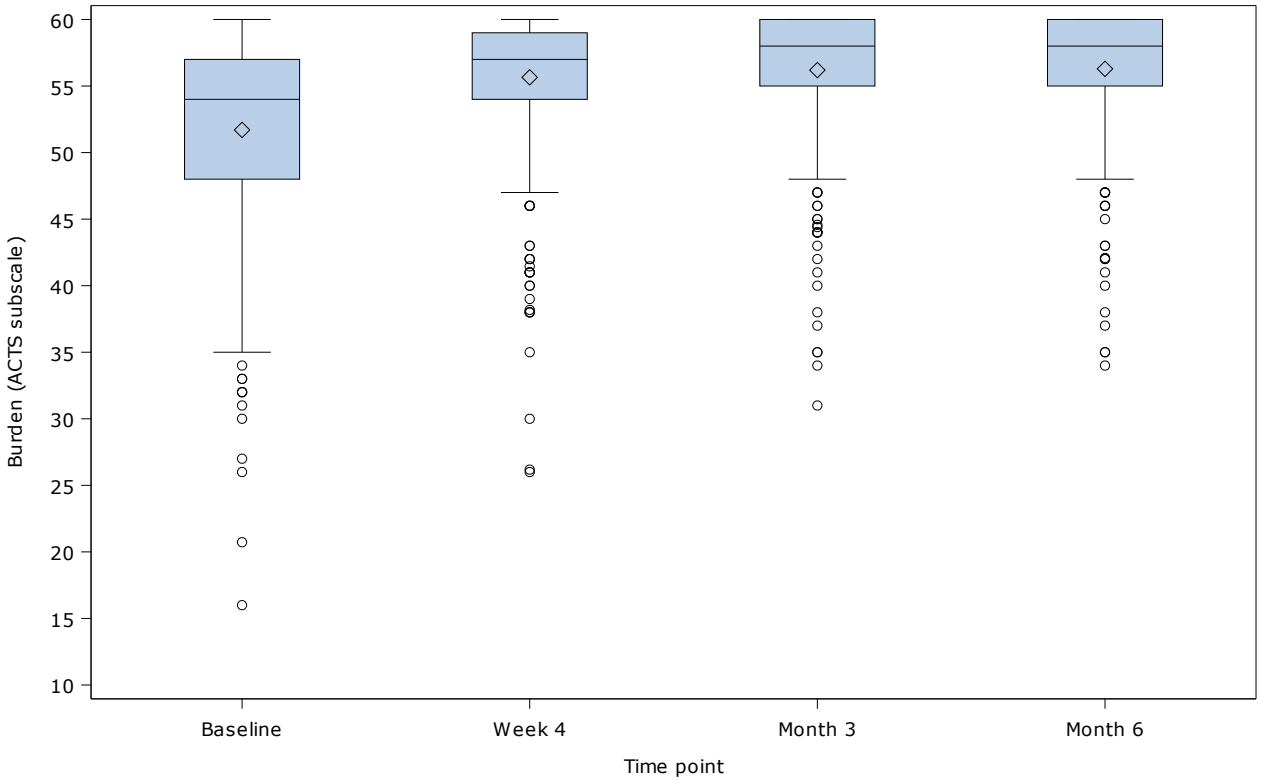
Source: Table 14.2.1.3.1
SD = standard deviation
* Wilcoxon signed-rank test, as data were not normally distributed; higher scores indicate higher satisfaction

Table 10.23: Secondary outcome: change of ACTS Burden score from baseline at Month 6 (ACTS Analysis Set Month 6)

ACTS Burden score	Rivaroxaban (N=253)
Baseline	
n (missing)	253 (0)
Mean (SD)	51.7 (7.31)
Median	54.0
Minimum - Maximum	16.0 – 60.0
Month 6	
n (missing)	253 (0)
Mean (SD)	56.5 (4.81)
Median	58.0
Minimum - Maximum	34.0 – 60.0
Change from baseline	
n (missing)	253 (0)
Mean (SD)	4.8 (7.33)
Median	4.0
Minimum - Maximum	-19.5 – 44.0
p-value*	< 0.0001

Source: Table 14.2.1.3.2
SD = standard deviation
* Wilcoxon signed-rank test, as data were not normally distributed; higher scores indicate higher satisfaction

Figure 10-3: Box plot over time for ACTS Burden score (ACCTS Analysis Sets)



Source: Figure 14.2.2.1
Vertical lines show 25%-, 50%-, 75%-quartiles, ad diamond represents the mean, upper/lower whisker = 1.5 x inter quartile range, circles represent outliers
Higher scores indicate higher satisfaction

Mixed repeated measurement models (both with or without interaction) revealed that none of the baseline characteristics used for the subgroup analyses (see Section 10.5.2) had a significant impact on the ACTS Burden score over time with the exception of the countries of the participating sites (Tables 14.2.1.4.1 to Table 14.2.1.4.10).

10.4.2.2 ACTS Benefit score

The mean (SD) ACTS Benefit score was 11.2 (2.73) at baseline (median. 12.0), which did not change considerably in the first 4 weeks of treatment (mean change 0.1 [3.17]). Over time, the ACTS Benefit score increased, with a mean (SD) change from baseline at Month 3 of 0.4 (3.13), and at Month 6 of 0.5 (3.01). The median score did not change over time. Overall, the changes of the ACTS Benefit score vs. baseline were significant at Months 3 and 6 (Table 10.24).

A box plot of the ACTS Benefit score at baseline, Week 4 (comprising 381 patients with ACTS Burden score at baseline and Week 4 +/- 2 weeks), Month 3 and Month 6 (comprising 341 and 253 patients with ACTS Burden score at baseline and Month 3 / Month 6 +/- 2 weeks, respectively) is additionally provided in Figure 10-4 for the ACTS Analysis Set (comprising a total of 423 patients with ACTS Burden score at baseline and at least one valid ACTS Burden score at any time post-baseline).

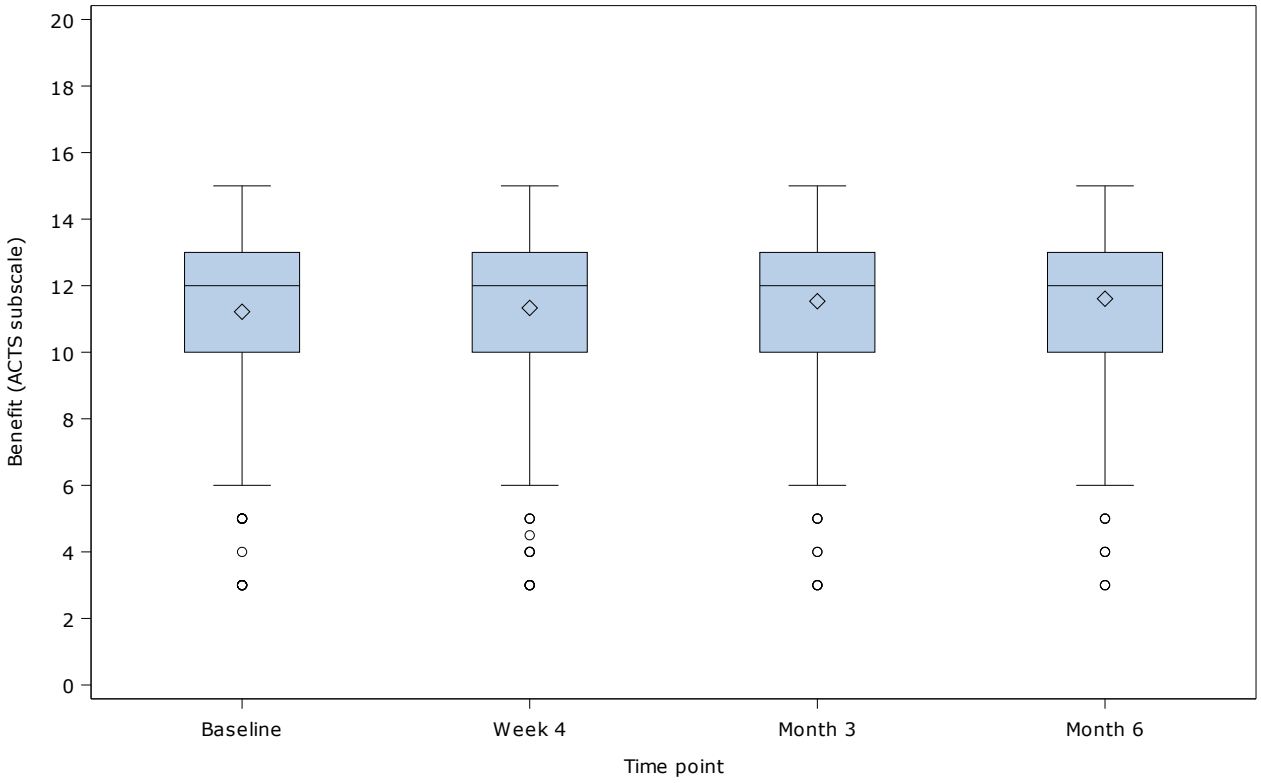
A descriptive analysis of the ACTS total score by visit can be found in Table 14.2.2.3.19 and of the single items by visit in Table 14.2.2.3.20 (ACTS Analysis Set).

Table 10.24: ACTS Benefit score – change from baseline at Week 4, Month 3 and Month 6 (ACTS Analysis Sets)

Mean change of ACTS Benefit score	Rivaroxaban
Change from baseline at Week 4	**N=381**
n (missing)	367 (14)
Mean (SD)	0.1 (3.17)
Median	0.0
Minimum - Maximum	-12.0 – 12.0
p-value	0.5135
Change from baseline at Month 3	**N=341**
n (missing)	327 (14)
Mean (SD)	0.4 (3.13)
Median	0.0
Minimum - Maximum	-12.0 – 12.0
p-value	0.0374
Change from baseline at Month 6	**N=253**
n (missing)	245 (8)
Mean (SD)	0.5 (3.01)
Median	0.0
Minimum - Maximum	-10.0 – 10.0
p-value*	0.0114

Source: Table 14.2.2.3.18.1, Table 14.2.2.3.18.2, Table 14.2.2.3.18.3
SD = standard deviation
* Wilcoxon signed-rank test, as data were not normally distributed; higher scores indicate higher satisfaction

Figure 10-4: Box plot over time for ACTS Benefit score (ACTS Analysis Set)



Source: Figure 14.2.2.2
Vertical lines show 25%-, 50%-, 75%-quartiles, ad diamond represents the mean, upper/lower whisker = 1.5 x inter quartile range, circles represent outliers
Higher scores indicate higher satisfaction

10.4.2.3 FACIT-Fatigue

The quality of life (fatigue related) questionnaire FACIT was completed by 450 patients at baseline (100.0%), by 423 patients (94.0%) at Week 4, by 377 patients (83.8%) at Month 3, and by 323 patients (71.8%) at Month 6 (Table 14.2.3.1).

