Post Authorization Safety Study (PASS) Information

Acronym/Title	**Xa**relto **Pae**diatric VTE PASS **D**rug **U**tilization **S**tudy: An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS)
Protocol version and date	v 2.1, 16 NOV 2022
IMPACT study number	22195
Study type / Study phase	Observational ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
NCT number	Study not yet registered
Active substance	B01AF01 Antithrombotic agents, Direct factor Xa inhibitors, Rivaroxaban
Medicinal product	Xarelto® 1mg/1mL granules for oral suspension
Product reference	EU/1/08/472/050-EU/1/08/472/051
Procedure number	EMEA/H/C/000944
Comparator / Reference therapy	Standard of care (SOC); (heparins, vitamin K antagonists, other direct oral anticoagulants)
Study Initiator and Funder	Bayer AG
Research question and objectives	The research question for this Post-Authorization Safety Study (PASS) is to evaluate the patterns of drug utilization and safety of rivaroxaban granules for oral suspension and of SOC in children under two years of age diagnosed with venous thromboembolism (VTE) and receiving anticoagulation therapy. Primary objectives are to describe: • Clinical characteristics and demographics of patients using anticoagulation therapy for the treatment of VTE (rivaroxaban oral suspension or SOC)

	• Use of anticoagulation therapy (including selected drug, dose, and duration) for treatment of VTE • Incidence and severity of bleeding (major bleeding, and clinically relevant non-major bleeding) according to anticoagulation therapy (rivaroxaban oral suspension or SOC) Secondary objectives are to describe: • Time trends in patient characteristics and anticoagulation treatment patterns at the population-level over the study period • Incidence of recurrent symptomatic VTE according to anticoagulation therapy (rivaroxaban oral suspension or SOC) • Specialty and care setting of physicians who prescribe anticoagulation therapy (rivaroxaban oral suspension or SOC)
Countries of study	Approximately four countries in Europe (France, Sweden, Denmark, Spain)
Author	PPD PPD PPD Bayer AG PPD PPD PPD PPD IQVIA PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	PPD

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

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

1. Table of contents

2. List of abbreviations

ATC	Anatomical Therapeutic Chemical (Classification System)
CI	Confidence interval
CPR	Danish Civil Registration System
CRNM	Clinically relevant non-major
DCIR	Données De Consommation Inter-Régimes
DNPR	Danish National Patient Register
DOAC	Direct oral anticoagulant
DRG	Diagnosis Related Group
DUS	Drug utilization study
DVT	Deep vein thrombosis
EMA	European Medicines Agency
EMR	Electronic Medical Records
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethical Review Boards
EU	European Union
GDPR	General Data Protection Regulation
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
LMWH	Low molecular weight heparin
LTD	Long-Term Chronic Disease
MAH	Marketing Authorization Holder
MBR	Medical Birth Register
NPR	National Patient Register
PASS	Post-Authorization Safety Study
PE	Pulmonary embolism
PIN	Personal Identification Number
PMSI	Programme de Médicalisation des Systèmes d'Information
QPPV	Qualified Person Responsible For Pharmacovigilance
RMPS	Register of Medicinal Products Statistics
SAP	Statistical Analysis Plan
SIDIAP	Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària
SMR	Hospital Patient Medication Register
SNDS	Système National Des Données De Santé
SOC	Standard of care
UFH	Unfractionated heparin

VKA	Vitamin K antagonist
VTE	Venous thromboembolism

3. Responsible parties

3.1. Study initiator and funder

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

Role: OS Medical Expert
Name: PPD

Role: OS Statistician
Name: PPD

Role: OS Epidemiologist
Name: PPD

Role: OS Safety Lead
Name: PPD

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

Role: Global Regulatory Strategist
Name: PPD

Role: OS Health Economics and Outcomes Research (HEOR) responsible
Name: PPD

Contact details of the responsible parties at Bayer AG are available upon request. Signatures of the responsible parties are collected in Annex 5.

Administrative changes of responsible persons will be documented in the study management system, but do not require formal protocol amendments.

3.2. Contractors, Collaborators, Committees

Study feasibility and protocol development

Role: Project Manager
Name, Company: PPD IQVIA

Role: Lead Epidemiologist

Name, Company:	PPD IQVIA
Role:	Scientific Advisor
Name, Company:	PPD IQVIA

Contact details of the responsible parties at IQVIA are kept as a stand-alone document (Annex 1).

Information on the Steering and Publication Committee Members and the respective Charters are kept as stand-alone documents (Annex 1).

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

4. Abstract

Acronym/Title	**Xa**relto **Pae**diatric VTE PASS **D**rug **U**tilization **S**tudy: An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS)
Protocol version and date	v 2.1, 16 NOV 2022
IMPACT study number	22195
Study type / Study phase	☒ PASS Joint PASS: ☐ YES ☒ NO
Author	PPD PPD PPD Bayer AG PPD PPD PPD PPD IQVIA PPD
Rationale and background	Xarelto® (rivaroxaban), a direct oral anticoagulant (DOAC), was approved on JAN 2021 by the European Medicines Agency (EMA) for a new pharmaceutical formulation of granules for oral suspension 1 mg/mL, and for the indication in the paediatric population for treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years. To supplement the limited information from the paediatric rivaroxaban clinical trial program in the youngest children, the EMA requested a category 3 post-authorization safety study (PASS) addressing the risk of bleeding in the young population. This drug utilization study will evaluate drug utilization patterns, bleeding, and recurrent VTE outcomes in children with VTE and under two years of age who are treated with rivaroxaban granules for oral suspension 1 mg/mL or standard of care (SOC) anticoagulation.
Research question and objectives	The research question for this PASS is to evaluate the patterns of drug utilization and safety of rivaroxaban granules for oral suspension and of SOC in children under two years of age diagnosed with VTE and receiving anticoagulation therapy. Primary objectives are to describe:

	• Clinical characteristics and demographics of patients using anticoagulation therapy for the treatment of VTE (rivaroxaban oral suspension or SOC) • Use of anticoagulation therapy (including selected drug, dose, and duration) for treatment of VTE • Incidence and severity of bleeding (major bleeding, and clinically relevant non-major bleeding) according to anticoagulation therapy (rivaroxaban oral suspension or SOC) Secondary objectives are to describe: • Time trends in patient characteristics and anticoagulation treatment patterns at the population-level over the study period • Incidence of recurrent symptomatic VTE according to anticoagulation therapy (rivaroxaban oral suspension or SOC) • Specialty and care setting of physicians who prescribe anticoagulation therapy (rivaroxaban oral suspension or SOC)
Study design	Observational, retrospective, descriptive, multi-national cohort study of new users of anticoagulation therapy conducted using secondary data sources
Population	The study population will consist of children aged under two years who initiate an anticoagulation therapy with rivaroxaban oral suspension or any other anticoagulation drug (index date) following a VTE diagnosis. Two exposure categories will be defined, one for rivaroxaban and one for SOC, and patients will contribute time to each exposure category if they switch from SOC to rivaroxaban or vice versa.

