PASS information

Title	A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany
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Active substance	B01AF01 Antithrombotic agents, direct Factor Xa Inhibitors, Rivaroxaban
Medicinal product	Xarelto®
Product reference	BAY 59-7939
Procedure number	EMEA/H/C/00944
Marketing authorization holder(s)	Bayer Pharma AG, D-13353 Berlin, Germany
Joint PASS	No
Research question and objectives	To assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in new users of rivaroxaban compared with new users of standard of care in routine clinical practice in Germany. Particularly, to provide a description of patients who are dispensed oral rivaroxaban for the first time in comparison with those who are dispensed standard of care for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration). To determine time-trends in the characteristics of first-time use of rivaroxaban. To study the occurrence of hospitalizations for three bleeding events: (a) intracranial haemorrhage, (b) gastrointestinal bleeding and (c) urogenital bleeding among users of rivaroxaban (for the treatment of deep vein thrombosis [DVT] or pulmonary embolism [PE] and prevention of recurrent DVT and PE, stroke prevention in atrial fibrillation and prevention of atherothrombotic events following an acute coronary syndrome) in comparison with users of standard of

	care. Secondary objectives: to study the occurrence of other bleeding events leading to hospitalization, non-infective liver disease (secondary safety outcomes) and to study outcomes related to effectiveness (DVT, PE, myocardial infarction and ischaemic stroke), and all-cause mortality.
Country(-ies) of study	Germany
Author	Professor Edeltraut Garbe Leibniz Institute for Epidemiology and Prevention Research – BIPS GmbH, Bremen, Germany In collaboration with the Xarelto Epidemiology PASS Programme Group.

Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG, D-13353 Berlin, Germany
MAH contact person	Gunnar Brobert

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

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

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2 List of abbreviations

ACS	Acute Coronary Syndromes
ALT	Alanine aminotransferase
ASA	Acetylsalycylic acid
AST	Asparagine aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CrCl	Creatinine Clearance
DVT	Deep Vein Thrombosis
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicine Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GePaRD	German Pharmacoepidemiological Research Database
INR	International Normalized Ratio
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
PAS	Post-authorization study
PASS	Post-authorization safety study
PBRER	Periodic Benefit Risk Evaluation Report
PCI	Percutaneous intervention
PCP	Primary Care Practitioner
PE	Pulmonary Embolism
PRAC	Pharmacovigilance Risk Assessment Committee
REC	Research Ethics Committee
RMP	Risk Management Plan
SPAF	Stroke Prevention in Atrial Fibrillation
UK	United Kingdom
VTE	Venous thromboembolism

3 Responsible parties

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4 Abstract

A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany

Version 5.2, 20 Jan 2015

Principal investigator: Professor Edeltraut Garbe

Leibniz Institute for Epidemiology and Prevention Research – BIPS GmbH, Bremen, Germany

In collaboration with the Xarelto Epidemiology PASS Programme Group.

Rationale and background

Rivaroxaban is an oral, direct Factor Xa inhibitor with multiple indications, including: treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE; stroke prevention in atrial fibrillation (SPAF); and prevention of atherothrombotic events (when combined with antiplatelet therapy) following an acute coronary syndrome (ACS). The use of anticoagulants is associated with the risk of bleeding, and monitoring of the safety profile and patterns of rivaroxaban use in routine care is required. This study in Germany forms part of a post-authorization safety study programme in several European countries.

Research question and objectives

To provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment). To determine time-trends in the characteristics of first-time use of rivaroxaban. Primary safety outcomes are the occurrence of hospitalization for intracranial haemorrhage, gastrointestinal bleeding or urogenital bleeding, among users of rivaroxaban in comparison with individuals receiving current standard of care.

Study design

This study has a cohort design.

Population

All patients aged 2 years and above who have been enrolled in The German Pharmcoepidemiological Research Database (GePaRD) for at least 1 year.

Variables

Detailed descriptive variables will be captured for the population, including co-medications and comorbidities. Primary safety outcomes are the occurrence of hospitalization for intracranial haemorrhage, gastrointestinal bleeding and urogenital bleeding. Other outcomes of interest include hospitalization for bleeding events not defined in the primary outcome (other bleeding), non-infective liver disease, outcomes related to effectiveness (VTE, ischaemic stroke, myocardial infarction), and deaths.

Data sources

GePaRD. The age distribution of the population covered by the GePaRD is broadly similar to the German general population for men, whereas there is some over-representation of women over the age of 40 years.

Study size

The size of the population receiving rivaroxaban will be dependent on market uptake across the indications of interest. Based on an incidence of haemorrhagic stroke in warfarin-treated patients of 5 per 1000 person-years, 12,000 phenprocoumon-treated patient-years and 48,000 phenprocoumon-treated patient-years would be required to exclude a 50% increased risk of haemorrhagic stroke in rivaroxaban-treated patients compared with phenprocoumon-treated patients with a power of 80%.

Data analysis

The patient populations will be described according to the descriptive overall and stratified by indication (VTE prevention, DVT/PE treatment, SPAF, ACS, other) where possible, and by naïve or non-naïve status and switching status. Age- and sex-adjusted odds ratios and 95% confidence intervals for the descriptive variables, will be computed using logistic regression models both overall and stratified by indication and by naïve or non-naïve status, and switching status.

Crude incidence rates for the safety and effectiveness outcomes will be estimated in both cohorts for DVT/PE treatment, SPAF and ACS. Incidence will be computed using the person–time contribution of the study cohorts, stratified into current, recent, past and non-use.

Age- and sex-adjusted rate ratios with 95% CIs will be estimated for each of the three primary adverse outcomes comparing rivaroxaban with standard of care using Poisson regression analysis based on person–time contribution.

Milestones

Data collection will start from 09 December, 2011 (when rivaroxaban received marketing authorization for DVT treatment in Germany) and finish on 31 December, 2018.