The mean (SD) FACIT score was 34.4 (9.44) at baseline, which did not change considerably in the first 4 weeks of treatment (mean change 0.1 [8.09]). Over time, the FACIT score increased, with a mean (SD) change from baseline at Month 3 of 1.4 (8.6), and at Month 6 of 2.1 (8.9), as shown in Table 10.25 (FACIT Analysis Set). The median FACIT score was 36.0 at baseline and Week 4 and changed to 38.0 and 40.0 at Months 3 and 6, respectively. This indicates an improvement of fatigue-related quality of life over time, which was significant vs. baseline at Months 3 and 6.

Table 10.25: FACIT score – change from baseline (FACIT Analysis Set)

Mean change of FACIT score	Rivaroxaban (N=450)
Change from baseline at Week 4	
n (missing)	423 (27)
Mean (SD)	0.1 (8.09)
Median	0.0
Minimum - Maximum	-35.0 – 28.0
p-value	0.4523
Change from baseline at Month 3	
n (missing)	377 (73)
Mean (SD)	1.4 (8.61)
Median	1.0
Minimum - Maximum	-34.0 – 32.0
p-value	0.0010
Change from baseline at Month 6	
n (missing)	323 (127)
Mean (SD)	2.1 (8.88)
Median	1.0
Minimum - Maximum	-24.0 – 30.0
p-value*	< 0.0001

Source: Table 14.2.3.3.1, Table 14.2.3.3.2, Table 14.2.3.3.3
FACIT = Functional Assessment of Chronic Illness Therapy, SD = standard deviation
* Wilcoxon signed-rank test, as data were not normally distributed; higher scores indicate higher quality of life

10.5 Other analyses

10.5.1 Sensitivity analyses of the primary outcome

A first sensitivity analysis on the ACTS Burden score at Week 4 was conducted to investigate the potential impact of patients who dropped out from the study earlier than Week 4 due to other reasons than death due to cancer (adjudicated event) on the outcome. For this analysis, the SAF was used (N=389).

The mean (SD) ACTS Burden subscale was 51.7 (7.31) at baseline, which increased by 3.0 (8.96) to 54.7 (8.22) at Week 4. The median increased from 54.0 to 57.0 by a median of 2.6. The increase was statistically significant (Table 10.26) (SAF). Thus, the sensitivity analysis confirmed the primary outcome and shows that drop-outs had no impact on the primary outcome.

Furthermore, the second sensitivity analysis, using a different period definition for Week 4 (28 days after initial visit ± 7 days instead of 14 – 56 days) confirmed the primary outcome, as the ACTS Burden score increased from baseline to Week 4 (mean (SD) change 4.3 (6.46); median change: 3.0; $p < 0.0001$ – Wilcoxon signed rank test), as provided in Table 14.2.1.1.3 (ACTS analysis Set Week 4).

Table 10.26: Sensitivity analysis of investigating potential impact of drop-outs on the change of ACTS Burden score from baseline at Week 4 (Safety Analysis Set)

ACTS Burden score	Rivaroxaban (N=389)
Baseline	
n	389
Mean (SD)	51.7 (7.31)
Median	54.0
Minimum - Maximum	16.0 – 60.0
Week 4	
n	389
Mean (SD)	54.7 (8.22)
Median	57.0
Minimum - Maximum	12.0 – 60.0
Change from baseline	
n	389
Mean (SD)	3.0 (8.96)
Median	2.6
Minimum - Maximum	-48.0 – 41.0
p-value*	< 0.0001

Source: Table 14.2.1.1.2
SD = standard deviation
* Wilcoxon signed-rank test, as data were not normally distributed
Patient population = ACTS Week 4 + patients from the safety population who dropped out before Week 4 due to other reason than death due to cancer (adjudicated).
One patient who dropped out had no baseline assessment and was excluded from the analysis.
The worst possible value of ACTS Burden score (=12) was imputed for missing value.

10.5.2 Subgroup analyses

Pre-specified subgroup analyses of the primary parameter (ACTS Burden score) were performed to further examine whether the treatment satisfaction under treatment with rivaroxaban varied according to the patients' baseline characteristics and to investigate the consistency of the primary outcome.

Results of the subgroup analyses are summarized in the following tables:

Table 14.2.1.2.1	ACTS Burden score - change from baseline at week 4 by gender - ACTS analysis set wk 4
Table 14.2.1.2.2	ACTS Burden score - change from baseline at week 4 by age group - ACTS analysis set wk 4
Table 14.2.1.2.3	ACTS Burden score - change from baseline at week 4 by index VTE event symptomatic - ACTS analysis set wk 4
Table 14.2.1.2.4	ACTS Burden score - change from baseline at week 4 by type of initial VTE treatment - ACTS analysis set wk 4
Table 14.2.1.2.5	ACTS Burden score - change from baseline at week 4 by duration of initial VTE treatment - ACTS analysis set wk 4
Table 14.2.1.2.6	ACTS Burden score - change from baseline at week 4 by main reason for choosing Rivaroxaban - ACTS analysis set wk 4
Table 14.2.1.2.7	ACTS Burden score - change from baseline at week 4 by cancer category - ACTS analysis set wk 4
Table 14.2.1.2.8	ACTS Burden score - change from baseline at week 4 by type of cancer - haematological malignancies - ACTS analysis set wk 4
Table 14.2.1.2.9	ACTS Burden score - change from baseline at week 4 by type of cancer - solid tumor - ACTS analysis set wk 4
Table 14.2.1.2.10	ACTS Burden score - change from baseline at week 4 by country - ACTS analysis set wk 4

The increase in patient treatment satisfaction as assessed by the mean change in ACTS Burden score was larger in female than in male (4.4 vs. 3.3; median: 3.0 vs. 2.6) and larger in younger (< 60 years) than in older (≥ 60 years) patients (4.4 vs. 3.6; median: 9.0 vs. 6.0). Patients whose index VTE was symptomatic were more satisfied at Week 4 than those without symptoms (4.3 vs. 2.7; median: 3.0 vs. 2.0).

The type of initial treatment (LMWH, VKA, Fondaparinux) did not seem to have a clear impact on the treatment satisfaction at Week 4. However, patient numbers in the VKA and Fondaparinux groups were small. Patients with a very long duration of initial VTE treatment of >90 days reported higher treatment satisfaction than patients with a shorter duration, but there was no uniform trend over the classes of duration.

Patients who switched to rivaroxaban due to their own choice were slightly more satisfied at Week 4 than patients in whom the treatment switch was based on their physician's decision (4.0 vs. 3.4; median: 2.9 vs. 2.5).

The other subgroups (different cancer categories, cancer types, or countries) differed largely in size, thus no clear conclusion can be drawn from the data.

10.5.3 Analyses of individual items (ACTS Burden score)

The improvement of the ACTS Burden score was – with some differences – visible in all individual items. The highest response was seen in the items addressing bruising (item 3), daily (6) and occasional (7) hassle of treatment, and the difficulty (8), time-consumption (9), frustration (11) and burden (12) of treatment.

10.5.4 Discrete Change Experiment (DCE)

The majority of the patients interviewed was able to provide consistent DCE data (93% of all patients who participated in the DCE interview). The descriptive analysis showed that patients had a

clear preference for treatment regimen that offer an oral route of administration instead of a subcutaneous application. All other attributes showed a weaker preference order.

The conditional logit model estimation confirmed that the attribute "route of administration" was the most important treatment characteristic (73.8% of the overall decision was influenced by this attribute), followed by the possibility of interaction with food/alcohol (11.8% of the overall decision of a patient for/against a treatment option), distance to treating physician and the frequency of intake (7.2% and 6.5% of the overall treatment decision, respectively).

The "Need of regular INR controls" had no influence on the patient's treatment decision (overall patient sample); in the subgroup of Canadian patients the attribute "need of regular INR controls" showed the same impact on the treatment decision as the attributes "intake frequency" and "possibility of interactions". The impact of the attribute "route of administration" remained high in all subgroups analyzed.

More detailed analyses are contained in Annex 2.

10.6 Adverse events/adverse reactions

Safety evaluation is based on the SAF.

10.6.1 Treatment-emergent adverse events

10.6.1.1 Summary of treatment-emergent adverse events

Overall (SAF), any TEAEs were documented in 61.8% (n=312/505) of patients during the study. Most of the patients had TEAEs of Grade 1 (14.1%, n=71/505), Grade 2 (18.4%, n=93/505), or Grade 3 (14.3%, n=72/505) according to NCI CTC Grade (worst grade). Grade 4 was recorded in 2.6% of patients (n=13/505) and Grade 5 (death) in 8.3% (n=42/505). In 4.2% of patients (n=21/505), grading was not possible (Table 14.3.1.1.1).

An overview of the number and percentage of patients with TEAEs, cancer-related TEAEs, cancer-therapy-related TEAEs, TEAEs excluding bleeding events, TEAEs leading to discontinuation, to (prolonged) hospitalization or to death, and AEs > 2 days after stop of study medication, including incidence rate per 100 person-years is provided in Table 10.27.

Overall (SAF), 61.8% of patients (n=312/505) experienced any TEAE during the study (54.9% of patients had TEAEs excluding bleeding events, n=277/505); in 21.8% of patients (n=110/505) TEAEs were suspected to be drug-related. TEAEs were suspected to be cancer-related in 35.8% of patients (n=181/505) and related to cancer-therapy in 26.7% of patients (n=135/505).

Serious TEAEs (as reported by the investigator) were documented in 29.3% of patients (n=148/505) and in 4.4% of patients (n=22/505) the serious TEAEs were suspected to be drug-related. In 0.4% of patients (n=2/505), the drug-related serious TEAEs led to death.

In 12.3% of patients (n=62/505), TEAEs led to discontinuation of study treatment and in 22.0% of patients (n=111/505) TEAEs led to (prolonged) hospitalization.

In 7.7% of patients (n=39/505), the AEs started > 2 days after stop of study treatment and in 0.4% of patients (n=2/505) the AEs were drug-related (details in Section 10.6.1.5).

Table 10.27: Overview of number of patients with TEAEs (Safety Analysis Set)

	Number of patients with event (%)	95%-CI	Incidence rate per 100 person-years	95%-CI
AEs	312 (61.8)	[57.4,66.0]	246.00	[219.46,274.45]
AEs excluding bleeding events*	277 (54.9)	[50.4,59.3]	203.11	[179.90,228.11]
Serious AEs	148 (29.3)	[25.4,33.5]	81.42	[68.83,95.35]
Serious AEs excluding bleeding events*	137 (27.1)	[23.3,31.2]	74.86	[62.85,88.20]
Drug-related AEs	110 (21.8)	[18.3,25.6]	60.98	[50.12,73.19]
Serious drug-related AEs	22 (4.4)	[2.7,6.5]	10.77	[6.75,16.01]
Cancer-related AEs	181 (35.8)	[31.7,40.2]	106.49	[91.54,122.86]
Serious cancer-related AEs	110 (21.8)	[18.3,25.6]	57.25	[47.05,68.72]
Cancer-therapy related AEs	135 (26.7)	[22.9,30.8]	81.00	[67.92,95.55]
Serious cancer-therapy related AEs	36 (7.1)	[5.0,9.7]	18.17	[12.72,24.86]
AEs leading to discontinuation	62 (12.3)	[9.5,15.5]	30.40	[23.31,38.70]
AEs leading to (prolonged) hospitalization	111 (22.0)	[18.4,25.8]	59.13	[48.64,70.92]
AEs starting > 2 days after stop of study medication	39 (7.7)	[5.5,10.4]	105.10	[74.74,142.12]
Drug-related AEs starting > 2 days after stop of study medication	2 (0.4)	[0.0,1.4]	5.18	[0.63,16.63]
Serious AEs starting > 2 days after stop of study medication	26 (5.1)	[3.4,7.5]	69.04	[45.10,99.57]
Serious AEs leading to death	42 (8.3)	[6.1,11.1]	20.58	[14.83,27.54]

Source: Table 14.3.1.1.1, Table 14.3.1.2.1, Table 14.3.1.3.1, Table 14.3.1.4.1, Table 14.3.1.5.1, Table 14.3.1.6.1, Table 14.3.1.7.1, Table 14.3.1.8.1, Table 14.3.1.9.1, Table 14.3.1.11.1, Table 14.3.1.13.1, Table 14.3.1.14.1, Table 14.3.1.15.1, Table 14.3.1.16.1, Table 14.3.1.17.1, Table 14.3.1.19.1
* as reported by the investigator
CI = Confidence Interval, AE = Treatment-emergent Adverse Event

The most frequently documented TEAEs by MedDRA SOC and PT (≥ 2.0% of patients) are summarized in Table 10.28.