Variables	**Exposure**
	• Recorded prescriptions or dispensed prescriptions of rivaroxaban oral suspension or SOC (heparins, vitamin K antagonists [VKAs] and other DOACs)
	• Data extracted from the data sources:
	  ○ Active substance
	  ○ Route of administration

	○ Date of prescription issuance (or filling) ○ Prescribed drug amount or days' supply ○ Prescribed daily dose (if available) • Derived variables: ○ Treatment episode by agent ○ Anticoagulation treatment period: sequence of treatment episodes of rivaroxaban and SOC ○ Drug switch(es) between anticoagulant agents within the same anticoagulation treatment period **Primary outcomes** • Patient characteristics: ○ Age, sex, and bodyweight at index date ○ Gestational age, if available ○ Characteristics of index VTE, if available ○ Co-morbidities before index date ○ Previous treatment before index date ○ Comedication during follow-up ○ Health resource utilization before index date ○ Duration of oral, nasogastric/gastric feeding before index date, if available • Drug utilization patterns: ○ Index drug therapy: substance and class of anticoagulant drug therapy, duration of use, dosing, route of administration ○ Maintenance therapy: substance and class of anticoagulant drug therapy, duration of use, dosing, route of administration ○ Switching to other anticoagulant therapy ○ Number and sequence of successive anticoagulation agents during an anticoagulant treatment period • Safety outcomes: ○ Major bleeding ○ Clinically relevant non-major (CRNM) bleeding

	Secondary outcomes • Time trends by calendar year in patient characteristics and anticoagulation treatment patterns • Effectiveness outcome: recurrent symptomatic VTE • Specialty and care setting of the physician(s) who prescribe anticoagulation therapy
Data sources	Due to the rarity of VTE in the targeted paediatric population and low incidence of the primary safety outcome, the planned data sources include existing secondary health data sources with broad coverage and/or population size. According to the results of the feasibility study, the following data sources are planned to be included: • National health registers in Denmark and Sweden • Système National Des Données De Santé (SNDS) in France • Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) in Spain
Study size	Based on the patient count estimations, the expected total study size in the four target countries (Denmark, France, Spain, and Sweden) is about 850 children under two years with VTE, with approximately 280 of them using rivaroxaban oral suspension. All children from the target population present in the data sources will be analysed.
Data analysis	**Descriptive analyses by data source** Categorical variables will be presented as counts (n) and proportions (%), with 95% confidence intervals (CI) where relevant. Continuous variables will be presented as means with standard deviation and as medians with interquartile range, where appropriate. The following descriptive analyses will be presented: • Patients' characteristics according to exposure category (rivaroxaban or SOC), with stratification on the status of exposure, i.e., initiators versus switchers • Drug utilization patterns of initial therapy and maintenance therapy (dose, frequency, route of administration, treatment duration, treatment switch)

	• Crude incidence rate, cumulative incidence and Kaplan-Meier analysis of the safety and effectiveness outcomes, using an as-treated exposure definition. Sensitivity analyses will be applied for the exposure (considering only the first treatment agent episode) and for the safety and effectiveness outcomes (considering a more restrictive definition). **Combined descriptive analyses of aggregated data across data sources** • Characteristics of patients and drug use patterns • Safety and effectiveness outcomes (if sample size allows)
Milestones	Start of study period: market entry date of rivaroxaban oral suspension in each country Start of data collection: 12 months from the PRAC endorsement of the full study protocol End of data collection: Q2 2029 Study progress report: Annually, from Q4 2023 to Q4 2027 Final report of study results: Estimated Q4 2029 The annual progress reports will allow to monitor the uptake of rivaroxaban oral suspension and follow-up the number of patients for the study population as well as opportunities to finalize the study earlier.

5. Amendments

None

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrolment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are tracked in a stand-alone document (Annex 1).

Table 1: Milestones

Milestone	Planned date
Start of study period	Market entry date of rivaroxaban oral suspension in each country
Start of data collection[a]	12 months from the PRAC endorsement of the full study protocol (*)
End of data collection[b]	Q2 2029
Study progress report 1	Q4 2023
Study progress report 2	Q4 2024
Study progress report 3	Q4 2025
Study progress report 4	Q4 2026
Study progress report 5	Q4 2027
Registration in the EU PAS register	Study to be registered after PRAC approval of the protocol
Final report of study results	Estimated Q4 2029

[a] Date from which data extraction starts, in the case of secondary use of data.
[b] Date from which the analytical dataset is completely available. The analytical dataset is the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.
(*)Time needed for data access process in data sources (applications, approvals) and other tasks to launch the study.

Time lag for data availability in the different data sources is an essential element in estimating overall timelines for milestones and study completion. It is estimated that the achievement of the target study size would require data observed until end of 2027, with end of data extraction by Q1 2029 (due to long time lag in some data sources), end of data collection by Q2 2029 and final report by Q4 2029. However, one of the key objectives of the annual progress reports will be to identify

opportunities to finalize the study earlier. In parallel with the follow-up of the overall uptake of rivaroxaban oral suspension, the number of children under two years with venous thromboembolism (VTE), and those among them receiving rivaroxaban oral suspension will be monitored annually in each data source as far as possible, and reported in annual progress reports. Due to small sample size and General Data Protection Regulation (GDPR) obligations to suppress small cell counts, the primary objective on the incidence and severity of bleeding is only feasible in the largest data source(s). The progress reports will also contain a status update of data source applications for approvals and any relevant amendments.

7. Rationale and background

7.1. Strategic rationale

Xarelto® (rivaroxaban), a direct oral anticoagulant (DOAC), was approved on 21 JAN 2021 by the European Medicines Agency (EMA) for a new pharmaceutical formulation of granules for oral suspension 1 mg/mL for the following paediatric indication: treatment of VTE and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment (1). To supplement the limited information from the paediatric rivaroxaban clinical trial program in the youngest children, the EMA requested a category 3 post-authorization safety study (PASS) addressing the risk of bleeding in the young population. This drug utilization study (DUS) will evaluate drug utilization patterns, bleeding, and recurrent VTE outcomes in children with VTE and under two years of age who are treated with rivaroxaban granules for oral suspension 1 mg/mL or standard of care (SOC) anticoagulation.

7.2. Scientific background

VTE is a condition of forming a blood clot in the deep veins of the arm, groin, leg, jugular, caval, renal, and portal veins (known as deep vein thrombosis [DVT]). It may travel through the circulation and occlude the pulmonary vasculature (known as pulmonary embolism [PE]).

In the paediatric population, VTE is a rare condition, with an incidence of about 100 times lower than in adults. The annual incidence of VTE has been reported between 0.14 and 0.49 per 10,000 children in the community overall, and between 5.3 and 5.7 per 10,000 among hospitalized children (2). The distribution of events is bimodal with the majority occurring in neonates/infants and in adolescents. Paediatric VTE is rarely idiopathic; more than 80% of children who experience a VTE have one or more risk factors. The most important risk factor is the presence of a central venous catheter. Other factors include infection, immobility, trauma, malignancy, congenital heart disease, chronic inflammatory conditions, and thrombophilia (3). Risk factors for recurrent VTE include age at onset, absence of anticoagulant treatment, persistent venous occlusion, or presence of the prothrombin gene mutation (4). The risk of recurrence for paediatric VTE ranges from 7% to 20%, however, recurrence is uncommon if the underlying cause is removed or resolved.