5 Amendments and updates

Table 1: Amendments

Number	Date	Section of study protocol	Amendment	Reason
6	Jan 2015	9.3.2.1 9.7.2 9.7.2.1	Addition to section on bleeding definition Addition to section on renal failure definition Addition of section to handle missing data	Response to PRAC review
5	Nov 2014	8.2 9.3.1 9.7.1	Additional variables for patient characterisation and analyses thereof; strengthened analyses of renal impairment	Response to PRAC review
4	May 2014	General	Extension of study timelines. Comparator updated for acute coronary syndromes. Added secondary safety outcome: “other bleeding” Transfer to EMA protocol template. Label wording updated. Current protocol is V5.0.	PRAC request
3	Mar 2012		Inclusion of additional indication, treatment of pulmonary embolism. V4.0 of protocol.	Label expansion
2	Dec 2011		Inclusion of additional indication, acute coronary syndrome. V3.0 of protocol submitted with EU RMP V 7.1	Label expansion
1	Apr 2011		Inclusion of additional indication, stroke prevention	Label expansion

			in atrial fibrillation. V2.0 of protocol submitted with EU RMP V 6.1.	

6 Milestones

Table 2: Milestones

Milestone	Planned date
Start of data collection (Marketing Authorization granted for DVT treatment)	Q1 2012
Interim report 1 2 years drug utilization data and crude incidences for primary safety outcomes	Q4 2015
Interim report 2 4 years drug utilization data and crude incidences for primary safety outcomes	Q4 2017
End of data collection (final patient follow-up completed)	Q4 2018
Final data availability	Q4 2020
Progress reports	Annual in November 2014–19
Final report of study results with full outcomes analysis	Q4 2020
Registration in the EU PAS register	Study to be registered after PRAC approval

7 Rationale and background

Rivaroxaban, a direct Factor Xa inhibitor, is licensed for multiple indications:

- The treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients (15 mg rivaroxaban twice daily [bid] for 3 weeks, then 15 mg or 20 mg once daily [od]).
- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (stroke prevention in atrial fibrillation [SPAF]) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (20 mg rivaroxaban od).
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (recommended dose: 10 mg rivaroxaban od for 35 days following hip replacement surgery and 14 days following knee replacement surgery).
- Co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (recommended dose 2.5 mg bid).

As is the case with other anticoagulants, clinical studies of rivaroxaban have identified haemorrhage as an important safety outcome (Lassen et al. 2008; Turpie et al. 2009). A post-authorization safety study programme is planned for several European countries. The aim of this document is to summarize the design of a population-based study to characterize new users of rivaroxaban, assess patterns of drug utilization, including adherence to label recommendations, and to assess the risk of bleeding associated with rivaroxaban treatment in comparison with standard of care in routine clinical practice in Germany for treatment of DVT/PE and prevention of recurrent DVT and PE, SPAF and prevention of atherothrombotic events in patients with ACS (outcomes related to safety and effectiveness are to be studied for the indications requiring long-term treatment). For DVT/PE treatment and SPAF, standard of care is treatment with the most widely used vitamin K antagonist, phenprocoumon, and for the secondary prevention of ACS, standard of care is antiplatelet drug(s) such as low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor.

8 Research questions and objectives

This post-authorization study was designed to assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in new users of rivaroxaban compared with new users of standard of care.

8.1 Primary objectives

8.1.1 Patient characteristics and drug utilization

- To provide a description of patients who are dispensed oral rivaroxaban for the first time in comparison with those who are dispensed standard of care for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration).
- To determine time-trends in the characteristics of first-time use of rivaroxaban.

8.1.2 Safety and effectiveness outcomes

- To study the occurrence of hospitalizations for three bleeding events: (a) intracranial haemorrhage, (b) gastrointestinal bleeding and (c) urogenital bleeding among users of rivaroxaban (for treatment of DVT/PE and prevention of recurrent DVT and PE, SPAF and prevention of atherothrombotic events in patients with ACS) in comparison with users of standard of care.

8.2 Secondary objective(s)

- To study the occurrence of hospitalization for bleeding events not specified as primary safety outcomes ("other bleeding") in comparison with individuals receiving current standard of care (secondary safety outcome).
- To study the occurrence of non-infective liver disease (secondary safety outcome).
- To study outcomes related to effectiveness (DVT, PE, myocardial infarction and ischaemic stroke).
- To study all-cause mortality.
- To conduct sub-group analysis of safety and effectiveness outcomes in populations of special interest:
  - elderly patients
  - patients with decreased renal function
  - patients with cardiovascular comorbidities e.g. hypertension or diabetes.

9 Research methods

9.1 Study design

This study has a cohort design.

Cohorts of first-time users of either rivaroxaban or comparators will be identified using the date of first dispensation of the respective drug (the index drug) as the index date (Figure 1). Prescription data are linked to a reference database which provides information on e.g. the anatomical-therapeutic-chemical (ATC) code and the defined daily dose (DDD).

A patient will be considered eligible to enter a study cohort as a first-time user of rivaroxaban or a first-time user of "standard of care" when he or she has a first prescription of the drug dispensed during the enrolment period. In Germany, for VTE prevention, DVT/PE treatment and SPAF, standard of care is treatment with the most widely used vitamin K antagonist, phenprocoumon, and for the secondary prevention of ACS, standard of care is antiplatelet drug(s) such as low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor.

Patients who have any record of being dispensed their index drug in the year before index date (i.e. cohort entry), or who qualify for both cohorts on the same day will be excluded. If a patient qualifies as first-time user of both rivaroxaban and "standard of care" comparison drug during the enrolment period, she/he will be assigned to the cohort of drug first prescribed during the enrolment period, with the date of this prescription being the index date.