Most frequently documented TEAEs on SOC-level were ‘Gastrointestinal disorders’ (19.6% of patients, n=99/505), ‘Infections and infestations’ (13.7%, n=69/505), ‘Neoplasms benign, malignant and unspecified (incl cysts and polyps)’ (13.7%, n=69/505), ‘General disorders and administration site conditions’ (13.5%, n=68/505), and ‘Respiratory, thoracic and mediastinal disorders’ (13.3%, n=67/505).

Most frequently recorded TEAEs on PT-level were epistaxis (5.7%, n=29/505), fatigue (4.2%, n=21/505), hematuria (4.0%, n=20/505), constipation (3.8%, n=19/505), and nausea (3.8%, n=19/505).

Most frequently documented cancer-related TEAEs were fatigue (14 patients), abdominal pain (11 patients), constipation (9 patients), hematuria (9 patients), back pain (8 patients), deep vein thrombosis (8 patients), and dyspnea (7 patients) (Table 14.3.1.5.2).

Table 10.28: Most frequently recorded treatment-emergent adverse events (in ≥ 2.0% of patients on SOC and PT level) by primary SOC and PT (Safety Analysis Set)

SOC Preferred term	Number of patients with event n (%)
Any AE	**312 (61.8)**
Blood and lymphatic system disorders	**29 (5.7)**
Anaemia	11 (2.2)
Cardiac disorders	**11 (2.2)**
Eye disorders	**10 (2.0)**
Gastrointestinal disorders	**99 (19.6)**
Abdominal pain	15 (3.0)
Constipation	19 (3.8)
Diarrhoea	16 (3.2)
Nausea	19 (3.8)
General disorders and administration site conditions	**68 (13.5)**
Asthenia	10 (2.0)
Fatigue	21 (4.2)
Peripheral swelling	10 (2.0)
Pyrexia	12 (2.4)
Hepatobiliary disorders	**10 (2.0)**
Infections and infestations	**69 (13.7)**
Urinary tract infection	12 (2.4)
Injury, poisoning and procedural complications	**18 (3.6)**
Investigations	**19 (3.8)**
Metabolism and nutrition disorders	**15 (3.0)**
Musculoskeletal and connective tissue disorders	**35 (6.9)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**69 (13.7)**
Nervous system disorders	**54 (10.7)**
Psychiatric disorders	**13 (2.6)**
Renal and urinary disorders	**31 (6.1)**
Haematuria	20 (4.0)
Reproductive system and breast disorders	**13 (2.6)**
Respiratory, thoracic and mediastinal disorders	**67 (13.3)**
Dyspnoea	15 (3.0)
Epistaxis	29 (5.7)
Skin and subcutaneous tissue disorders	**43 (8.5)**
Alopecia	10 (2.0)
Rash	12 (2.4)
Vascular disorders	**25 (5.0)**

Source: Table 14.3.1.1.
PT = Preferred Term, SOC = System Organ Class
MedDRA version 21.1

10.6.1.2 Drug-related treatment-emergent adverse events

In 21.8% of patients (n=110/505) TEAEs were suspected to be drug-related (Table 14.3.1.3.1).

The most frequently documented drug-related TEAEs by MedDRA SOC and PT (≥ 0.6% of patients) are summarized in Table 10.29.

Most frequently documented drug-related TEAEs on SOC-level were ‘Respiratory, thoracic and mediastinal disorders’ (6.5% of patients, thereof the PT "epistaxis" in 5.3% of patients, n=27/505), ‘Gastrointestinal disorders’ (5.5% of patients, n=28/505, thereof the PT "rectal haemorrhage" in 1.6%, n=8/505; the other events in this SOC occurred only once or twice), ‘Renal and urinary disorders’ (3.6% of patients, all of them affected by the PT "haematuria"), and ‘Skin and subcutaneous tissue disorders’ (3.2%).

In 4.4% of patients (n=22/505) the drug-related TEAEs were serious (see Section 10.6.1.3).

Table 10.29: Most frequently recorded drug-related treatment-emergent adverse events (in ≥ 0.6% of patients on SOC and PT level) by primary SOC and PT (Safety Analysis Set)

SOC Preferred term	**Number of patients with event n (%)**
Any AE	**110 (21.8)**
Blood and lymphatic system disorders	**3 (0.6)**
Eye disorders	**3 (0.6)**
Gastrointestinal disorders	**28 (5.5)**
Rectal haemorrhage	8 (1.6)
General disorders and administration site conditions	**5 (1.0)**
Injury, poisoning and procedural complications	**4 (0.8)**
Nervous system disorders	**7 (1.4)**
Headache	3 (0.6)
Renal and urinary disorders	**18 (3.6)**
Haematuria	18 (3.6)
Reproductive system and breast disorders	**9 (1.8)**
Menorrhagia	3 (0.6)
Vaginal haemorrhage	5 (1.0)
Respiratory, thoracic and mediastinal disorders	**33 (6.5)**
Epistaxis	27 (5.3)
Haemoptysis	4 (0.8)
Skin and subcutaneous tissue disorders	**16 (3.2)**
Alopecia	3 (0.6)
Ecchymosis	4 (0.8)
Pruritus	4 (0.8)
Vascular disorders	**8 (1.6)**
Haematoma	4 (0.8)

Source: Table 14.3.1.3.2; PT = Preferred Term, SOC = System Organ Class; MedDRA version 21.1

10.6.1.3 Serious treatment-emergent adverse events

Serious TEAEs (as reported by the investigator) were documented in 29.3% of patients (n=148/505) (Table 14.3.1.2.1).

Most frequently documented serious TEAEs on SOC-level were 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' (10.7%, n=54/505), 'Infections and infestations' (7.1%, n=36/505), 'Gastrointestinal disorders' (6.1% of patients, n=31/505), and 'Respiratory, thoracic and mediastinal disorders' (3.2%, n=16/505), as provided in Table 14.3.1.2.2.

Most frequently recorded serious TEAEs on PT-level were gastrointestinal pneumonia (9 patients), malignant neoplasm progression (7 patients), pyrexia (5 patients), and colon cancer (5 patients).

The most frequent documented serious TEAEs by MedDRA on PT-level (in ≥ 3 patients) are summarized in Table 10.30.

There were 22 patients (4.4%), in whom serious TEAEs were suspected to be drug-related (Table 14.3.1.4.1).

These drug-related serious TEAEs most often were Gastrointestinal disorders (11 patients; 2.2%), Respiratory, Thoracic and mediastinal disorders (4 patients; 0.8%), and Vascular disorders (3 patients; 0.6%). For more details refer to Table 14.3.1.4.2.

Table 10.30: Most frequently recorded (in ≥ 3 patients) treatment-emergent serious adverse events by PT (Safety Analysis Set)

Preferred term	Number of patients with event n (%)
Any serious TEAE	**148 (29.3)**
Pneumonia	9 (1.8)
Malignant neoplasm progression	7 (1.4)
Pyrexia	5 (1.0)
Colon cancer	5 (1.0)
Gastrointestinal haemorrhage	4 (0.8)
Urinary tract infection	4 (0.8)
Metastases to central nervous system	4 (0.8)
Metastases to lung	4 (0.8)
Cerebrovascular accident	4 (0.8)
Dyspnoea	4 (0.8)
Febrile neutropenia	3 (0.6)
Abdominal pain	3 (0.6)
Intestinal obstruction	3 (0.6)
Vomiting	3 (0.6)
Pain	3 (0.6)
Respiratory tract infection	3 (0.6)
Urosepsis	3 (0.6)
Metastases to liver	3 (0.6)
Haematuria	3 (0.6)
Pleural effusion	3 (0.6)
Pulmonary embolism	3 (0.6)

Source: Table 14.3.1.2.2
PT = Preferred Term
MedDRA version 21.1

10.6.1.4 Treatment-emergent adverse events leading to discontinuation of treatment

In 12.3% of patients, TEAEs led to discontinuation of study treatment.

These TEAEs leading to discontinuation most often were ‘Nervous system disorders’ (8 patients; 1.6%), ‘Renal and urinary disorders’ (8 patients; 1.6%), ‘Respiratory, Thoracic and mediastinal disorders’ (8 patients; 1.6%), ‘Gastrointestinal disorders’ (7 patients; 1.4%), ‘Neoplasms benign, malignant and unspecified (incl cysts and polyps)’ (6 patients; 1.2%), and ‘Vascular disorders’ (6 patients; 1.2%). For more details refer to Table 14.3.1.13.2.

10.6.1.5 Treatment-emergent adverse events starting > 2 days after stop of study treatment

In 39 patients (7.7%), TEAEs started > 2 days after stop of study medication and in 2 patients, the TEAEs were suspected to be drug-related (Table 14.3.1.15.1). On PT-level, these were ‘Pruritus’ (1 patient) and ‘Haematoma’ (1 patient) (Table 14.3.1.16.2).

The TEAEs starting > 2 days after stop of study treatment were serious in 26 patients (5.1%) (Table 14.1.17.1). Most frequently, these were 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' (13 patients) (Table 14.3.1.17.2). None of the latter were serious (Table 14.3.1.18.1).

10.6.2 Deaths

Overall (SAF), 47 patients died from start of rivaroxaban treatment until end of observation, thereof 18 fatal cases occurred more than 2 days after rivaroxaban withdrawal. According to Kaplan-Meier analysis, the survival rate at the end of the observation, i.e. 6 months after start of rivaroxaban treatment was 81.7% (95% CI [70.0; 89.2]) (Table 14.3.1.21). The cumulative event rate is visualized in Figure 10-5.