The aim of VTE therapy is generally to prevent disease progression, prevent VTE recurrence and the development of sequelae such as post thrombotic syndrome. The type of anticoagulation and optimal duration of therapy in the paediatric population is not clearly defined. Due to a moderate level of evidence, treatment guidelines for paediatric VTE are mainly extrapolated from adult studies. The

current SOC includes parenteral treatment with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) and oral anticoagulation with vitamin K antagonists (VKA). For children with idiopathic VTE, the suggested treatment duration has a minimum of 3 months and a maximum of 6 to 12 months. Children with recurrent unprovoked VTE are usually treated indefinitely(5).

Rivaroxaban is the first centrally approved oral anticoagulant product in the European Union (EU) for treatment of secondary prevention of VTE in children. Besides, this orally administered alternative requires less monitoring than existing SOC. Rivaroxaban should be initiated following at least 5 days of initial anticoagulation treatment with parenteral heparins, with dose and frequency of administration based on body weight. In children weighting less than 30 kg, rivaroxaban oral suspension is the only available formulation.

In the pivotal Phase III EINSTEIN Junior study, in the rivaroxaban group, during the main treatment period, a total of four (1.2%; 4/335) children had recurrent VTE, which occurred during heparinization in two children, during tablet treatment in one child, and during suspension treatment in one child. In the comparator group, a total of five (3.0%; 5/165) children had recurrent VTE, resulting in a hazard ratio of 0.40 (95% CI 0.11 – 1.41). All four recurrent VTEs in the rivaroxaban group occurred in the 184 children aged 12 to <18 years (6).

Like for the other anticoagulants, bleeding is an important identified risk for rivaroxaban. In the paediatric population, the safety evaluation of rivaroxaban was mainly based on the pivotal Phase III EINSTEIN Junior study(6). Among 491 included children (329 rivaroxaban, 162 comparator), the incidence of the principal safety outcome during the main treatment period (major bleeding + clinically relevant non-major [CRNM] bleeding) was numerically higher in the rivaroxaban group (10 children, 3%; all CRNM bleeding) compared to the comparator group (three children, 1.9%; two major bleeding, one CRNM bleeding). In the youngest children aged less than two years, there were only 53 patients included (21 and 9 [0.5 to <2 years] and 15 and 8 [<0.5 year], in rivaroxaban and comparator groups, respectively), with two patients (5.6%) in the rivaroxaban group and one patient (5.9%) in the comparator group having a CRNM bleeding. Furthermore, the coagulation system in neonates and infants aged <6 months is different from older children and adults, and extrapolation from adults is less straightforward than for elderly children (1).

Thus, although the pivotal Phase III EINSTEIN Junior study showed similar low risk of recurrent VTE without significant increased risk in bleeding with rivaroxaban compared to SOC, the experience of using rivaroxaban in children younger than 2 years is limited and safety data in this population is lacking in the real-world setting. The results from this PASS are intended to address this need for real-world data by characterizing drug utilization patterns, bleeding leading to hospitalization, and recurrent symptomatic VTE in clinical practice in children less than 2 years of age with VTE who are treated with rivaroxaban or other anticoagulants.

8. Research questions and objectives

This proposed PASS study is intended to evaluate the patterns of drug utilization and safety of rivaroxaban granules for oral suspension and of SOC in children under two years of age diagnosed with VTE and receiving anticoagulation therapy.

8.1. Primary objectives

The primary objectives in this study are to describe:

- Clinical characteristics and demographics of patients using anticoagulation therapy for the treatment of VTE (rivaroxaban oral suspension or SOC)
- Use of anticoagulation therapy (including selected drug, dose, and duration) for treatment of VTE
- Incidence and severity of bleeding (major bleeding, and CRNM bleeding) according to anticoagulation therapy (rivaroxaban oral suspension or SOC)

8.2. Secondary objectives

The secondary objectives in this study are to describe:

- Time trends in patient characteristics and anticoagulation treatment patterns at the population-level over the study period
- Incidence of recurrent symptomatic VTE according to anticoagulation therapy (rivaroxaban oral suspension or SOC)
- Specialty and care setting of physicians who prescribe anticoagulation therapy (rivaroxaban oral suspension or SOC)

9. Research methods

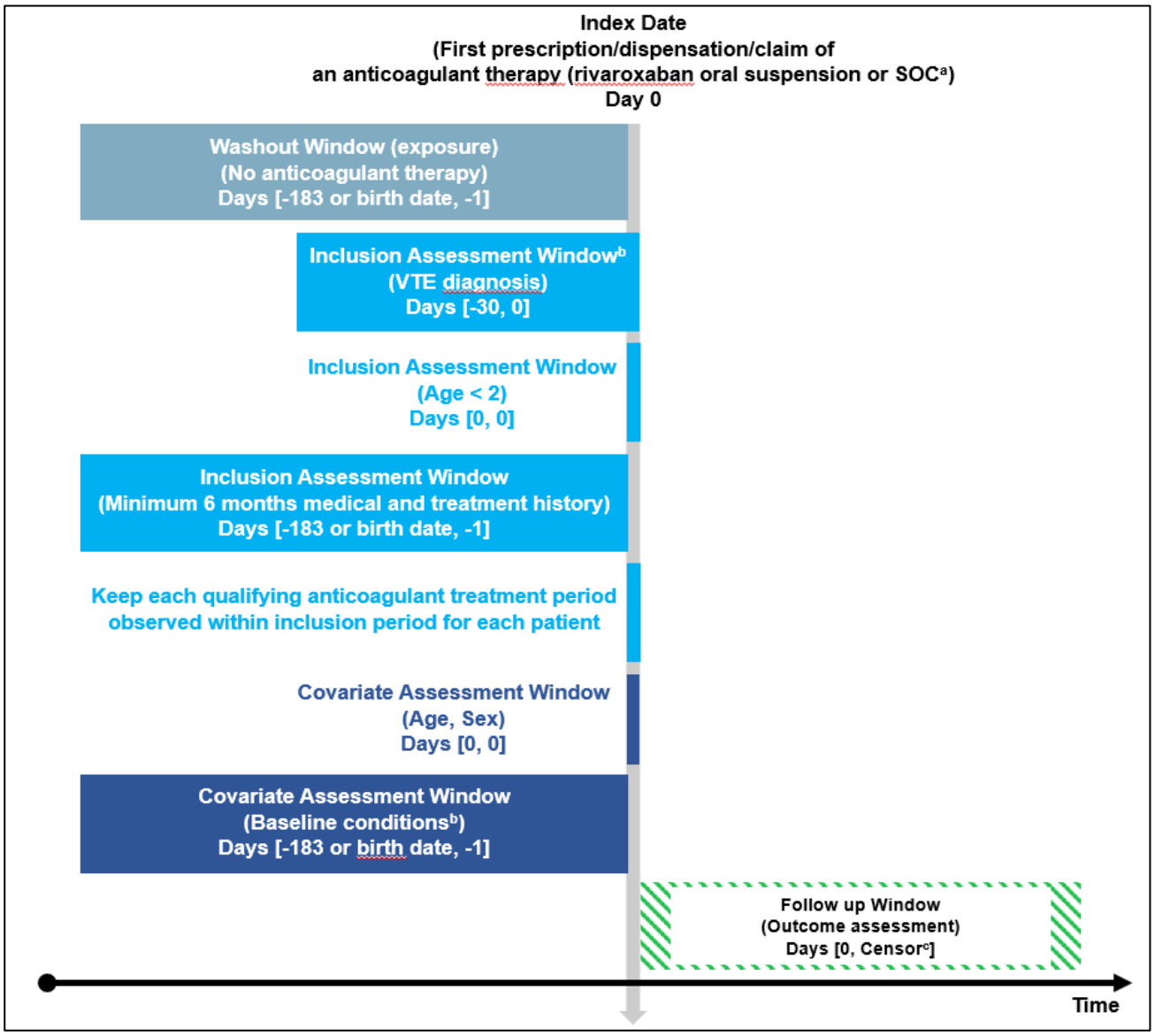
9.1. Study design

This will be an observational, retrospective, descriptive, multi-national cohort study of children initiating anticoagulation therapy. The study will be conducted using secondary data derived from multiple data sources including electronic health records and administrative health insurance claims data in four European countries (France, Sweden, Denmark, Spain).