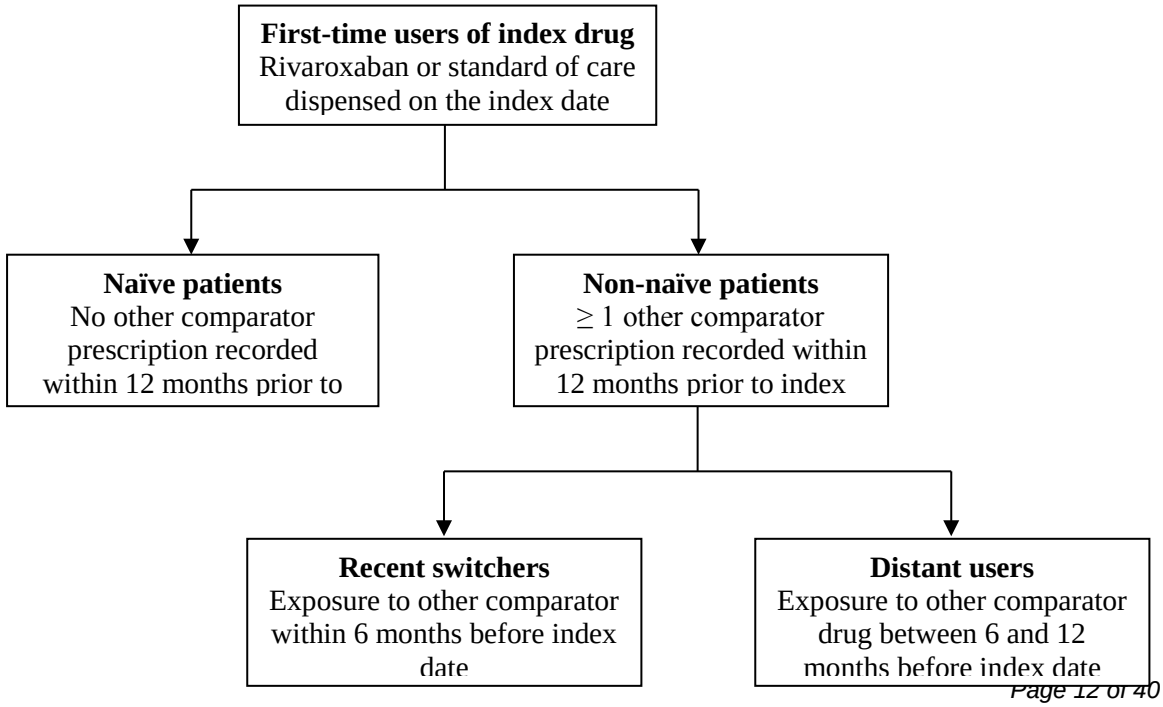
Many patients with ACS have a history of ischaemic heart disease for which platelet inhibition is standard treatment, and thus exclusion of patients with prior use of platelet inhibitors risks excluding a majority of typical ACS patients. Therefore, those who have been using one or more platelet inhibitors will remain eligible to enter the study.

Standard of care for ACS patients is combination therapy, and as such cohort assignment will be based on first use of rivaroxaban (in combination with aspirin or clopidogrel, or multi-antiplatelet therapy), or use of aspirin and clopidogrel and/or other antiplatelet medications.

Study subjects for DVT/PE treatment and SPAF, where the comparator is VKA, will be categorized as naïve or non-naïve patients according to their previous use of any other oral or parenteral anticoagulants. Naïve patients will be those without a previous anticoagulant prescription dispensed in the year before the index date. Non-naïve patients will be those with one or more anticoagulant prescriptions dispensed in the year before the index date.

Non-naïve patients will be further subdivided into recent switchers (patients exposed to another study drug in the 6 months prior to the index date) and distant switchers (patients exposed to another study drug more than 6 six months prior to the index date).

Figure 1. Subdivision of study cohorts for DVT/PE treatment and SPAF.



Data collected for comparison of cohorts is described in Section 9.3. The characteristics of the two study cohorts in the first year and subsequent years of the enrolment period will be compared.

Strengths of the study pertaining to the research question include:

- Use of observational data from routine clinical practice with no selection and no possibility to influence prescribing behaviour.
- GePaRD contains core data, hospitalization data, outpatients prescription data and outpatient care data/diagnoses; patients' records are linked through an unique subject ID. GePaRD is a well-used resource for pharmacoepidemiology research (see Section 9.2).
- Complete coverage of all age groups.
- Lack of non-response or recall bias due to the administrative nature of the data.
- Data captured in pharmacy dispensing allows an assignment to the respective indication (DVT/PE treatment, SPAF, ACS).

9.2 Setting

All patients aged 2 years and above who have been enrolled in GePaRD for at least one year.

The age distribution of the population covered by the GePaRD is broadly similar to the German general population for men, whereas there is some over-representation of women over the age of 40 years. The GePaRD has been used successfully to study haemorrhagic complications of drug treatment (Behr et al. 2010; Jobski et al. 2011; Garbe et al. 2013).

The enrolment period will start on the day after rivaroxaban receives marketing authorization for the 'treatment of DVT and long-term secondary prevention of recurrent DVT and PE' in Germany. End of enrolment will be 31 December 2017 and end of follow-up will be 31 December 2018. Interim reports will be provided for data collected 2 and 4 years after that date (see Section 6 for detailed milestones). The characteristics of the study cohorts in the first year and subsequent years of the enrolment period will be compared.

To study outcomes of interest (Section 8) for patients receiving rivaroxaban and standard of care for treatment of DVT/PE and prevention of recurrent DVT or PE, SPAF and prevention of atherothrombotic events in patients with ACS, the same source population will be used as in the drug utilization study.