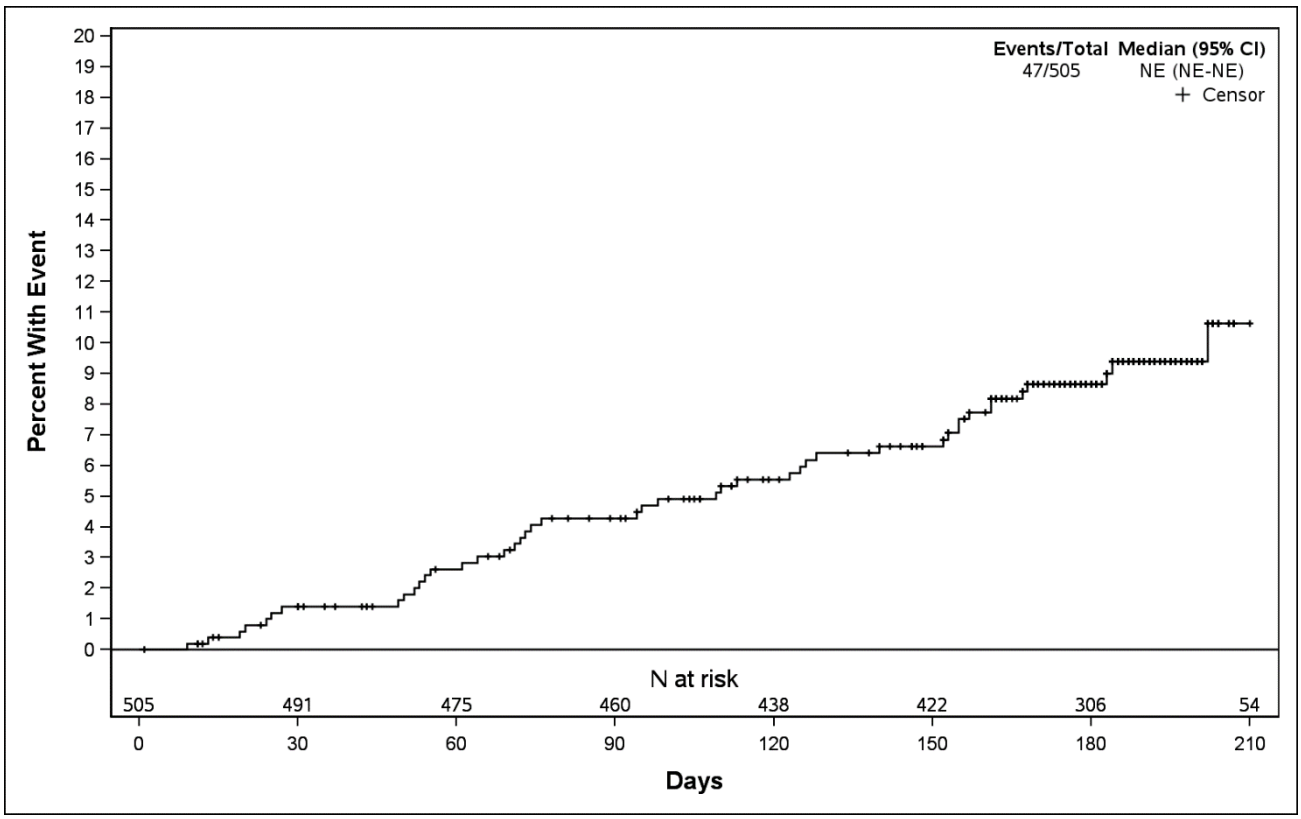


Figure 10-5: Cumulative rate (Kaplan-Meier) for death from start of rivaroxaban (Safety Analysis Set)

Source: Figure 14.3.1.22
Time at risk restricted to the period in which at least approximately 10% of patients were at risk
NE = Not estimable

10.6.3 Bleeding adverse events (as reported by the investigator)

A brief summary of the number and percentage of patients with treatment-emergent bleeding events as reported by the investigator, including incidence rate per 100 person-years is provided in Table 10.31.

Overall (SAF), a total of 114 treatment-emergent bleeding events were documented in 18.8% of patients during the study (n=95/505) (Table 14.3.2.1.1); in 16.2% of patients (n=82/505) the bleeding events were suspected to be drug-related. In 16.2% of patients (n=82/505) the bleeding

events were non-major, and in 3.2% of patients (n=16/505) the bleeding event was recorded as major by the investigator. Note: a patient could experience more than one bleeding event during the study (Table 10.31).

Serious treatment-emergent bleeding events were documented in 5.1% (n=26/505) of patients and in 3.4% of patients (n=17/505) the serious bleeding events were drug-related.

In 2 patients (0.4%), the major bleeding event had a fatal outcome. The adjudicated cause of death was extracranial bleeding (PT of the investigator-reported event: "haemoptysis") and intracranial bleeding (PT of the investigator-reported event: "subdural haemorrhage"). None of the fatal bleeding events started > 2 days after stop of rivaroxaban treatment.

The different treatment-emergent bleeding events stratified by bleeding type, provocation of bleeding, diagnostic test, medical intervention, associated discomfort, collection of hematological laboratories, and transfusions are provided in Table 14.3.2.2.1 to Table 14.3.2.8.8.

Table 10.31: Overview of number of patients with treatment-emergent bleeding events, as reported by the investigator (Safety Analysis Set)

Treatment-emergent events	Number of patients with event (%)	95%-CI	Incidence rate per 100 person-years	95%-CI
Any bleeding event	95 (18.8)	[15.5,22.5]	51.71	[41.84,62.91]
Any drug-related bleeding event	82 (16.2)	[13.1,19.7]	43.90	[34.91,54.19]
Any serious bleeding event	26 (5.1)	[3.4,7.5]	12.84	[8.39,18.52]
Any serious drug-related bleeding event	17 (3.4)	[2.0,5.3]	8.32	[4.85,13.02]
Any major bleeding event	16 (3.2)	[1.8,5.1]	7.85	[4.49,12.44]
Any non-major bleeding event	82 (16.2)	[13.1,19.7]	44.31	[35.24,54.70]
Any fatal major bleeding event	2 (0.4)	[0.0,1.4]	0.97	[0.12,3.12]
Any fatal major bleeding event starting > 2 days after stop of medication	0 (0.0)	-	-	-

Source: Table 14.3.2.1.1, Table 14.3.2.1.2, Table 14.3.2.1.3, Table 14.3.2.1.4, Table 14.3.2.1.5, Table 14.3.2.1.6, Table 14.3.2.1.7, Table 14.3.2.1.8
CI = Confidence Interval

10.6.4 Thromboembolic events (as reported by the investigator)

Overall (SAF), in 20 patients (4.0%) a thromboembolic event was recorded by the investigator during the study. In 13 patients (2.6%), the thromboembolic event was a DVT, in 5 patients (1.0%) a PE, and in 1 patient (0.2%) a catheter-associated DVT. The VTE type was missing in 1 patient (Table 10.32).

In 7/13 patients with a DVT the clot was located at the left lower limb, in 3/13 patients at the right lower limb, in 2/13 patients at the caval vein, in 1/13 patients in the left upper limb, and in 3/13 patient at another location (Table 14.3.3.4).

The median time of onset of the first treatment-emergent thromboembolic event since start of rivaroxaban treatment was 38.0 days, ranging from 2.0 to 166.0 days (Table 14.3.3.2).

Table 10.32: Thromboembolic events – clinical presentation (Safety Analysis Set)

VTE type* Presentation	Rivaroxaban (N=505) n (%)
Patients with at least one treatment emergent thromboembolic event	**20 (4.0)**
DVT	13 (2.6)
Swollen leg	7 (1.4)
Edema	4 (0.8)
Pain	4 (0.8)
Erythema	3 (0.6)
Asymptomatic	2 (0.4)
Shortness of breath	1 (0.2)
PE	5 (1.0)
Asymptomatic	3 (0.6)
Shortness of breath	2 (0.4)
Chest pain	1 (0.2)
Catheter associated DVT	1 (0.2)
Edema	1 (0.2)
VTE Type missing	1 (0.2)

Source: Table 14.3.3.1 DVT = deep vein thrombosis, PE = pulmonary embolism
* a patient could have more than one presentation for an event

10.6.5 Bleeding and thromboembolic events (adjudicated events)

Any bleeding and any thromboembolic event that were recorded by the investigator as serious or non-serious AE were adjudicated and categorized by a Central Adjudication Committee (see Section 4). In addition, all events resulting in death (as reported by the investigator) were adjudicated and categorized by the Committee.

10.6.5.1 Bleeding

Overall (SAF), 18 patients had at least one adjudicated major bleeding event during the study, with an incidence proportion of 3.6% (95% CI [2.1; 5.6]) (Table 10.33). Fifteen patients (3.0%) had 1 major bleeding event and 3 patients (0.6%) had 2 major bleeding events during the study (Table 14.3.4.1.18). In 1 patient, the major bleeding event (1 gastrointestinal bleeding event; Table 14.3.4.1.19.2) occurred > 2 days after stop of rivaroxaban (Table 14.3.4.1.2). The total number of adjudicated treatment-emergent major bleeding events was 21 (Table 14.3.4.1.19.1).

According to Kaplan-Meier analysis, the cumulative proportion of patients without any major bleeding event was 98.8 (95% CI [97.3;99.5]) up to 30 days, which slightly decreased until the end of observation (180 days). Up to an observation period of 180 days, 96.1% of all patients (95% CI [93.9;97.6]) were free from any adjudicated major bleeding event. This is also visualized in Figure 10-6.

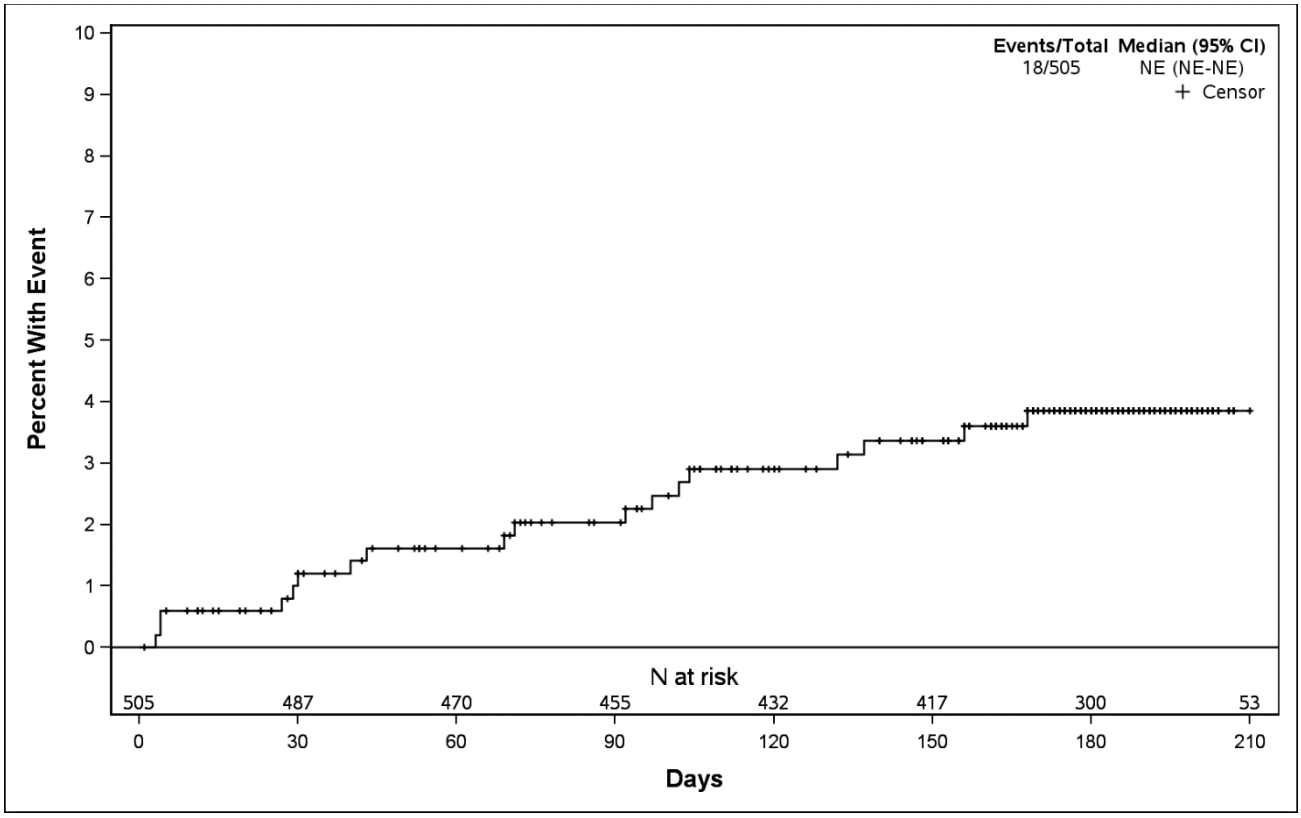


Figure 10-6: Kaplan-Meier estimates of cumulative event rates of any treatment-emergent adjudicated major bleeding event (Safety Analysis Set)