The study cohort will include all children aged under two years and initiating anticoagulant therapy following a VTE diagnosis. The inclusion period will be from the market launch date of rivaroxaban oral suspension in each country until end of 2026, with follow-up until end of 2027. Patients will be followed up from the anticoagulation therapy initiation (index date), until occurrence of bleeding (major bleeding, and CRNM bleeding as co-primary outcomes) or recurrent symptomatic VTE (as secondary outcome) – with time at risk specific to each outcome, discontinuation of all study drugs, death, exit or last available data from the data source, or end of study period, whichever occurs first. Two exposure categories will be defined, one for rivaroxaban and one for SOC, using an as-treated exposure definition. Patients will contribute time to both exposure categories if they switch from SOC to rivaroxaban or vice versa. As long as the anticoagulant treatment period is continuing, patients will be allowed to switch multiple times between SOC and rivaroxaban and contribute time accordingly to both exposure categories.

If patients have another initiation of anticoagulant therapy for a VTE diagnosis before the age of two years, and for which they fulfil all inclusion and exclusion criteria (including a 6-month washout period), they will be allowed to enter the study cohort again with a new index date.

An overview of the study design is presented in Figure 1.



DOAC = direct oral anticoagulant; SOC = standard of care; VKA = vitamin K antagonist; VTE = venous thromboembolism

a. Patients will be followed in two exposure categories, rivaroxaban or SOC (heparins, VKAs, other DOACs). Treatment episode of rivaroxaban oral suspension OR SOC defined by cumulative days of supply from consecutive dispensations, until discontinuation (grace period of 30 days allowed and 30-day carry-over period) or switch to other anticoagulation therapy. During an anticoagulation treatment period, switches from SOC to rivaroxaban and vice versa are allowed.

b. Baseline conditions: demographics, characteristics of the index VTE, co-morbidities, prior treatment.

c. Censoring criteria will be the earliest of: discontinuation of all study drugs (rivaroxaban and SOC), death, disenrollment/de-registering/emigration, last available data, end of the study period.

Adapted from Schneeweiss S et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med. 2019 Mar 19;170(6):398-406.

Figure 1 Study design diagram

The strengths of this study design to answer the research question include:

- Use of population-based secondary health data sources which capture observational data from routine clinical practice. This avoids the possibility to influence prescribing behaviour and reduces the risk of selection bias or recall bias due to the secondary nature of the data. The results will reflect prescribing behaviour and risk of outcomes in real-world clinical practice.
- Selection of secondary health data sources providing large population coverage and/or population size, as well as broad coverage of health care settings from different geographical locations and health care systems. This will help: i) maximizing study size in this rare clinical condition, ii) providing ability to identify and follow-up the study population by capturing relevant diagnoses, drugs, and outcomes, and iii) ensuring representativeness for the general target population.
- Use of a new user design, where the at-risk period begins on the date of first observed record of anticoagulation therapy (index date), instead of the preceding VTE date.
- Contextualization of the use of and outcomes with rivaroxaban oral suspension by available contemporary treatment options.

9.2. Setting

9.2.1. Study population

The source population will consist of children aged under two years who initiate an anticoagulation therapy with rivaroxaban oral suspension or any other anticoagulation drug following a VTE diagnosis. The study population will be drawn from population-based data sources in four countries and include all patients who fulfil all inclusion and exclusion criteria during the study period.

9.2.2. Study time frame

9.2.2.1. Index date and follow-up

The index date will be the day of initiation of any anticoagulation therapy (rivaroxaban oral suspension or SOC). Patients will be assigned to two exposure categories, rivaroxaban or SOC, according to their actual use of the respective anticoagulation therapy. They may contribute time at risk to more than one exposure category if they switch from one to the other. More specifically, patients will be allowed to switch multiple times between SOC and rivaroxaban and contribute time accordingly to both exposure categories, as long as the same anticoagulant treatment period is continuing.

Patients will be followed from the index date to the earliest of the following censoring criteria:

- End of the anticoagulation treatment period, i.e., discontinuation of all study drugs (rivaroxaban and SOC),
- Death,
- Disenrollment/de-registering/emigration or last available data,

- End of the study period.

Moreover, patients will be followed until the first occurrence of each safety/effectiveness outcome event, with time at risk defined separately for each outcome analysis.

If patients have another initiation of anticoagulant therapy (SOC or rivaroxaban) for a VTE diagnosis before the age of two years, i.e., another qualifying anticoagulant treatment period for a recurrent VTE observed during the inclusion period for which they fulfil all inclusion and exclusion criteria (including a 6-month washout period), they will be allowed to enter the study cohort again, with a new index date.

9.2.2.2. Study period

At this stage it is assumed that the study will last at least seven years to provide enough time to ensure the achievement of the sample size (see Section 9.5). The inclusion period will start on the market launch date of rivaroxaban granules for oral suspension 1 mg/mL in the respective countries. The countries were selected based on the potential data sources that were investigated during the feasibility phase (see Section 9.4.1). A description of market authorization status in the different potential countries along with launch date is provided in Table 2.

The study period would end 31 DEC 2027, with the inclusion period ending 31 DEC 2026 to allow a minimum potential follow-up of 12 months.

Table 2: Market presence of rivaroxaban granules for oral suspension 1 mg/mL (as of August 2022)

Country	Marketing authorization status	Marketing authorization date	Reimbursement status	Reimbursement date	Market entry date	Distribution channel[a]	Availability of rivaroxaban oral suspension after market penetration[b]
Denmark	Granted	February 2021	Y	17/05/2021	October 21	Hospital and Retail	High
Finland	Granted	February 2021	Y	08/05/2021	September 2021	Hospital and Retail	High
Sweden	Granted	February 2021	Y	22/10/2021	September 2021	Hospital and Retail	High
France	Granted	February 2021	Y	18/04/2022	April 2022	Hospital and Retail	High
Germany	Granted	February 2021	Y	21/01/2021	May 21	Hospital and Retail	High
Italy	Granted	February 2021	N	Expected September 2022	Pending	Pending	Moderate
Netherlands	Granted	February 2021	Y	07/01/2021	July 2021	Hospital and Retail	High
Spain	Granted	February 2021	N	Pending	Pending	Hospital and Retail	Moderate
UK	Granted	February 2021	Y	21/01/2021	April 2021	Hospital and Retail	High
Canada	Granted	January 2021	N	Pending	May 2021	Pending	High