9.3 Variables

9.3.1 Patient characteristics and drug utilization

The following variables, including risk factors/potential confounders for the outcomes under study, will be collected for comparison between the two cohorts:

- age and sex distribution at index date, i.e. time of cohort entry;
- estimated dose of index drug at index date and estimated duration of treatment;
- where available, the diagnosis associated with the prescribing of the index drug (where not available, estimated dose and duration of index drug will be used as a proxy for the associated diagnosis among rivaroxaban users);
- proportion of patients defined as naïve, non-naïve, recent switchers and distant switchers;
- type and estimated duration of other anticoagulant use before the index date among the non-naïve group and during time in the cohort for all patients;
- number of pregnant women at index date;
- pregnancy events during the treatment period (i.e. reconstructed using a recently evaluated algorithm (Mikolajczyk et al. 2013));
- use of specific prescribed medications both in the year before the index date and during the time in the cohort following the index date confirming the ACS indication: antiplatelet drugs (low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor);
- use of other prescribed medications both in the year before the index date and during the time in the cohort following the index date: anticoagulants (including dabigatran etexilate and apixaban), antiarrhythmic drugs, antihypertensive drugs, statins, antidiabetic agents, non-steroidal anti-inflammatory drugs, oral steroids, acid-suppressive drugs, disease-modifying anti-rheumatic drugs, antidepressants, antipsychotic drugs, hormone-replacement therapy, strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein (e.g. the systemic azole antimycotics ketoconazole, itraconazole, voriconazole and posaconazole and the HIV-protease inhibitor ritonavir), strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine or phenobarbital) and fluconazole;
- where available, comorbidity based on inpatient and outpatient diagnoses both in the year before the index date and during the time in the cohort following the index date, such as haemorrhagic disease, liver disease, pancreatic disease, cancer (including the presence of malignant neoplasm), cardiovascular disease, cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia and obesity), peripheral arterial disease, respiratory disease (asthma and chronic obstructive pulmonary disease), rheumatoid arthritis, osteoarthritis, gastrointestinal disease (recent gastrointestinal ulceration [including peptic ulcer disease], gastritis and duodenitis, dyspepsia and gastroesophageal reflux disease), oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities, thyroid disease, surgical procedures (including PCI, CABG and recent brain, ophthalmic or spinal surgery, where recorded), presence of a prosthetic heart valve (if recorded), alcohol-related disorders, ventricular arrhythmia, anaemia, and history of intracranial haemorrhage; if possible, a CHADS score will be calculated based on the presence of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke or transient ischaemic attack; also, where possible, a HAS-BLED score for major bleeding risk (hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age > 65, medication usage predisposing to bleeding, alcohol usage history, labile INR [if available]) will be calculated;

- renal disease based on in- and outpatient diagnoses for renal insufficiency, procedure codes for dialysis as well as dispensations of phosphate binders; 
- healthcare utilization in the year prior to the index date (e.g. number of hospital admissions). 

9.3.2 Safety and effectiveness outcomes

For each outcome, potential cases will be identified using diagnostic ICD-10-GM codes (Annex 3), claim codes for outpatient services and procedures (EBM codes) and inpatient operations and procedures codes (OPS codes).

For the purpose of this study, clinically relevant bleedings will be defined as bleedings leading to hospital admission. This restriction is needed to minimize differential misclassification caused by the variability in patients' behavior in seeking care for less severe bleedings. Similarly, the physicians' attitude towards recording these events may differ between new drugs and standard of care. The consequence of restricting to bleedings identified through hospitalization or referrals is that bleedings leading to death before hospital admission will be ignored. It is assumed that the number of bleeding events missed due to this restriction is small. Nevertheless, the magnitude and impact of this restriction will be assessed in another study of this PASS program (Swedish Record-linkage study).

9.3.2.1 Occurrence of intracranial haemorrhage, gastrointestinal bleeding and urogenital bleeding: case definitions

Intracranial haemorrhage (Annex 3, Table 4*)*

Cases of intracranial haemorrhage will be identified in hospitalized patients with a discharge diagnosis of intracranial haemorrhage that meet the criteria for one of the three following categories:

- incident cases of intracerebral haemorrhage recorded following or in association with computed tomography, magnetic resonance imaging (MRI) or x-ray angiography, or an appropriate therapeutic procedure.
- incident cases of subarachnoid haemorrhage recorded following computed tomography, MRI, x-ray angiography or lumbar puncture, or an appropriate therapeutic procedure.
- incident cases of epidural, dural, subdural and arachnoid haemorrhage recorded following computed tomography, MRI, x-ray angiography or lumbar puncture, or an appropriate therapeutic procedure.

Gastrointestinal bleeding (Annex 3, Table 5*)*

A patient will have to meet the following criteria to be considered a case of gastrointestinal bleeding:

- a hospital admission with a discharge diagnosis of gastrointestinal bleeding, i.e. a bleeding originating in the upper or lower gastrointestinal tract or, more specifically, in the oesophagus, stomach, duodenum, jejunum, ileum, colon or rectum.
- and for upper gastrointestinal bleeding, the lesion type being erosion, gastritis, duodenitis or peptic (gastric or duodenal) ulcer.

Urogenital bleeding (Annex 3, Table 6*)*

A patient will have to meet the following criteria to be considered a case of urogenital bleeding:

- a hospital admission with a discharge diagnosis of urogenital bleeding.

9.3.2.2 Secondary safety outcomes: case definition

Other bleeding leading to hospitalization (Annex 3, Table 7*)*

A patient will have to meet the following criteria to be considered a case of "other bleeding":

- a hospital admission with a discharge diagnosis of other bleeding.

Non-infective liver disease (Annex 3, Table 8*)*

A patient will have to meet all of the following criteria to be considered a case of non-infective liver disease:

- A hospital admission with a discharge diagnosis of acute liver injury.
- No diagnosis of cancer, other liver disease (including infectious hepatitis, chronic liver disease etc.), gallbladder or pancreatic disease, or alcoholism during the year before the index date.

9.3.2.3 Secondary outcomes related to effectiveness

Deep vein thrombosis or pulmonary embolism (Annex 3, Table 9*)*

A patient will have to meet the following criteria to be considered a case of DVT or PE:

- A hospital admission with a discharge diagnosis of DVT or PE, or an ambulatory diagnosis of DVT with a dispensation of another antithrombotic agent.