Source: Figure 14.3.4.1.3
CI = confidence interval, NE = not estimable
Time at risk restricted to the period in which at least approximately 10% of patients were at risk

The incidence proportion and incidence rates for treatment-emergent adjudicated major bleeding events by patient characteristics is summarized in Table 10.33. The overall incidence proportion was higher in patients ≥ 60 years (4.4%, n=15/342) than in patients < 60 years (1.8%, n=3/163) and in patients with solid tumors (3.8%, n=17/449) than in patients with hematological malignancies (1.8%, n=1/56). The incidence proportion was highest in patients who were treated with corticosteroids (6.1%, n=9/148) and with immuno-modulators (5.3%, n=16/303), followed by antiemetics/anti-nauseants (4.3%, n=7/164), and cancer therapies (3.3%, n=6/184). The incidence rate was highest in patients with incidental VTE (5.2%, n=7/135), followed by symptomatic DVT (3.3%, n=6/181) and symptomatic DVT+PE (2.9%, n=1/34). The incidence proportion was higher in fragile (6.9%, n=8/116) than in non-fragile patients (3.2%, n=10/312).

Subgroups by cancer type varied considerably in size so that no meaningful conclusions can be drawn (Table 14.3.4.1.6). Also, most patients in this study did not use concomitant medications (antiplatelet therapy, Cyp3A4, P-gp steroids) and most had normal or mildly impaired renal clearance, so that the number in the subcategories of the respective parameters were too small to interpret the data (Table 14.3.4.1.9 to Table 14.3.4.1.13).

Table 10.33: Incidence proportion and incidence rates for any treatment-emergent adjudicated major bleeding event (Safety Analysis Set)

	N	N patients with event	Number events	Incidence proportion (%)	95%-CI Incidence proportion (%)	Incidence rate (per 100 person-years)	95%-CI Incidence rate
All patients	505	18	21	3.6	[2.1, 5.6]	8.84	[5.2, 14.0]
Age							
< 60 years	163	3	4	1.8	[0.4, 5.3]	4.48	[0.9, 13.1]
≥ 60 years	342	15	17	4.4	[2.5, 7.1]	10.98	[6.1, 18.1]
Cancer type							
Hematologic cancer	56	1	1	1.8	[0.0, 9.6]	4.43	[0.1, 24.7]
Solid tumor	449	17	20	3.8	[2.2, 6.0]	9.39	[5.5, 15.0]
Cancer-related therapy							
Cancer therapies	184	6	6	3.3	[1.2,7.0]	7.91	[2.9, 17.2]
Antiangiogenic drugs	87	2	2	2.3	[0.3,8.1]	5.53	[0.7, 20.0]
Corticosteroids	148	9	10	6.1	[2.8, 11.2]	15.22	[7.0, 28.9]
Immunomodulators	303	16	19	5.3	[3.0,8.4]	13.44	[7.7, 21.8]
Monoclonal antibodies		0	0	n/a	n/a	n/a	n/a
Antiemetics and antinauseants	164	7	8	4.3	[1.7, 8.6]	10.64	[4.3, 21.9]
Type of index VTE							
Symptomatic DVT	181	6	7	3.3	[1.2, 7.1]	8.23	[3.0, 17.9]
Symptomatic PE	116	2	3	1.7	[0.2, 6.1]	4.12	[0.5, 14.9]
Symptomatic DVT+PE	34	1	1	2.9	[0.1, 15.3]	7.04	[0.2, 39.2]
Incidental VTE*	135	7	8	5.2	[2.1, 10.4]	13.25	[5.3, 27.3]
Catheter associated DVT	38	1	1	2.6	[0.1, 13.8]	6.74	[0.2, 37.5]
Fragile yes/no							
Yes	116	8	9	6.9	[3.0, 13.1]	18.37	[7.9, 36.2]
No	312	10	12	3.2	[1.5, 5.8]	7.92	[3.8, 14.6]

Source: Table 14.3.4.1.1, Table 14.3.4.1.4, Table 14.3.4.1.5, Table 14.3.4.1.7, Table 14.3.4.1.8, Table 14.3.4.1.14
CI=confidence interval, DVT = deep vein thrombosis, N=number of patients analyzed, n/a = not applicable, PE = pulmonary embolism, VTE = venous thromboembolism
* DVT / PE / DVT+PE
Note: one patient with an adjudicated major bleeding event had a missing VTE Type and was not included in the analysis

Adjudicated major bleeding events occurred most often in patients with gastrointestinal malignancies (9 of 18 patients) followed by genitourinary cancer (4 of 18 patients), as shown in Table 10.34.

Accordingly, most bleeding events were gastrointestinal (13/22 events in 2.2% patients) and most bleeding events occurred spontaneously (14/22 events in 2.8% of patients), as shown in Table 10.35.

Most bleeding events were clinically overt (13/22 events), but some were diagnosed by laboratory testing (3/22 events), CT (1/22 events), MRT (1/22 events), or other diagnostic procedures (3/22 events) (Table 14.3.4.1.21).

15 of the 21 adjudicated treatment-emergent bleeding (in 2.8% of patients), required medical or surgical intervention and 5/21 did not (unknown for 1 bleeding event; Table 14.3.4.1.22.1). Transfusions following the bleeding event was not required for most events (17 of 21 treatment-emergent bleeding events) (Table 14.3.4.1.26.1) and 3 of 18 patients required other blood products to manage the major bleeding (Table 14.3.4.1.28).

Table 10.34: Frequency of treatment-emergent adjudicated major bleeding events by cancer type (Safety Analysis Set)

Type of cancer	Rivaroxaban (N=505) n (%)
Patients with at least one major adjudicated bleeding event	**18 (3.6)**
Gastrointestinal	9 (1.8)
Genitourinary	4 (0.8)
Lung	3 (0.6)
Gynecological	1 (0.2)
Other hematological	1 (0.2)

Source: Table 14.3.4.1.15

Table 10.35: Bleeding site of adjudicated major bleeding (Safety Analysis Set)

Bleeding site	Rivaroxaban (N=505)	
	Number of patients with event n (%)*	Number of events
Treatment emergent adjudicated major bleeding event	**18 (3.6)**	**21**
Bleeding site		
Gastrointestinal	11 (2.2)	13
Genitourinary	3 (0.6)	3
CNS	2 (0.4)	2
Head/neck	1 (0.2)	1
Other	1 (0.2)	1
Thorax	1 (0.2)	1
Provocation of bleeding event		
Spontaneous	14 (2.8)	16
Diagnostic/therapeutic procedure (e.g. catheter)	1 (0.2)	1
Other	4 (0.8)	4
Events occurring > 2 days after stop of rivaroxaban	**1 (0.2)**	**1**
Gastrointestinal	1 (0.2)	1

Source: Table 14.3.4.1.19.1, Table 14.3.4.1.19.2, Table 14.3.4.1.20.1

* A patient may have experienced more than one bleeding event

According to the ISTH definitions of major bleeding, the bleeding led to transfusions in 13 patients (2.6%). The bleeding event resulted in death of 2 patients (0.4%) and occurred at a critical site in 1 patient (0.2%) (Table 10.36). For 3 patients- none of the ISTH criteria shown in Table 10.36 applies, major bleeding was adjudicated as Hb drop of ≥2 g/dl (1.24 mmol/L).

Table 10.36: Frequency of type of bleeding according to ISTH definiton for treatment-emergent adjudicated major bleeding (Safety Analysis Set)

	Rivaroxaban (N=505)	
	n patients (%)*	n events
Patients with at least one adjudicated major bleeding event	**18 (3.6)**	**21**
Bleeding leading to transfusion of ≥ 2 units of packed red blood cells	13 (2.6)	16
Fatal bleeding	2 (0.4)	2
Occurrence at a critical site**	1 (0.2)	1

Source: Table 14.3.4.1.29
* A patient may report more than one ISTH criterion
** intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome

Bleeding events that were reported by the investigator but not adjudicated as major bleeding event, were classified as minor bleeding events. Overall (SAF), 106 minor bleeding events were documented in 81 (16.0%) patients (Table 14.3.4.6.1). Of those, 4 events (in 4 patients) occurred > 2 days after stop of rivaroxaban treatment (Table 14.3.4.6.2).

10.6.5.2 Thromboembolic events

There were 15 patients with at least one symptomatic and 3 patients with at least one incidental VTE event. Most of the adjudicated recurrent VTE events (symptomatic and incidental) were DVT events (symptomatic) in 2.4% (n=12/505) of patients (Table 10.37).

There was 1 symptomatic and 1 incidental adjudicated thromboembolic event each in 1 patient that were classified as ‘other thromboembolic events’ (Table 14.3.4.7.1 and Table 14.3.4.8.1).