[a] Retail pharmacy, hospital pharmacy, other institutional care
[b] High (marketing authorization and reimbursement obtained, and has entered market), moderate (marketing authorization obtained, but reimbursement and/or market entry pending), poor (marketing authorization, reimbursement and market entry pending)

9.2.3. Selection criteria

9.2.3.1. Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

- Evidence of initiation of an anticoagulant therapy (index drug), either rivaroxaban oral suspension or other anticoagulation therapies (heparins, VKAs, other DOACs). Initiation will be defined as a first record of any anticoagulation therapy (rivaroxaban or SOC) without any anticoagulation therapy in the previous 6 months, or since date of birth for children less than 6 months (see codes for anticoagulant drugs in Annex 3).
- Evidence of a prior VTE diagnosis (index VTE), defined as the presence of at least one primary/main or secondary diagnosis code for VTE recorded in inpatient setting in the previous 30 days (see preliminary list for VTE codes in Annex 3).
- Age less than two years on index date.
- Baseline period for availability of patient data history in the data source. A minimal baseline period of six months before index date for children aged between six months and two years, and a baseline period since birth for children less than six months of age will be required.

According to its indication, rivaroxaban oral suspension should be used after at least five days of initial parenteral anticoagulation treatment. In order to describe the actual clinical practice in real world settings, there will no requirement on this initial parenteral anticoagulation treatment to include patients in the study population, so patients will be identified independently of this. In theory, all patients receiving rivaroxaban should be switchers. In practice, they may appear as initiating directly with rivaroxaban: the observed initial anticoagulant therapy might be different from the actually received initial therapy, if patients have switched drug during hospital stay and if inpatient drug data is not captured. Depending on availability of inpatient drug data in each data source, the observed initiation of the anticoagulant therapy will be identified either in outpatient or in inpatient setting, as shown in Figure 2 below (see Section 9.4).

SOC for treatment of VTE in children usually include UFH, LMWH and VKA and may vary across countries. With other DOACs receiving indication for VTE in paediatrics, SOC may also evolve over time.

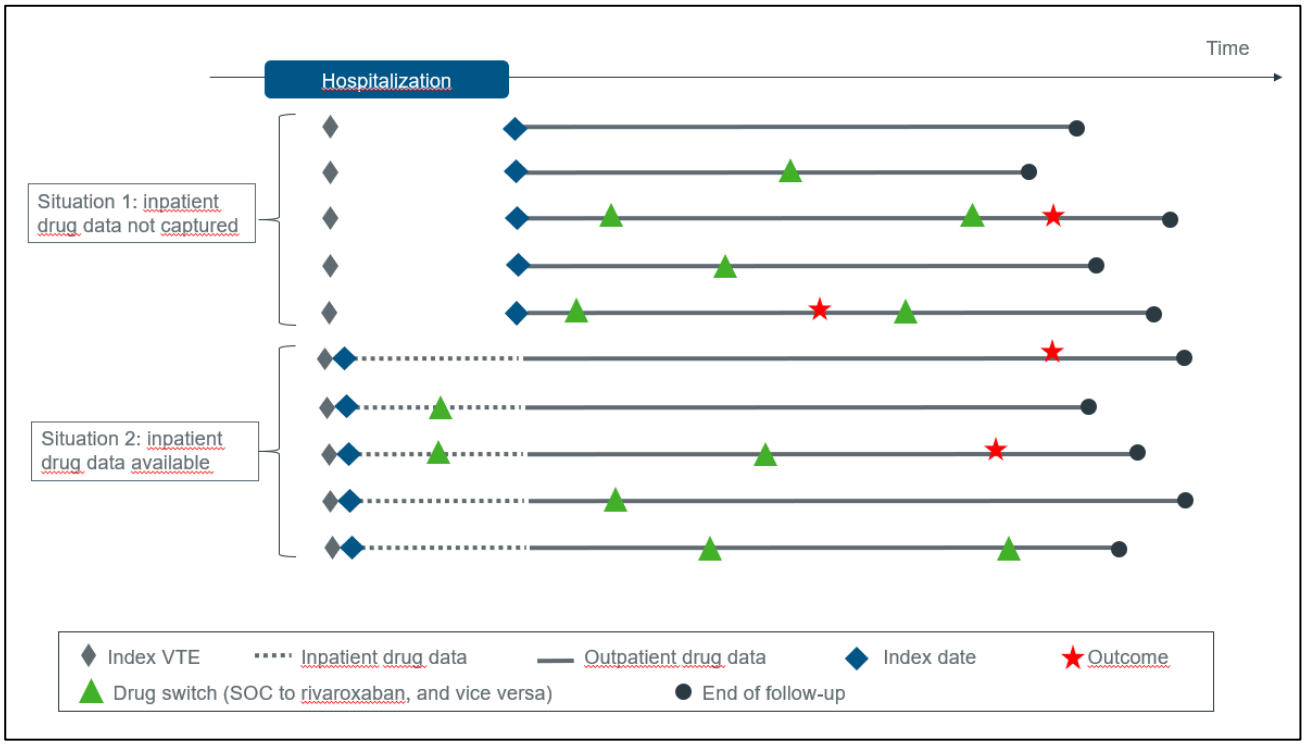


Figure 2 Visualization of patient journey

9.2.3.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

- None.

9.2.4. Representativeness

The paediatric patients with VTE documented in the country/source databases will be selected only based on eligibility according to inclusion and exclusion criteria. No further selection will be applied.

By abstracting the patient details in routine clinical practice from the population-based data sources of different countries, the study is expected to be representative for different geographical locations and health care systems. Moreover, each planned data source is considered representative of the corresponding country's population.

9.3. Variables

9.3.1. Exposure

- Information on exposure will be ascertained based on recordings of issued prescriptions, prescriptions dispensed at community pharmacies, or insurance claims registrations, according to availability and contents of data in each of the different data sources. For simplicity, prescription is used for the rest of the document.

- The study drugs will be identified through their Anatomical Therapeutic Chemical (ATC) code (see Annex 3) and will include heparins, VKAs and other DOACs in addition to rivaroxaban oral suspension.
- Following variables will be extracted from the data sources:
    - Active substance
    - Route of administration
    - Date of prescription issuance (or filling)
    - Prescribed drug amount or days' supply
    - Prescribed daily dose (if available)
- Patients will be classified into two exposure categories: the exposed will include patients with rivaroxaban oral suspension, and the unexposed will include patients receiving all other study drugs consolidated in a single group as SOC.
- Following the index date, patients will contribute follow-up time and safety/effectiveness event outcomes to their respective exposure category(ies) until they are censored (see Section 9.2.2).

Following definitions of the variables related to exposure will be used:

- **Treatment episode by agent**: this will include rivaroxaban, heparins, VKAs, and other DOACs.
    - For each agent with fixed dose, and whenever information is available, the duration of the episode will be based on days of supply, by summing the lengths of individual consecutive prescriptions of the respective agent. Drug stockpiling will be accounted for: in case of overlapping prescriptions for the same agent (i.e., the next prescription is recorded before the end of the prior prescription supply), the overlap will be added to the end date of the second prescription.
    - For agents where the dose is not fixed but titrated continuously over time according to body weight (rivaroxaban oral suspension) or to a biomarker (VKAs), the duration of a treatment episode will be based on the actual distribution of intervals between filled prescriptions.
    - For all agents, a grace period of 30 days will be used. Thus, a treatment episode will be considered discontinued if a gap >30-day grace period is observed between consecutive prescriptions of the same agent. A 30-day period will be added at the end of the treatment episode of each agent to account for a carry-over effect unless a drug switch is observed.
- **Drug switch:** defined whenever a prescription of another anticoagulant agent is recorded during a treatment episode of the prior anticoagulant agent.
- Treatment episodes for the individual SOC agents that are overlapping or separated by less than the 30-day grace period will be collapsed into a single SOC treatment episode.