Ischaemic stroke (Annex 3, Table 10*)*

A patient will have to meet the following criteria to be considered a case of ischaemic stroke:

- A hospital admission with a main discharge diagnosis of ischaemic stroke.

MI (Annex 3, Table 11*)*

A patient will have to meet all of the following criteria to be considered a case of acute myocardial infarction:

- A hospital admission with a main discharge diagnosis of acute myocardial infarction.

9.3.2.4 Death

Deaths can be identified from core data and hospital data.

9.4 Data sources

The data source for this study will be the German Pharmacoepidemiological Research Database (GePaRD), which includes information on over 14 million members of four statutory health insurance schemes in Germany (Behr et al. 2010). The database records details of patients' sociodemographic characteristics, inpatient and outpatient diagnoses and procedures, and outpatient drugs dispensed.

9.5 Study Size

All patients enrolled in GePaRD and meeting the inclusion criteria will be included. The size of the population receiving rivaroxaban will be dependent on market uptake across the indications of interest (DVT/PE treatment, ACS and SPAF).

According to a preliminary sample size calculation, based on an incidence of haemorrhagic stroke in warfarin-treated patients of 5 per 1000 person-years, 12,000 rivaroxaban-treated patient-years and 48,000 phenprocoumon patient-years would be required to exclude a 50% increased risk of haemorrhagic stroke in rivaroxaban-treated patients compared with phenprocoumon-treated patients with a power of 80%.

9.6 Data management

The raw data as delivered by the statutory health insurance providers (SHIs) is pseudonymized and transferred to Oracle tables which are stored at an oracle database server at the Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH. As the database is updated regularly, a database snapshot will be stored at the Oracle database server to fix the current status of the database.

- SHI data in BIPS are checked by numerous plausibility checks before they are entered into GePaRD.
- Only validated software (SAS, SAS Institute Inc., Cary, NC, USA) will be used for the statistical analyses.
- All programs will be programmed according to agreed coding standards and will be validated by double-programming or source code review with second programmer involvement.
- The study will be conducted according to the Guidelines for Good Pharmacoepidemiology Practice, Good Practice of Secondary Data Analysis , the ENCePP Guide on Methodological Standards in Pharmacoepidemiology as well as Good Epidemiological Practice.

9.7 Data analysis

The following analyses will be performed.

9.7.1 Patient characteristics and drug utilization

The overall patient populations will be described according to the descriptive variables mentioned in Section 9.3.1, and stratified by naïve or non-naïve status, and switching status, and where possible stratified by indication (VTE prevention, treatment of DVT/PE and prevention of recurrent DVT or PE, SPAF, prevention of atherothrombotic events in patients treated for ACS, other).

The baseline risk of being dispensed one of the comedications or presenting with one of the comorbidities prior to the index date will be assessed by computing the odds ratio of being dispensed that drug or having a comorbidity of interest among first-time users of rivaroxaban compared with first-time users of standard of care. Age- and sex-adjusted odds ratios and 95% confidence intervals will be computed using logistic regression models both overall and stratified by indication and by naïve or non-naïve status, and switching status.

To address inter- and intra-individual differences in phenprocoumon dose requirements a previous study examining drug interactions with phenprocoumon conducted sensitivity analyses assuming that the daily dose of phenprocoumon was 1.5 mg and 4.5 mg, respectively, instead of the defined daily dose of 3 mg (Jobski et al. 2011). Additionally an average daily dose may be calculated for each patient and then be used to estimate the duration of exposure for the last recorded prescription as done in another previous study examining the risk of intracerebral hemorrhage associated with phenprocoumon exposure (Behr et al. 2010).

9.7.2 Safety and effectiveness outcomes

The cohorts (of first-time users of rivaroxaban and first-time users of comparators) will be followed up from the index date until 12 months after the end of the enrolment period for all potential outcomes. For each outcome, the first hospitalization for that outcome during the follow-up period will be identified. A separate follow-up will be performed for each of the three primary adverse outcomes.

Crude incidences will be estimated for each of the three primary adverse outcomes as well as the secondary safety and effectiveness outcomes in both cohorts for DVT/PE treatment, SPAF and ACS. Incidence will be computed using the person–time contribution of the study cohorts. Incidence rates will be calculated overall for both cohorts, as well as dividing person–time into current, recent, past and non-use. Current use will refer to person–time up to 7 days after the end of supply of the index drug, recent use will refer to person–time up to 90 days after the end of current use, past use will include all person–time contribution after the end of recent use up to 1 year after the end of current use, non-use will include all remaining time person–time contribution after past-use until end of follow-up.

Age- and sex-adjusted incidence rate ratios with 95% CIs will be estimated for each of the three adverse outcomes comparing rivaroxaban with standard of care using Poisson regression analysis. Where numbers and data permit, adjustments will be made for baseline medication and comorbidity described in the drug utilization section, including indication and history of adverse outcomes (diagnosis or hospitalization for haemorrhagic stroke, gastrointestinal bleeding or urogenital bleeding recorded during the 12 months before the index date).

If numbers of final cases permit, estimation of the relative risk among rivaroxaban users will be adjusted for known risk factors of the specific outcome using Poissonc regression analysis.

Missing data will only occur for core demographic variables (e.g. sex or age). Missing variables in these variables are very rare. If missings occur these patients will be included as far as possible in the analyses, but excluded for multivariate analyses. Diagnoses or dispensations can only be identified in the database if they are coded. Thus, all patients for whom a certain diagnosis/dispensation is found in the datbase will be coded as having the respective disease / being exposed to the respective drug. All others will be coded as not having the disease / not being exposed to the drug. Therefore, not coded diagnoses / dispensations result in missclassification and not in missing values.