Table 10.37: Type of treatment-emergent adjudicated recurrent (symptomatic and incidental) VTE events (Safety Analysis Set)

Type recurrent VTE	Rivaroxaban (N=505) n (%)
Patients with at least one adjudicated recurrent VTE event	**18 (3.6)**
DVT, symptomatic	12 (2.4)
PE	5 (1.0)
Incidental	3 (0.6)
Symptomatic	2 (0.4)
Catheter associated DVT, symptomatic	1 (0.2)

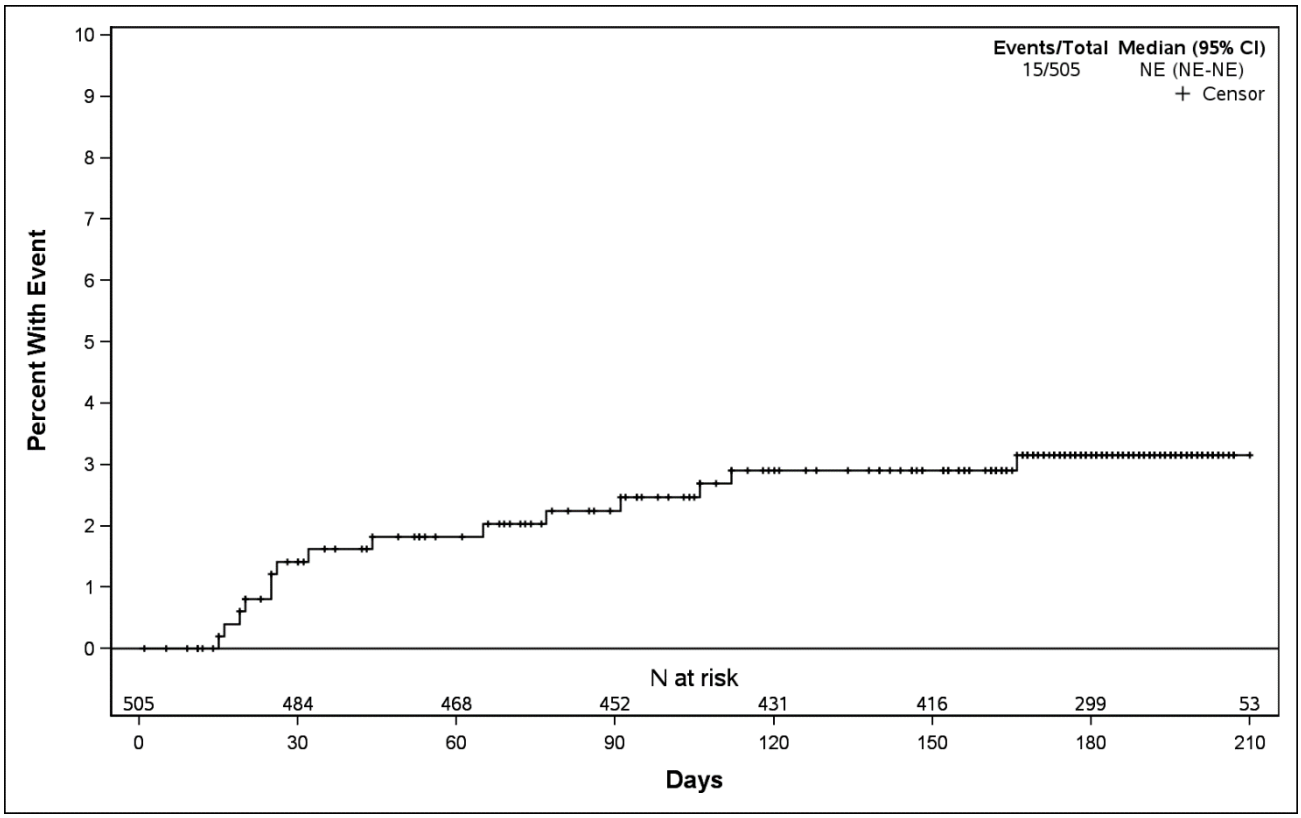
Source: Table 14.3.4.2.15
DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venous thromboembolism
Note: Type of recurrent VTE events as given by the investigator

10.6.5.2.1 Recurrent symptomatic VTE events

Overall (SAF), 15 patients had at least one adjudicated recurrent VTE event (symptomatic) during the study, with an incidence proportion of 3.0% (95% CI [4.1; 12.1]) (Table 10.38). In 3 patients, the recurrent symptomatic VTE event occurred > 2 days after stop of rivaroxaban (Table 14.3.4.2.2).

According to Kaplan-Meier analysis, the cumulative proportion of patients without any adjudicated recurrent symptomatic VTE event was 98.6 (95% CI [97.1;99.3]) which slightly decreased until the end of observation (180 days). Up to the end of treatment observation 96.8% of all patients (95% CI [94.8;98.1]) were free from any recurrent symptomatic VTE event. This is also visualized in Figure 10-7.

Figure 10-7: Kaplan-Meier estimates of cumulative event rates of any treatment-emergent adjudicated recurrent VTE event (symptomatic) (Safety Analysis Set)



Source: Figure 14.3.4.2.3
CI = confidence interval, NE = not estimable
Time at risk restricted to the period in which at least approximately 10% of patients were at risk

The incidence proportion and incidence rates for treatment-emergent adjudicated recurrent VTE events (symptomatic) by patient characteristics is summarized in Table 10.38. As for the major bleeding events, the overall incidence proportion was higher in patients ≥ 60 years (3.8%, n=13/342) than in patients < 60 years (1.2%, n=2/163).

Different from the major bleeding events, the incidence proportion for treatment-emergent adjudicated recurrent VTE events was higher in patients with hematological malignancies (5.4%, n=3/56) than in patients with solid tumors (2.7%, n=12/449).

The incidence proportion was highest in patients who were treated with antiangiogenic drugs (6.9%, n=6/87), followed by cancer therapies (4.9%, n=9/184) and corticosteroids (4.7%, n=7/148).

The incidence rate was highest in patients with catheter associated DVT (7.9%, n=3/38), followed by symptomatic DVT (4.4%, n=8/181) and symptomatic DVT+PE (2.9%, n=1/34). The incidence proportion was slightly higher in non-fragile (3.2%, n=10/312) than in fragile patients (2.6%, n=3/116).

Incidence proportions by subgroups of cancer type, concomitant medications and renal clearance are provided in Table 14.3.4.2.6 and Table 14.3.4.2.9 to Table 14.3.4.2.13.

Table 10.38: Incidence proportion and incidence rates for any treatment-emergent adjudicated recurrent VTE event (Safety Analysis Set)

	N	N patients with event	Number events	Incidence proportion (%)	95%-CI Incidence proportion (%)	Incidence rate (per 100 person-years)	95%-CI Incidence rate
All patients	505	15	15	3.0	[1.7, 4.9]	7.33	[4.1, 12.1]
Age							
< 60 years	163	2	2	1.2	[0.1, 4.4]	2.97	[0.4, 10.7]
≥ 60 years	342	13	13	3.8	[2.0, 6.4]	9.47	[5.0, 16.2]
Cancer type							
Hematologic cancer	56	3	3	5.4	[1.1, 14.9]	13.63	[2.8, 39.8]
Solid tumor	449	12	12	2.7	[1.4, 4.6]	6.57	[3.4, 11.5]
Cancer-related therapy							
Cancer therapies	184	9	9	4.9	[2.3, 9.1]	11.86	[5.4, 22.5]
Antiangiogenic drugs	87	6	6	6.9	[2.6, 14.4]	16.69	[6.1, 36.3]
Corticosteroids	148	7	7	4.7	[1.9, 9.5]	11.79	[4.7, 24.3]
Immunomodulators	303	11	11	3.6	[1.8, 6.4]	9.21	[4.6, 16.5]
Monoclonal antibodies	54	2	2	3.7	[0.5, 12.7]	8.98	[1.1, 32.4]
Antiemetics and antinauseants	164	7	7	4.3	[1.7, 8.6]	10.61	[4.3, 21.9]
Type of index VTE							
Symptomatic DVT	181	8	8	4.4	[1.9, 8.5]	10.95	[4.7, 21.6]
Symptomatic PE		0	0	n/a	n/a	n/a	n/a
Symptomatic DVT+PE	34	1	1	2.9	[0.1, 15.3]	6.89	[0.2, 38.4]
Incidental VTE*	135	3	3	2.2	[0.5, 6.4]	5.56	[1.1, 16.2]
Catheter associated DVT	38	3	3	7.9	[1.7, 21.4]	20.98	[4.3, 61.3]
Fragile yes/no							
Yes	116	3	3	2.6	[0.5, 7.4]	6.76	[1.4, 19.8]
No	312	10	10	3.2	[1.5, 5.8]	7.90	[3.8, 14.5]

Source: Table 14.3.4.2.1, Table 14.3.4.2.4, Table 14.3.4.2.5, Table 14.3.4.2.7, Table 14.3.4.2.8, Table 14.3.4.2.14
CI=confidence interval, DVT = deep vein thrombosis, N=number of patients analyzed, n/a = not applicable, PE = pulmonary embolism, VTE = venous thromboembolism
* DVT / PE / DVT+PE
Note: one patient with an adjudicated major bleeding event had a missing VTE Type and was not included in the analysis

10.6.5.2.2 Recurrent incidental VTE events

Overall (SAF), 3 patients had at least one adjudicated recurrent VTE event (incidental) during the study, with an incidence proportion of 0.6% (95% CI [0.1;1.7]) (Table 14.3.4.3.1). In 1 patient, the incidental VTE event occurred > 2 days after stop of rivaroxaban (Table 14.3.4.3.2).

According to Kaplan-Meier analysis, 99.4% of all patients (95% CI [98.1;99.8]) were free from any recurrent incidental VTE event until the end of observation (180 days) (Table 14.3.4.3.3).

No subgroup analyses were performed for this safety endpoint, as the total number of patients with a recurrent incidental VTE event was <5.

10.6.5.3 Major cardiovascular event

Overall (SAF), 12 (2.4%) patients had at least one adjudicated major cardiovascular event during the study, with an incidence proportion of 2.4% (95% CI [1.2; 4.1]). The total number of major cardiovascular events (MACE) was 13 (Table 14.3.4.4.1). In 1 patient, the major cardiovascular event occurred > 2 days after stop of rivaroxaban (Table 14.3.4.4.2).

The incidence proportion and incidence rates for treatment-emergent adjudicated major cardiovascular events by patient characteristics is summarized in Table 10.39.

The overall incidence rates were similar between the older (≥ 60 years: 2.0%, n=7/342) and the younger patients (< 60 years: 3.1%, n=5/163). All major cardiovascular events occurred in patients with solid cancer and none of them had a hematological malignancy.

The incidence proportion was highest in patients who were treated with corticosteroids (5.4%, n=8/148), followed by cancer therapies (4.9%, n=9/184) and anti-emetics and anti-nauseants (4.9%, n=8/164). MACE incidence proportion was higher in fragile (4.3%, n=5/116) than in non-fragile patients (1.9%, n=6/312).

Incidence proportions by subgroups of cancer type, concomitant medications and renal clearance are provided in Table 14.3.4.4.5 and Table 14.3.4.4.8 to Table 14.3.4.4.12.