- **Anticoagulant treatment period**: defined as a sequence of treatment episodes of rivaroxaban and SOC, i.e., from the initial treatment episode of the first agent at index date and all potential consecutive switch(es) to other agents. An anticoagulation treatment period will be considered discontinued when all study drugs of interest are discontinued.

9.3.2. Outcomes

9.3.2.1. Primary outcomes

9.3.2.1.1. Patient characteristics

The following patient characteristics, including risk factors for VTE will be considered:

- Demographic characteristics of patients: age, sex; bodyweight at index date and gestational age, if available
- Characteristics of index VTE, if available (depending on the granularity of codes):
    - Type of location of VTE
    - Central venous catheter related thrombosis
    - Symptomatic versus asymptomatic VTE
- Co-morbidities reported in the previous six months before index date, or since date of birth for children less than six months:
    - Major organ disease (cardiac, gastrointestinal, renal, neurological)
    - Malignancy (active cancer, haematological cancer, solid tumour)
    - Thrombophilia (congenital or acquired), including antithrombin, protein C or Protein S deficiency, factor V Leiden or prothrombin mutation
    - Major surgery or trauma
    - Major infectious disease
    - Major congenital venous anomaly
    - Use of central venous catheter
    - Morbid obesity
    - Hypertension
- Prior treatments reported in the previous six months before index date (or since date of birth for children less than six months): all drugs by third or fourth ATC level
- Comedication during follow-up: all drugs by third or fourth ATC level, and subgroup of all drugs that can increase the risk of bleeding, such as non-steroidal anti-inflammatory drugs, antiplatelets and aspirin
- Health resource utilization in the previous six months before index date (or since date of birth for children less than six months), e.g., marker of health status of the patients, including

- Outpatient visits
- Hospital admissions
- Length of hospital stay
- Admission to intensive care unit

- Duration of oral, nasogastric/gastric feeding before index date (identified via procedure codes), if available

9.3.2.1.2. Drug utilization patterns

Based on the above exposure definitions, the following variables will be derived for the drug utilization patterns:

- Index drug therapy: substance and class of anticoagulant drug therapy, duration of use, dosing, route of administration
- Maintenance therapy: substance and class of anticoagulant drug therapy, duration of use, dosing, route of administration
- Switching to other anticoagulant therapy
- Number and sequence of successive anticoagulation agents during an anticoagulant treatment period.

Operational definition for maintenance therapy and other study variables will be provided in the statistical analysis plan.

9.3.2.1.3. Safety outcomes

Potential cases will be identified using diagnostic codes according to the different coding systems in the data sources (preliminary list in Annex 3). The severity of bleeding might be difficult to determine accurately in secondary health data sources. However, to estimate the severity of bleeding to the extent possible, two co-primary bleeding outcomes with different severity grading will be assessed: Major bleeding or CRNM bleeding. The definitions for major bleeding and CRNM bleeding are based on prior definitions from the International Society on Thrombosis and Haemostasis (ISTH) and definitions used in the EINSTEIN Junior study, with further adaptation to take into account the availability of information in the data sources (6-8). Besides, the definitions for major bleeding and CRNM bleeding will be mutually exclusive.

Major bleeding

Defined as a hospitalization with one of the following primary, related or associated diagnoses:

- Intracranial haemorrhage
- Other critical organ or site bleeding (intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome)
- Gastrointestinal bleeding
- Urogenital bleeding

- Other bleeding with a transfusion during hospital stay or resulting in death.

A secondary analysis will be based on an analysis per bleeding site (as described above), if numbers permit.

Clinically Relevant Non-Major (CRNM) bleeding

Defined as bleeding not meeting the criteria for major bleeding, but reported as a primary, related or associated diagnosis during hospitalization.

A sensitivity analysis is planned for major and CRNM bleeding with a more restrictive definition using only main/primary diagnostic codes, excluding secondary diagnostic codes.

9.3.2.2. Secondary outcomes

9.3.2.2.1. Time trends in patient characteristics and anticoagulation treatment patterns

Description by calendar year of:

- Age group at index date
- Medical history at index date
- Class of anticoagulation therapy at initiation

9.3.2.2.2. Effectiveness outcome

A secondary outcome on effectiveness will be recurrent symptomatic VTE.

Potential cases will be identified using diagnostic codes according to the different coding systems in the data sources (preliminary list in Annex 3). Care for children with an incident VTE takes place in inpatient setting (i.e., hospital stay requiring at least one night). At the same time, it is highly likely that VTE diagnoses are recorded as complications, secondary to other main reasons for a hospital stay. Therefore, the main definition for VTE diagnoses will be based on a sensitive approach including all primary/main and secondary diagnoses captured during hospitalization. Thus, a case of recurrent symptomatic VTE will be defined as a hospitalization with one of the following primary, related or associated diagnoses:

- DVT
- PE
- Cerebral vein or sinus thrombosis
- Central venous catheter related thrombosis
- Any VTE resulting in death.

A sensitivity analysis is planned for VTE outcome with a more restrictive definition using only main/primary diagnostic codes, excluding secondary diagnostic codes.

9.3.2.2.3. Specialty and care setting of physicians

- Physician specialty and care settings (inpatient care, secondary outpatient care, primary care) for prescriptions of anticoagulation therapy

9.4. Data sources

9.4.1. Feasibility assessment

The study will make secondary use of existing data from multiple countries. A feasibility assessment was conducted with the aim to evaluate large electronic healthcare databases to guide the selection of the most relevant data sources for addressing the research question and study objectives. A report on this feasibility assessment is provided as a stand-alone document (see Annex 1) which is available upon request.

The choice of final data sources was guided by the following criteria:

- Representativeness of the overall population covered by the data source and the target population of children under two years with VTE receiving anticoagulant therapy
- Countries in which the estimated cumulative average number of children under two years with VTE and exposed to rivaroxaban in the data source is at least 15 during the inclusion period 2021-2026 (see Section 9.5.2)
- Availability of the information required to meet the study objectives, including the ability to identify and describe the target population of children under two years with VTE, and the availability and quality of exposure and outcomes data
- Procedure and timelines for data access
- Coverage of different regions in Europe

Based on the overall rating, the final list of recommended data sources include:

- Système National Des Données De Santé (SNDS) in France
- National health registers in Sweden
- National health registers in Denmark
- Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) in Spain

Depending on the actual accrual of patients over the study period, additional data sources might need to be considered in future.

General characteristics of the data sources are provided in Table 3.