9.7.2.1 Sub-analysis by renal status

The subset of patients with pre-existing renal impairment will be analysed to determine:

- proportion of patients with a diagnosis of renal failure (in total and divided by glomerular filtration rate (Table 12);
- initial indication for rivaroxaban;
- rivaroxaban dose received;
- crude incidences (calculated as described above) of primary safety outcomes and outcomes related to effectiveness by renal function and by dose.

It is likely that a potential misclassification of renal failure will be more pronounced in mild renal failure whereas severe forms of renal failure most likely will be readily identified.

9.7.2.2 Sensitivity analyses

Sensitivity analyses will be performed around the start and stop of treatment to account for differences in the mode of action of rivaroxaban, phenprocoumon and other comparators. This will be taken into account in the analyses of outcomes. Analysis of data gathered in the drug utilization/patient characteristics part of the study will allow for the recognition of any unexpected biases, which can subsequently be accounted for in the outcomes analyses.

9.8 Quality control

As medical charts cannot be reviewed, a separate validation study will be conducted. In this study several validation and plausibility efforts will be performed for each of the outcomes:

- Review of characteristics of patients with the respective outcome: demographics as well as comorbidities for the respective outcome will be examined and checked for plausibility.
- Calculation of age- and sex-adjusted incidence rates of the respective outcome: Incidence rates will be compared with literature.
- Review of patient profiles: 100 patient profiles during the time window respective outcome ± 1 year will be examined and checked for plausibility. This review will include in- and outpatient diagnoses (ICD-10-GM), in-patient procedures and therapies (Operations and Procedures Coding System, OPS) as well as outpatient services and procedures, (EBM “Einheitlicher Bewertungsmaßstab”).

9.9 Limitations of the research methods

Limitations of this study include:

- The possibility for unmeasured confounders for bleeding affecting the data e.g. inadequate or missing recording of ethnicity, alcohol intake or over-the-counter use of some medications.
- Medication in hospital with some exceptions is not included in GePaRD, thus inpatient treatment with rivaroxaban, comparator drugs or co-medication cannot be detected.
- Inadequate data concerning medication compliance.

- Potential for misclassification of exposure time to phenprocoumon due to complex and varying dosing schedules.
- For the effectiveness outcome of DVT/PE, it is possible that discharge diagnoses may lack sensitivity, and data may need to be interpreted with caution e.g. (Skeppholm and Friberg 2014).
- Low-dose aspirin is reimbursable in Germany only in some indications, such as following myocardial infarction. However, for patients who are not exempted from co-payment the price is the same independent of whether they have a prescription or not. Thus patients may buy low-dose aspirin over-the-counter which is not captured by claims data and an underestimation of low-dose aspirin use is likely.

9.10 Other aspects

None applicable.

10 Protection of human subjects

This study protocol will be conducted in accordance with Good Pharmacoepidemiology Practices (ISPE 2007).

11 Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. Reports of adverse events/reactions will be summarized in the study report (European Medicines Agency 2012).

12 Plans for disseminating and communicating study results

- The study is registered on clinicaltrials.gov (NCT01947959) and will be registered on the ENCePP/EU PAS Register website once PRAC approval is achieved.
- Reports will be shared with the authorities as outlined in Section 6.
- Routine updates will be provided annually in the PBRER.
- The principal investigator intends to present and/or publish data from this study in internationally recognized forums following Good Publication Practice.

13 List of references

Behr, S., F. Andersohn, et al. (2010). "Risk of intracerebral hemorrhage associated with phenprocoumon exposure: a nested case-control study in a large population-based German database." Pharmacoepidemiol Drug Saf **19**(7): 722-730.

European Medicines Agency (2012) "Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products."

Garbe, E., S. H. Kreisel, et al. (2013). "Risk of subarachnoid hemorrhage and early case fatality associated with outpatient antithrombotic drug use." Stroke **44**(9): 2422-2426.

ISPE. (2007). "Guidelines for good pharmacoepidemiology practices (second revision)." Retrieved 10 Oct, 2010, from http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

Jobski, K., S. Behr, et al. (2011). "Drug interactions with phenprocoumon and the risk of serious haemorrhage: a nested case-control study in a large population-based German database." Eur J Clin Pharmacol **67**(9): 941-951.

Lassen, M. R., W. Ageno, et al. (2008). "Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty." N Engl J Med **358**(26): 2776-2786.

Mikolajczyk, R. T., A. A. Kraut, et al. (2013). "Evaluation of pregnancy outcome records in the German Pharmacoepidemiological Research Database (GePaRD)." Pharmacoepidemiol Drug Saf **22**(8): 873-880.

Skeppholm, M. and L. Friberg (2014). "Adherence to warfarin treatment among patients with atrial fibrillation." Clin Res Cardiol.

Turpie, A. G., M. R. Lassen, et al. (2009). "Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial." Lancet **373**(9676): 1673-1680.

Annex 1. List of stand-alone documents

Table 3: List of stand-alone documents

None.

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009

Study title:
A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany.

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8
1.1.2 End of data collection[2]	☒	☐	☐	8
1.1.3 Study progress report(s)	☒	☐	☐	8
1.1.4 Interim progress report(s)	☒	☐	☐	8
1.1.5 Registration in the EU PAS register	☒	☐	☐	8
1.1.6 Final report of study results.	☒	☐	☐	8

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	9
2.1.2 The objective(s) of the study?	☒	☐	☐	9,10
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

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

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	10
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9,10
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	16,17

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12
4.2.2 Age and sex?	☒	☐	☐	12
4.2.3 Country of origin?	☒	☐	☐	12
4.2.4 Disease/indication?	☒	☐	☐	12,13
4.2.5 Co-morbidity?	☒	☐	☐	13,13
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	12

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	16,17
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the product?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	14,15
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	16,17

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	12,13
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	12,13,17

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	15
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	15
8.1.3 Covariates?	☒	☐	☐	15
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, product quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	14

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	14,15
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	

Comments:

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

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	16,17
10.3 Are descriptive analyses included?	☒	☐	☐	16,17
10.4 Are stratified analyses included?	☒	☐	☐	16,17
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	17
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	17

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	19, 20
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	16
11.3 Are methods of quality assurance described?	☒	☐	☐	17,18
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	18
11.5 Is there a system in place for independent review of	☐	☒	☐	

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
study results?				