Table 10.39: Incidence proportion and incidence rates for any treatment-emergent adjudicated major cardiovascular event (Safety Analysis Set)

	N	N patients with event	Number events	Incidence proportion (%)	95%-CI Incidence proportion (%)	Incidence rate (per 100 person-years)	95%-CI Incidence rate
All patients	505	12	13	2.4	[1.2, 4.1]	5.86	[3.0, 10.2]
Age							
< 60 years	163	5	6	3.1	[1.0, 7.0]	7.45	[2.4, 17.4]
≥ 60 years	342	7	7	2.0	[0.8, 4.2]	5.08	[2.0, 10.5]
Cancer type							
Hematologic cancer		0	0	n/a	n/a	n/a	n/a
Solid tumor	449	12	13	2.7	[1.4, 4.6]	6.58	[3.4, 11.5]
Cancer-related therapy							
Cancer therapies	184	9	10	4.9	[2.3, 9.1]	11.83	[5.4, 22.5]
Antiangiogenic drugs	87	3	4	3.4	[0.7, 9.7]	8.29	[1.7, 24.2]
Corticosteroids	148	8	9	5.4	[2.4, 10.4]	13.37	[5.8, 26.3]
Immunomodulators	303	11	12	3.6	[1.8, 6.4]	9.20	[4.6, 16.5]
Monoclonal antibodies		0	0	n/a	n/a	n/a	n/a
Antiemetics and antinauseants	164	8	9	4.9	[2.1, 9.4]	12.04	[5.2, 23.7]
Type of index VTE							
Symptomatic DVT	181	8	9	4.4	[1.9, 8.5]	11.02	[4.8, 21.7]
Symptomatic PE	116	2	2	1.7	[0.2, 6.1]	4.13	[0.5, 14.9]
Symptomatic DVT+PE	34	1	1	2.9	[0.1, 15.3]	6.89	[0.2, 38.4]
Incidental VTE*	135	1	1	0.7	[0.0, 4.1]	1.85	[0.0, 10.3]
Catheter associated DVT		0	0	n/a	n/a	n/a	n/a
Fragile yes/no							
Yes	116	5	5	4.3	[1.4, 9.8]	11.30	[3.7, 26.4]
No	312	6	7	1.9	[0.7, 4.1]	4.73	[1.7, 10.3]

Source: Table 14.3.4.4.1, Table 14.3.4.4.3, Table 14.3.4.4.4, Table 14.3.4.4.6, Table 14.3.4.4.7, Table 14.3.4.4.13
CI=confidence interval, DVT = deep vein thrombosis, N=number of patients analyzed, n/a = not applicable, PE = pulmonary embolism, VTE = venous thromboembolism
* DVT / PE / DVT+PE
Note: one patient with an adjudicated major bleeding event had a missing VTE Type and was not included in the analysis

MedDRA PTs were grouped to obtain 3 adjudicated major cardiovascular events. As a result, 9/12 patients were affected by a stroke and 2/12 patients by a myocardial infarction, while 1 cardiovascular death was reported (Table 10.40).

Table 10.40: Frequency of treatment-emergent adjudicated cardiovascular events (Safety Analysis Set)

	Rivaroxaban (N=505)	
	n patients (%)	n events
Patients with at least one adjudicated major cardiovascular event	**12 (2.4)**	**13**
Stroke	9 (1.8)	10
Myocardial infarction	2 (0.4)	2
Cardiovascular death	1 (0.2)	1

Source: Table 14.3.4.4.14

10.6.5.4 All-cause mortality

Overall (SAF), 47 patients died from start to rivaroxaban treatment until end of observation (see also Section 10.6.2). The most frequently adjudicated cause of death was the underlying cancer in 30 patients (5.9%), followed by infectious disease in 6 patients (1.2%) and ischemic stroke in 5 patients (1.0%) (Table 14.3.4.5.3.1). The adjudicated causes of death that were treatment-emergent (n=42) are summarized in Table 10.41. Out of the 30 adjudicated fatal cases due to the underlying cancer, 5 cases were not treatment-emergent, i.e. the patients died at least 2 days after having stopped rivaroxaban treatment.

Table 10.41: Adjudicated treatment-emergent causes of death (Safety Analysis Set)

Causes of death	Rivaroxaban (N=505) n (%)
Patients who died from adjudicated treatment-emergent fatal event	**42 (8.3)**
Cancer	25 (5.0)
Bleeding intracranial	1 (0.2)
Bleeding extracranial	1 (0.2)
Pulmonary embolism	0 (0.0)
Ischemic stroke	5 (1.0)
Cardiovascular - Myocardial infarction	1 (0.2)
Cardiovascular - Other vascular event	0 (0.0)
Infectious disease	6 (1.2)
Unexplained death	2 (0.4)
Other	1 (0.2)

Source: Table 14.3.4.5.3.2

The incidence proportion for adjudicated treatment-emergent fatal event was 8.3% (95% CI [6.1; 11.1]) (Table 10.42).

The incidence proportion and incidence rates for treatment-emergent adjudicated events leading to death by patient characteristics is summarized in Table 10.42. The overall incidence proportion was higher in patients ≥ 60 years (8.8%, n=30/342) than in patients < 60 years (7.4%, n=12/163) and in patients with solid tumors (8.9%, n=40/449) than in patients with hematological malignancies (3.6%, n=2/56). The incidence proportion was highest in patients who were treated with anti-emetics/anti-nauseants (16.5%, n=27/164), followed by corticosteroids (12.2%, n=18/148), cancer therapies (11.4%, n=21/184), and antiangiogenic drugs (11.5%, n=10/87). The incidence proportion

was slightly higher in patients with symptomatic DVT+PE as index VTE (11.8%, n=4/34, vs. in incidental index VTEs: 10.4%, n=14/135, symptomatic DVT only: 8.8%, n=16/181) and in fragile (10.3%, n=12/116) vs. in non-fragile patients (7.7%, n=24/312).

Incidence proportions by subgroups of cancer type, concomitant medications and renal clearance are provided in Table 14.3.4.5.6 and Table 14.3.4.1.9 to Table 14.3.4.1.13.

Table 10.42: Incidence proportion and incidence rates for any treatment-emergent adjudicated event leading to death (Safety Analysis Set)

	N	N patients with event	Number events	Incidence proportion (%)	95%-CI Incidence proportion (%)	Incidence rate (per 100 person-years)	95%-CI Incidence rate
All patients	505	42	42	8.3	[6.1, 11.1]	20.58	[14.8, 27.8]
Age							
< 60 years	163	12	12	7.4	[3.9, 12.5]	17.89	[9.2, 31.2]
≥ 60 years	342	30	30	8.8	[6.0, 12.3]	21.90	[14.8, 31.3]
Cancer type							
Hematologic cancer	56	2	2	3.6	[0.4, 12.3]	8.86	[1.1, 32.0]
Solid tumor	449	40	40	8.9	[6.4, 11.9]	22.04	[15.7, 30.0]
Cancer-related therapy							
Cancer therapies	184	21	21	11.4	[7.2, 16.9]	27.87	[17.3, 42.6]
Antiangiogenic drugs	87	10	10	11.5	[5.7, 20.1]	28.20	[13.5, 51.9]
Corticosteroids	148	18	18	12.2	[7.4, 18.5]	30.21	[17.9, 47.7]
Immunomodulators	303	32	32	10.6	[7.3, 14.6]	26.93	[18.4, 38.0]
Monoclonal antibodies	54	4	4	7.4	[2.1, 17.9]	17.78	[4.8, 45.5]
Antiemetics and antinauseants	164	27	27	16.5	[11.1, 23.0]	41.12	[27.1, 59.8]
Type of index VTE							
Symptomatic DVT	181	16	16	8.8	[5.1, 14.0]	22.05	[12.6, 35.8]
Symptomatic PE	116	8	8	6.9	[3.0, 13.1]	16.69	[7.2, 32.9]
Symptomatic DVT+PE	34	4	4	11.8	[3.3, 27.5]	27.83	[7.6, 71.3]
Incidental VTE*	135	14	14	10.4	[5.8, 16.8]	25.95	[14.2, 43.5]
Catheter associated DVT		0	0	n/a	n/a	n/a	n/a
Fragile yes/no							
Yes	116	12	12	10.3	[5.5, 17.4]	27.25	[14.1, 47.6]
No	312	24	24	7.7	[5.0, 11.2]	19.01	[12.2, 28.3]

Source: Table 14.3.4.5.1, Table 14.3.4.5.4, Table 14.3.4.5.5, Table 14.3.4.5.7, Table 14.3.4.5.8, Table 14.3.4.5.14
CI=confidence interval, DVT = deep vein thrombosis, N=number of patients analyzed, n/a = not applicable, PE = pulmonary embolism, VTE = venous thromboembolism
* DVT / PE / DVT+PE
Note: one patient with an adjudicated major bleeding event had a missing VTE Type and was not included

in the analysis

10.6.6 Case Narratives

Subject narratives can be provided in separate documents for the following cases: all deaths and treatment-emergent major bleeding events, recurrent symptomatic VTE and MACE.

10.7 Laboratory data

Results for continuous laboratory parameters tested (D-dimer, platelets, hemoglobin, hematocrit, white blood cells, lymphocytes, creatinine, creatinine clearance, bilirubin, sodium, calcium, C-reactive protein, thromboplastin time, INR) did not provide noteworthy changes from baseline during the study (Table 14.3.5.1). D-dimer was determined in few patients only and showed no consistent change over time.

Categorical laboratory parameters tested (ALT, AST, thrombocytes) were within the normal range for most patients during the study (Table 14.3.5.2.1, Table 14.3.5.2.2 and Table 14.3.5.2.3). Note, that in about 50% of patients, laboratory data was missing.

Shift tables show that most patients maintained their baseline laboratory value over time (Table 14.3.5.3.1 to Table 14.3.5.3.13).

11. Discussion

11.1 Key results

The non-interventional, prospective COSIMO study generates new and additional information on the real-world use of rivaroxaban in a population with cancer and VTE, particularly from a patient-centered perspective. Published studies at the time of the study start had generated only limited data in an active cancer population in this setting [Matzdorff A 2019; Cohen et al. 2018; Young A et al. 2018].

The primary results of the COSIMO study showed significant improvement in patient-reported anti-clot treatment satisfaction 4 weeks after change from SOC to rivaroxaban for treatment of CAT, measured by the ACTS burden score. This reported improvement in treatment satisfaction persisted over 6 months of observation.

Patient-reported improvement in treatment satisfaction was observed across the different components of treatment burden items that were measured, indicating improvement across several aspects of the patient's anti-clot treatment. The most substantial improvements were seen in the items addressing bruising, daily and occasional hassle of treatment, and the difficulty, time-consumption, frustration and burden of treatment.

It is noteworthy that the overall improvement in patient-reported treatment satisfaction was observed despite ~35% of the patients changing to rivaroxaban treatment based on the physician's decision.

Results of clinical phase III studies had suggested an improvement in patient-reported treatment satisfaction with rivaroxaban therapy in comparison with comparator treatment, when measured by the anti-clot treatment scale (ACTS). However, hitherto no comprehensive information on this topic in cancer patients with VTE under routine clinical practice conditions was available. Therefore, it was necessary to generate real-world insight around management of these patients, especially taking the patient's opinions into perspective.

The results of the COSIMO study were generally consistent with results of the randomized controlled trial EINSTEIN DVT of rivaroxaban vs. LMWH/VKA [Bamber L 2013]. Patient-reported mean ACTS Burden score with LMWH/VKA treatment was approx. 52 in both studies and approx. 56 with rivaroxaban therapy (in Months 1-6). Reported treatment satisfaction with rivaroxaban was slightly higher than in the XALIA study and in the EINSTEIN PE trial. While comparing the different studies, it should be considered that the proportion of cancer patients was not the same in the various populations [Cano S et al. 2018; Ageno W et al. 2017; Prins MH 2015].