Table 3: Summary characteristics of data sources

Country	Data source name	Data source type	Population size (active)	Source population coverage (%)	Data lag time	Coding system for drugs	Drugs data	Coding system for diagnoses	Diagnoses and procedures data
Denmark	**MBR, NPR, RMPS, SMR, Register of causes of death**	National health registers	5.8 million	100%	2-13 months	ATC	Drugs dispensed at community pharmacies. Drugs given in hospitals (expected release in 2022)	ICD-10	Secondary outpatient care, inpatient care, emergency
Sweden	**MBR, NPR, PDR, Cause of death register**	National health registers	10.3 million	100%	14 days-12 months	ATC	Prescribed drugs for outpatient use, dispensed drugs through retailed pharmacies, use of OTC drugs, reimbursed drugs	ICD-10	Inpatient care and specialized outpatient care
France	**SNDS**	Claims database	66 million	99%	3-7 months	ATC, UCD, CIP	Dispensed drugs through retailed pharmacies, reimbursed drugs, some costly drugs administered in hospital	ICD-10	Inpatient care, some ambulatory long-term diseases, all procedures
Spain (Catalonia)	**SIDIAP**	EMR database	5.6 million	74% (from Catalonia)	12 months	ATC	Primary care prescriptions, drugs dispensed through retailed pharmacies. Possible linkage with hospital pharmacy drugs databases	ICD-9, ICD-10-CM	Primary care linked to hospital admissions and deaths

ATC = Anatomical Therapeutic Chemical (Classification System); CIP = Club Inter-Pharmaceutique; CM = Clinical Modification; EMR = Electronic Medical Records; ICD = International Classification of Diseases; MBR = Medical Birth Register; NPR = National Patient Register; PDR = Prescribed Drug Register; RMPS = Register od Medicinal Products Statistics; SIDIAP = Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària; SNDS = Système National Des Données De Santé; SMR = Hospital Patient Medication Register; UCD = Unité Commune de Dispensation.

The feasibility of study objectives is summarized in Table 4.

Table 4: Feasibility of study objectives in the data sources

Data sources	Danish national registers	SNDS	SIDIAP	Swedish national registers
Primary objectives				
To describe clinical characteristics and demographics of patients using anticoagulation therapy for the treatment of VTE (rivaroxaban oral suspension or SOC)	Yes	Yes	Yes	Yes
To describe use of anticoagulation therapy (including selected drug, dose, and duration) for treatment of VTE	Yes[a]	Yes	Yes[a]	Yes
To describe the incidence and severity of bleeding (major bleeding, and CRNM bleeding) according to anticoagulation therapy (rivaroxaban oral suspension or SOC)	BT[b]	Yes	BT[b]	BT[b]
Secondary objectives				
To describe time trends in patient characteristics and anticoagulation treatment patterns at the population-level over the study period	Yes[a]	Yes	Yes[a]	Yes
To describe the incidence of recurrent symptomatic VTE according to anticoagulation therapy (rivaroxaban oral suspension or SOC)	BT[b]	BT[b]	BT[b]	BT[b]
To describe specialty and care setting of physicians who prescribe anticoagulation therapy (rivaroxaban oral suspension or SOC)	TBD	Yes[c]	TBD	Yes

BT = Below threshold; SIDIAP = Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària; SNDS = Système National Des Données De Santé; SOC = Standard of care; TBD = To be defined; VTE = Venous thromboembolism;

[a] Include intrahospital treatment

[b] Estimated average number of outcomes below disclosure threshold (see Section 9.5.2 for details)

[c] Partially available

In the next section details for the data sources are displayed.

9.4.2. Details of data sources

In order to meet the study objectives, the following data sources will be considered:

France – SNDS

The French National Health Data System (SNDS) is the largest and most comprehensive healthcare dataset available in Europe with a 10-year longitudinal follow-up for more than 50 million patients. SNDS includes anonymized administrative and healthcare claims data from the French national health care insurance system databases. In particular data from SNIIRAM (Système national d'information interrégimes de l'Assurance maladie) which consist of: hospital discharge summaries (Programme de Médicalisation des Systèmes d'Information, [PMSI]), all outpatients reimbursed health expenditures (données de consommation inter-régimes, [DCIR]), and national death registry (CépiDC database on causes of death) (9). SNDS data consist of anonymized data of reimbursed claims for all patients affiliated with compulsory health insurance providers (the general scheme covers about 86% of France residents, and 14 other schemes cover the rest) and cover about 99% of French residents.

Data from DCIR and PMSI have been linked for each patient to allow for follow-up across different settings of care including outpatient practice and hospital admissions related to medicine, surgery and obstetrics. At this time, date of death from the national death registry is linked to the other data for all the periods. Causes of death are progressively integrated (only available for 2013, 2014, and 2015). Healthcare use of the patient can then be tracked since birth/first residence in France for 10 years even if a subject is not working, changes occupation or retires and irrespective of socio-economic status. There is no loss to follow-up except for emigration.

For more information see Annex 3.

Denmark – National Registers

The Danish data sources for this study are owned, run and made accessible to research projects by Danish governmental and regional authorities (10). The Danish health care system is a tax-funded, one-payer system with full coverage for all residents (5.8 million) and some co-payment from the patients for prescriptions drugs and dental work.

Since introducing the Danish Civil Registration System in 1968, information on demographics (age, sex, and geographical region), migration and vital statistics data has been registered electronically on a daily basis for all Danish residents. Every individual in Denmark is provided with a unique personal identification number (PIN) at birth or upon immigration which allows for follow-up until death or emigration. The PIN forms the basis for the precise, deterministic linkage of individual-level data between all patient-level registers and databases in Denmark, allowing the creation of a study database with individual-level data for any given study. The PIN also allows for family linkage of data.

At least the following national registers are important for this study:

- Danish Register of Medicinal Products Statistics (RMPS)

- Danish Hospital Patient Medication Register (SMR)
- Danish National Patient Register (DNPR)
- Danish Register of Causes of Death

For more information see Annex 3.

Sweden – National Registers

Every individual in Sweden is provided with a unique PIN at birth or upon immigration which allows for follow-up until death or emigration. The PIN is used for many administrative purposes, such as an identifier in population and health care registers.

The patient-level data can be linked across registers using the PIN assigned to each citizen or permanent resident of Sweden. The PIN is a ten-digit number used as a unique identifier for a multitude of purposes, such as communication with government agencies, maintaining personal information in population-based registers and to keep track of patients and their medical records. The PIN has three parts: date of birth, a three-digit sex-specific birth number and a control digit. Using the control digit, errors to the date of birth or birth number can be detected. Once assigned, a person (usually) retains the same PIN throughout their lifetime. Thus, the registers are a mirror of clinical practice in Sweden. Furthermore, the data sources are also used extensively for epidemiological research.

At least the following national registers are important for this study:

- Swedish Prescribed Drug Register
- Swedish National Patient Register (NPR)
- Swedish Cause of Death Register

For more information see Annex 3.

Spain – SIDIAP

The SIDIAP (Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària) is a longitudinal patient-level Electronic Medical Records (EMR) database that contains anonymised healthcare data from the primary care setting in Catalonia. The database includes 279 of 370 primary care centres in Catalonia and represents a population of around 5.6 million people and approximately 74% of the Catalan population.