Comments:

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

Comments:

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

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	7

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	19
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	19

Comments:

Annex 3. Additional information: ICD-10-GM codes

Table 4. ICD-10-GM codes for intracranial haemorrhage.

ICD-10-GM code	Description
I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
I601	Subarachnoid haemorrhage from middle cerebral artery
I602	Subarachnoid haemorrhage from anterior communicating artery
I603	Subarachnoid haemorrhage from posterior communicating artery
I604	Subarachnoid haemorrhage from basilar artery
I605	Subarachnoid haemorrhage from vertebral artery
I606	Subarachnoid haemorrhage from other intracranial arteries
I607	Subarachnoid haemorrhage from intracranial artery, unspecified
I608	Other subarachnoid haemorrhage
I609	Subarachnoid haemorrhage, unspecified
I610	Intracerebral haemorrhage in hemisphere, subcortical
I611	Intracerebral haemorrhage in hemisphere, cortical
I612	Intracerebral haemorrhage in hemisphere, unspecified
I613	Intracerebral haemorrhage in brain stem
I614	Intracerebral haemorrhage in cerebellum
I615	Intracerebral haemorrhage, intraventricular
I616	Intracerebral haemorrhage, multiple localized
I618	Other intracerebral haemorrhage
I619	Intracerebral haemorrhage, unspecified
I6200	Subdural haemorrhage (acute, nontraumatic)
I6201	Subdural haemorrhage (subacute, nontraumatic)
I6202	Subdural haemorrhage (chronic, nontraumatic)
I6209	Subdural haemorrhage (not specified, nontraumatic)
I621	Nontraumatic extradural haemorrhage
I629	Intracranial haemorrhage (nontraumatic), unspecified
S0633	Circumscribed cerebral haematoma
S0634	Circumscribed cerebellar haematoma
S064	Epidural haemorrhage
S065	Traumatic subdural haemorrhage
S066	Traumatic subarachnoid haemorrhage

ICD, International Classification of Diseases.

Table 5. ICD-10-GM codes for gastrointestinal bleeding**.**

ICD-10-GM code	Description
I850	Oesophageal varices with bleeding
I9821	Oesophageal [and gastric] varices in diseases [with bleeding] classified elsewhere
K226	Mallory-Weiss syndrome
K228	Haemorrhage of oesophagus NOS
K250	Gastric ulcer, acute with haemorrhage
K252	Gastric ulcer, acute with both haemorrhage and perforation
K254	Gastric ulcer, chronic or unspecified with haemorrhage
K256	Gastric ulcer, chronic or unspecified with both haemorrhage and perforation
K260	Duodenal ulcer, acute with haemorrhage
K262	Duodenal ulcer, acute with both haemorrhage and perforation
K264	Duodenal ulcer, chronic or unspecified with haemorrhage
K266	Duodenal ulcer, chronic or unspecified with both haemorrhage and perforation
K270	Peptic ulcer, site unspecified, acute with haemorrhage
K272	Peptic ulcer, site unspecified, acute with both haemorrhage and perforation
K274	Peptic ulcer, site unspecified, chronic or unspecified with haemorrhage
K276	Peptic ulcer, site unspecified, chronic or unspecified with both haemorrhage and perforation
K280	Gastrojejunal ulcer, site unspecified, acute with haemorrhage
K282	Gastrojejunal ulcer, site unspecified, acute with both haemorrhage and perforation
K284	Gastrojejunal ulcer, site unspecified, chronic or unspecified with haemorrhage
K286	Gastrojejunal ulcer, site unspecified, chronic or unspecified with both haemorrhage and perforation
K290	Acute haemorrhagic gastritis
K3182	[K31.8] Other specified diseases of stomach and duodenum [with bleeding]
K5522	[K55.2] Angiodysplasia of colon [with bleeding]
K5701	[K57.0] Diverticular disease of small intestine with perforation and abscess [with bleeding]
K5703	[K57.0] Diverticular disease of small intestine with perforation and abscess [with bleeding]
K5711	[K57.1] Diverticular disease of small intestine without perforation or abscess [with bleeding]
K5713	[K57.1] Diverticular disease of small intestine without perforation or abscess [with bleeding]
K5721	[K57.2] Diverticular disease of large intestine with perforation and abscess [with bleeding]
K5723	[K57.2] Diverticular disease of large intestine with perforation and abscess [with bleeding]
K5731	[K57.3] Diverticular disease of large intestine without perforation or abscess [with bleeding]
K5733	[K57.3] Diverticular disease of large intestine without perforation or abscess [with bleeding]
K5741	[K57.4] Diverticular disease of both small and large intestine with perforation and abscess [with bleeding]
K5743	[K57.4] Diverticular disease of both small and large intestine with perforation and abscess [with bleeding]
K5751	[K57.5] Diverticular disease of both small and large intestine without perforation or abscess [with bleeding]
K5753	[K57.5] Diverticular disease of both small and large intestine without

ICD-10-GM code	Description
	perforation or abscess [with bleeding]
K5781	[K57.8] Diverticular disease of intestine, part unspecified, with perforation and abscess [with bleeding]
K5783	[K57.8] Diverticular disease of intestine, part unspecified, with perforation and abscess [with bleeding]
K5791	[K57.9] Diverticular disease of intestine, part unspecified, without perforation or abscess [with bleeding]
K5793	[K57.9] Diverticular disease of intestine, part unspecified, without perforation or abscess [with bleeding]
K625	Haemorrhage of anus and rectum
K920	Haematemesis
K921	Melaena
K922	Gastrointestinal haemorrhage, unspecified

ICD, International Classification of Diseases; NOS, not otherwise specified.

