Science For A Better Life

Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

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).