In COSIMO, patient-reported fatigue burden using the FACIT quality-of-life score improved steadily after 4 weeks and over 6 months of observation upon change from standard of care to rivaroxaban.

Analyses of the ACTS benefits score revealed a steady improvement over 6 months from baseline in the COSIMO study. The EINSTEIN DVT, EINSTEIN PE, and XALIA studies, on their part, reported a superior ACTS benefits score for patients treated with rivaroxaban when compared to treatment with LMWH/VKA.

The incidence of adjudicated major bleeding events in the COSIMO study were lower than those previously reported in the randomized select-d and Hokusai-VTE-Cancer studies (3.6% of patients at 6 months vs 6% of patients at 6 months and 6.9% of patients at 12 months, respectively). As to adjudicated recurrent symptomatic VTE events, the incidence rate amounted to 3.0%. The clinical outcomes from COSIMO were also within the range of database analyses and observational studies of rivaroxaban treatment or patients with CAT, which report VTE recurrence rates of 1.2% to 13.2%, and major bleeding event rates of 1.9% to 8.2% at 6 months. Similarly, the all-cause mortality rate (adjudicated) in COSIMO (9.3%) is within the range reported in previous real-world studies with DOACs (4.8% to 17.8%)

In COSIMO, patient treatment persistence was sufficiently high. Overall, 117 (23.2%) patients discontinued the study: 59 (11.7%) died, 21 (4.2%) withdrew consent, and 17 (3.4%) were lost to follow-up. During the study, approximately 80.2% and 44.2% of patients were treated with rivaroxaban for at least 3 and 6 months, respectively.

<u>DCE Key Results</u>

When presented with the hypothetical DCE treatment options, patients strongly preferred oral administration compared to self-injections (importance of this attribute for overall treatment decisions: 73.8%) and a treatment without known interactions with specific food or alcohol (11.8%). Although the following attributes were relatively less important (7.2% and 6.5%, respectively), patients indicated a preference for a shorter distance to the treating physician and a once-daily dosing regimen compared to a twice-daily intake. The attribute “INR controls” showed no significant impact on the patient’s treatment decision (0.7%).

11.2 Limitations

This study has dealt with a cancer population, which may have led to a high drop-out rate due to worsening condition. Thus, time point for the primary endpoint was set early, at week 4 after the initiation of rivaroxaban treatment. Another source of drop-out was treatment dissatisfaction, representing a limitation of this study since it may have occurred at any time.

The analysis allowed to describe the evolution of certain variables over time. In the absence of a reasonable control arm though, no causal relationship can be concluded from the changes observed in the study endpoints.

There was a possibility of carry-over effects from the treatment administered before the intervention of interest; hence baseline measurements were crucial to mitigate it.

In addition, patients might switch to another treatment during the observation period. However, those patients would still be followed until the end of the study, with patients included in the rivaroxaban group's analyses only during therapy.

There is potential overestimation of the reported treatment satisfaction as patients are likely to have reported high satisfaction immediately after change from SOC to rivaroxaban.

DCE limitations

As possible with the overall COSIMO study, potential selection bias arising from differences in patient characteristics between those willing to participate in the DCE and those who declined to participate cannot be ruled out. Secondly, only patients who changed from SoC anticoagulation with either VKA or LMWH to rivaroxaban were included in the DCE component. Thirdly, the information presented to patients in the DCE is a simplification of reality and it is most likely that unobserved attributes (as for example drug interference, bleeding risk or efficacy) influence the decisions of patients.

Furthermore, a DCE can be perceived in principle as a complex approach for both interviewers and patients, so lack of understanding of the treatment options might have been an issue in this experiment. Patients were surveyed in writing and by telephone and therefore the possibility of false answers cannot be excluded. Finally, another source of selection bias as patients with inconsistent responses were excluded from the final analysis on the assumption that inconsistent responses are strongly indicative of a lack of understanding of the treatment choices.

11.3 Interpretation

Data describing patient satisfaction with DOACs for the treatment of CAT are limited, and the present study is the first dedicated evaluation of DOAC treatment satisfaction in patients with active cancer. The patients recruited in the COSIMO study were representative of patients with CAT who are likely to be selected for rivaroxaban therapy in routine clinical practice, particularly with minimal inclusion and exclusion criteria. Similar to the Hokusai-VTE-Cancer and select-d trials, approximately half of patients enrolled in the current study had metastases and ~90% had solid tumors

The incidence of adjudicated major bleeding events in this single-arm COSIMO study were relatively low at 3.6% over 6 months.

The randomized select-d and Hokusai-VTE-Cancer studies reported major bleeding incidence of 6% over 6 months and 6.9% of over 12 months, respectively. AEs reported in the COSIMO study were mostly cancer- or cancer therapy-associated events, and were similar to those observed in the randomized controlled trials of DOACs in patients with CAT. These data suggest that despite the less restrictive inclusion criteria for the present study, the investigators were able to include appropriate patients with CAT to change to rivaroxaban therapy. The clinical outcomes from this study were also within the range of database analyses and observational studies of rivaroxaban treatment or patients with CAT, which report VTE recurrence rates of 1.2% to 13.2%, and major bleeding event rates of 1.9% to 8.2% at 6 months. Similarly, the all-cause mortality rate

(adjudicated) in COSIMO (9.3%) is within the range reported in previous real-world studies with DOACs (4.8% to 17.8%).

11.4 Generalizability

Notwithstanding the limitations stated in Section 11.2, and considering the broad patient population included as well as the consistent reduction of burden seen in sub-items of the burden score and in several sub-populations (see Section 11.1), the results of this study are generally representative of and applicable to a patient population switched from current standard-of-care anti-coagulation to rivaroxaban for treatment of cancer-associated venous thromboembolism. The wide range of patients included in this study provides the opportunity for further insights into the benefit–risk profile of rivaroxaban in patients with CAT who have been considered suitable for rivaroxaban treatment by treating physicians.

12. Other information

Data indicated that patients receiving corticosteroids possess an adjudicated major bleeding risk increasing with the duration of rivaroxaban therapy. On the other hand, patients with gastrointestinal cancer tended to bleed early under rivaroxaban therapy, with the risk decreasing again after continued treatment. The risk for adjudicated recurrent VTE also tended to appear early after the switch to rivaroxaban in patients with gastrointestinal cancer and decreased later. A similar profile was observed in patients with renal impairment.

These aspects are clinically relevant, if verified in further studies, as they enable tailored surveillance of the patients at elevated risk.

13. Conclusion

The results of the COSIMO study demonstrate that patients with CAT who change their VTE treatment from LMWH, fondaparinux or VKA therapy to rivaroxaban in routine clinical practice experience an improvement in treatment satisfaction, particularly in reducing patient-reported anticoagulation burden. Analyses suggest that rivaroxaban provides a more convenient, easy-to-follow treatment regimen that is less time-consuming and less likely to cause frustration, worry and bruising than SOC therapy (predominately LMWH). Improved treatment satisfaction following a change to rivaroxaban for the treatment of CAT has conceivable positive implications for long-term persistence with therapy and clinical outcomes.

Almost 80% of the patients received rivaroxaban treatment for at least 3 months providing further evidence to support the long-term use of rivaroxaban treatment to prevent the recurrence of VTE in patients with active cancer.

In COSIMO, substantial proportion of patients chosen to be treated with rivaroxaban had advanced stages of cancer and demonstrated similar cancer characteristics to previous trials investigating the use of DOACs for the treatment of CAT. Observed incidence rates of VTE and bleeding events in COSIMO were similar to previous studies of DOACs for VTE treatment in patients with active cancer [Young AM et al. 2018, Raskob GE et al. 2018].

Regarding patient treatment preferences, COSIMO-DCE results demonstrate that treatment-related decision-making of patients with CAT, assuming equal effectiveness and safety of treatments, is predominantly driven by “route of administration”, indicating a strong preference for oral intake.

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Appendices

Annex 1: List of stand-alone documents

Please list any stand-alone documents available upon request in the table below. Documents listed in Annex 1 can be maintained separately from the final OS report. They should be clearly identifiable and provided on request

Table: List of stand-alone documents

Document Name	**Final version and date (if available) ***
Investigator list	*03 December 2019*
Country & Site list	*03 December 2019*
Steering Committee Charter>	*V1.0, 26 January 2017*
Adjudication Committee Charter	*V1.0, 26 January 2017*
CRF	*V1.7, 05 Sep 2017*
SAP	*V1.2, 05 Sep 2019*

Annex 2 Additional information

- COSIMO – DCE study part: Preferences of patients with cancer and a previous VTE event in terms of their anticoagulation therapy. Final report. Ingress GmbH. 2nd September 2019

Annex 3 Signature Pages

Please use the following Signature Page template to prepare signature pages for each OS Core Team member and other functions as applicable in accordance to their roles and involvement in generation and review of the OS Report.

Signature Page - Study medical expert

Title	COSIMO Cancer associated thrombosis – patient reported outcomes with rivaroxaban
Report version and date	V 1.0, 19 December 2019
IMPACT study number	18137
Study type / Study phase	Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	ENCEPP/SDPP/12608
Medicinal product	Rivaroxaban, BAY 59-7939
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD PPD

Date, Signature: 20-Dec-2019, _____

Signature Page - Study conduct responsible

Title	COSIMO Cancer associated thrombosis – patient reported outcomes with rivaroxaban
Report version and date	V 1.0, 19 December 2019
IMPACT study number	18137
Study type / Study phase	Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☐ YES ☒ NO
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Print Name: PPD

Date, Signature: 19 Dec 2019 PPD

Signature Page - Study safety lead

Title	COSIMO Cancer associated thrombosis – patient reported outcomes with rivaroxaban
Report version and date	V 1.0, 19 December 2019
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Print Name: PPD

Date, Signature: 02 Jan 2020, PPD

Signature Page - Study statistician

Title	COSIMO Cancer associated thrombosis – patient reported outcomes with rivaroxaban
Report version and date	V 1.0, 19 December 2019
IMPACT study number	18137
Study type / Study phase	Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☐ YES ☒ NO
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Print Name: PPD

Date, Signature: 20 DEC 2019, PPD

Signature Page - Study data manager

Title	COSIMO Cancer associated thrombosis – patient reported outcomes with rivaroxaban
Report version and date	V 1.0, 19 December 2019
IMPACT study number	18137
Study type / Study phase	Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☐ YES ☒ NO
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The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 23 Dec 2019, PPD

Signature Page - Study epidemiologist

Title	COSIMO Cancer associated thrombosis – patient reported outcomes with rivaroxaban
Report version and date	V 1.0, 19 December 2019
IMPACT study number	18137
Study type / Study phase	Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	ENCEPP/SDPP/12608
Medicinal product	Rivaroxaban, BAY 59-7939
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 19 Dec 2019, PPD

Signature Page - Study health economics and outcomes research (HEOR) responsible

Title	COSIMO Cancer associated thrombosis – patient reported outcomes with rivaroxaban
Report version and date	V 1.0, 19 December 2019
IMPACT study number	18137
Study type / Study phase	Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	ENCEPP/SDPP/12608
Medicinal product	Rivaroxaban, BAY 59-7939
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 02.01.2020, PPD