Table 6. ICD-10-GM codes for urogenital bleeding.

ICD-10-GM code	Description
N020	Recurrent and persistent haematuria, minor glomerular abnormality
N021	Recurrent and persistent haematuria, focal and segmental glomerular lesions
N022	Recurrent and persistent haematuria, diffuse membranous glomerulonephritis
N023	Recurrent and persistent haematuria, diffuse mesangial proliferative glomerulonephritis
N024	Recurrent and persistent haematuria, diffuse endocapillary proliferative glomerulonephritis
N025	Recurrent and persistent haematuria, diffuse mesangiocapillary glomerulonephritis
N026	Recurrent and persistent haematuria, dense deposit disease
N027	Recurrent and persistent haematuria, diffuse crescentic glomerulonephritis
N028	Recurrent and persistent haematuria, other
N029	Recurrent and persistent haematuria, unspecified
N421	Congestion and haemorrhage of prostate
N836	Haematosalpinx
N857	Haematometra
N897	Haematocolpos
N920	Excessive and frequent menstruation with regular cycle
N921	Excessive and frequent menstruation with irregular cycle
N922	Excessive menstruation at puberty
N923	Ovulation bleeding
N924	Excessive bleeding in the premenopausal period
N930	Postcoital and contact bleeding
N938	Other specified abnormal uterine and vaginal bleeding
N939	Abnormal uterine and vaginal bleeding, unspecified
N950	Postmenopausal bleeding
R31	Unspecified haematuria
S314	Open wound of vagina and vulva

ICD, International Classification of Diseases.

Table 7. ICD-10-GM codes for “other bleeding” leading to hospitalization will be provided on request.

Table 8. ICD-10-GM codes for non-infective liver disease.

ICD-10-GM code	Description
K71.0	Toxic liver disease with cholestasis
K71.1	Toxic liver disease with hepatic necrosis
K71.2	Toxic liver disease with acute hepatitis
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.9	Toxic liver disease, unspecified
K72.0	Acute and subacute hepatic failure
K72.7-!	Hepatic encephalopathy and hepatic coma
K72.9	Hepatic failure, unspecified
R74.0	Elevation of levels of transaminase and lactic acid dehydrogenase [LDH]
R94.5	Abnormal results of liver function studies

ICD, International Classification of Diseases.

Table 9. ICD-10-GM codes for deep vein thrombosis and pulmonary embolism.

ICD-10-GM code	Description
I801	Thrombosis, phlebitis and thrombophlebitis of femoral vein
I802	Thrombosis, phlebitis and thrombophlebitis of other deep vessels of lower extremities
I803	Thrombosis, phlebitis and thrombophlebitis of lower extremities, unspecified
I809	Thrombosis, phlebitis and thrombophlebitis of unspecified site
I26	Pulmonary embolism
I260	Pulmonary embolism with mention of acute cor pulmonale
I269	Pulmonary embolism without mention of acute cor pulmonale

ICD, International Classification of Diseases.

Table 10. ICD-10-GM codes for ischaemic stroke.

ICD-10-GM code	Description
I630	Cerebral infarction due to thrombosis of precerebral arteries
I631	Cerebral infarction due to embolism of precerebral arteries
I632	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I633	Cerebral infarction due to thrombosis of cerebral arteries
I634	Cerebral infarction due to embolism of cerebral arteries
I635	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I636	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I638	Other cerebral infarction
I639	Cerebral infarction, unspecified
G465	Pure motor lacunar syndrome
G466	Pure sensory lacunar syndrome

ICD, International Classification of Diseases.

Table 11. ICD-10-GM codes for acute myocardial infarction.

ICD-10-GM code	Description
I210	Acute transmural myocardial infarction of anterior wall
I211	Acute transmural myocardial infarction of inferior wall
I212	Acute transmural myocardial infarction of other sites
I213	Acute transmural myocardial infarction of unspecified site
I214	Acute subendocardial myocardial infarction
I219	Acute myocardial infarction, unspecified

ICD, International Classification of Diseases.

Table 12. ICD-10-GM codes for renal failure by glomerular filtration rate.

ICD-10-GM code	Description
N18.8	Other chronic renal failure
N18.81	Chronic renal failure, Stadium I Glomerular filtration rate (GFR) 90 mL/min/1.73m^2 body surface area or higher
N18.82	Chronic renal failure, Stadium II Glomerular filtration rate (GFR) 60 to 90 mL/min/1.73m^2 body surface area
N18.83	Chronic renal failure, Stadium III Glomerular filtration rate (GFR) 30 to 60 mL/min/1.73m^2 body surface area
N18.84	Chronic renal failure, Stadium IV Glomerular filtration rate (GFR) 15 to 30 mL/min/1.73m^2 body surface area

ICD, International Classification of Diseases.

Annex 4. Signature pages

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany
Protocol version identifier	5.2
Date of last version of protocol	20 Jan 2015
IMPACT study number	16159
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not registered
Active substance (medicinal product)	B01AF01 Antithrombotic agents, direct Factor Xa Inhibitors, Rivaroxaban
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Qualified person responsible for pharmacovigilance (QPPV)
Name	Michael Kayser
Title	Dr
Address	Bayer Pharma AG, D-13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: Jan. 22nd, 2015, Michael Kayser

Signature Page – Principal Investigator

Title	A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany
Protocol version identifier	5.2
Date of last version of protocol	20 Jan 2015
IMPACT study number	16159
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not registered
Active substance (medicinal product)	B01AF01 Antithrombotic agents, direct Factor Xa Inhibitors, Rivaroxaban
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Principal Investigator
Name	Professor Edeltraut Garbe
Title	MD, PhD
Address	Leibniz Institute for Epidemiology and Prevention Research – BIPS GmbH, Bremen, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 26.1.15 , Edeltraut Garbe