The database contains information collected by healthcare professionals during routine visits in primary care. It includes individual data on patients' demographics (age, gender) and other characteristics (e.g., smoking status); clinical measurements such as body mass index or blood pressure; diagnoses (incl. ICD-10 code, date); prescriptions (incl. ATC code, duration, daily dose); healthcare contacts (visits in primary care, referrals); diagnostic procedures and laboratory tests and sick leave. For all patients, information available in the database is linked to a unique anonymous identifier. Information on drugs prescribed by a professional of the Catalan Institute of Health and

dispensed in pharmacies is available. For studies requested by the EMA, SIDIAP data can also be linked with hospital discharge data and hospital dispensation medication capturing most of the drugs administered in hospitals.

The SIDIAP is highly representative of the population of Catalonia in terms of geographical, age, and sex distributions (11). The database has been used extensively in medical research, including DUS, since 2010 and across Europe, and has been found to be a valid source for research (12). Moreover, several recent studies have been conducted in SIDIAP on oral anticoagulant therapy (13-18).

9.5. Study size

9.5.1. Estimation of sample size

This study is descriptive in nature with no intent for hypothesis generating or testing, and thus does not require power calculation. This study will be conducted on several data sources from different countries, with different degree of coverage, and all patients fulfilling inclusion and exclusion criteria will be analysed.

The sample size estimation according to different levels of precision and proportion of interest is proposed below. The size of the sample population will determine the precision of the estimations, measured as the range of their 95% CI. The assumptions for the precision estimation are based on the results of bleeding and recurrent VTE events from the pivotal Phase III EINSTEIN Junior study (6). The incidence of CRNM bleeding among children under two years old was 5.6% with rivaroxaban and 5.9% with comparator, while the incidence of recurrent VTE among children was 1.2% and 3.0% for rivaroxaban and comparator, respectively.

Table 5 shows the required number of patients by acceptable precision (95% CI) and proportions of interest using the exact approximation formula for CI for proportions.

For example, for an outcome with an incidence of 5%, at least 94 patients are required for a precision of 5% for the 95% CI, and 29 patients are required for a precision of 10%.

Table 5: Required number of patients by acceptable precision (95% CI) and proportions of interest using the exact approximation formula for CI for proportions

Proportion of interest	Margin of error for 95% CI (absolute precision)		
	5%	7.2%	10%
0%	35	24	17
1%	43	28	19
3%	67	37	23
5%	94	50	29
8%	133	68	38
10%	157	80	43

CI = Confidence interval
Exact approximation formula according to the Clopper-Pearson method.

9.5.2. Estimation of patient counts

It is assumed that four countries will be targeted to collect the data from the respective country's' data source. The actual study size will depend on the number of final selected data sources, product uptake over time and study duration. All paediatric patients from the target population present in the selected data sources will be analysed. An estimation of patient counts is provided in Table 6. The method to estimate the patient count comprised two steps:

- First step consisted in estimating the cumulative number of children under two years with VTE in each data source over an inclusion period of 2021-2026. This estimation was based on the following parameters: i) the incidence rate of VTE in the general paediatric population, ranging from 0.14 to 0.49 per 10,000 patients (2); ii) the percentage of patients under two years among children with VTE, ranging from 20% to 25% (19); iii) the population size of children in each country; and iv) the data source coverage in each country. The cumulative number of children under two years with VTE were provided for each data source with three estimates: the lowest estimate was based on incidence rate of VTE of 0.14/10,000 and 20% of children under two years among children with VTE; the highest estimate was based on incidence rate of VTE of 0.49/10,000 and 25% of children under two years among children with VTE; finally, an average estimate was reported as the mean of the lowest and the highest estimates. For instance, the average estimate of the cumulative number of children under two years with VTE included over 2021-2026 ranges from 45 children in SIDIAP in Spain to 650 children in SNDS in France.
- Second step consisted in estimating the number of those paediatric patients exposed to rivaroxaban oral suspension. This estimation was based on assumptions of market share of the product over the period of 2021-2026: 10% in 2021, 32% in 2022, 38% in 2023, 42% in 2024, 50% in 2025 and 30% in 2026. Similarly, to the first step, a lowest, a highest and an average estimate were provided for each data source. As a result, the average estimate of the cumulative number of children under two years with VTE and exposed to rivaroxaban oral suspension ranges from 15 patients in SIDIAP in Spain to 219 patients in SNDS in France.

Then, for each data source and population (i.e., overall study population and subgroup of patients with rivaroxaban oral suspension), the lowest, highest, and average number of expected outcomes were estimated by using the incidence rates of the pivotal Phase III EINSTEIN Junior study as reference for the CRNM bleeding (5.6% with rivaroxaban, 5.9% with comparator) and the VTE events (1.2% with rivaroxaban, 3.0% with comparator).

Over 2021-2026, an average of 650 children under two years with VTE would be identified in the SNDS (range from 242 to 1058), with an average of 219 of them (range 81-356) using rivaroxaban oral suspension, and an average of 12 of them (range 5-20) having a bleeding with hospitalization. In the Swedish national registers, this would lead to an average total of 98 children under two years with VTE (range 37-160), with 33 of them receiving rivaroxaban oral suspension (range 12-54), and 2 of them with a bleeding with hospitalization (range 1-3). In the Danish national registers, an average total of 52 children under two years with VTE (range 19-85) is expected, with 18 of them receiving rivaroxaban oral suspension (range 7-29), and 1 of them with a bleeding with hospitalization (range 0-2). In SIDIAP, we could expect an average total of 45 children under two

years with VTE (range 17-73), with 15 of them receiving rivaroxaban oral suspension (range 6-25), and 1 of them with a bleeding with hospitalization (range 0-1).

Based on these patient count estimations, the expected total study size in the four target countries (Denmark, France, Spain, and Sweden) is about 850 children under two years with VTE, with approximately 280 of them using rivaroxaban oral suspension.

Of note, small cell counts must be suppressed in results from all data sources to mitigate the risk of re-identification. Due to the small sample size and low frequency of the outcomes, it is expected that the outcomes analysis with respect to bleedings and recurrent VTE should only be feasible in the SNDS (as shown in Table 6).

Table 6: Estimation of patient counts

Country - Data source(s)	Denmark national registers	France SNDS	Spain SIDIAP	Sweden national registers	Overall
Children <2y with VTE[a]					
Annual number					
Lowest estimate	3	40	3	6	52
Highest estimate	14	176	12	27	229
Average estimate	9	108	7	16	141
Cumulative number of patients over 2021-2026					
Lowest estimate	19	242	17	37	315
Highest estimate	85	1058	73	160	1376
Average estimate	52	650	45	98	846
Cumulative number of outcomes over 2021-2026[b]					
Bleeding with hosp. - Lowest estimate	1	14	1	2	18
Bleeding with hosp. - Highest estimate	5	61	4	9	79
Bleeding with hosp. - Average estimate	3	37	3	6	49
Recurrent VTE - Lowest estimate	0	5	0	1	7
Recurrent VTE - Highest estimate	2	22	2	3	29
Recurrent VTE - Average estimate	1	14	1	2	18
Children <2y with VTE and receiving rivaroxaban granules for oral suspension[c]					
Cumulative number of patients over 2021-2026					
Lowest estimate	7	81	6	12	106
Highest estimate	29	356	25	54	463
Average estimate	18	219	15	33	285
Cumulative number of outcomes over 2021-2026[b]					
Bleeding with hosp. - Lowest estimate	0	5	0	1	6
Bleeding with hosp. - Highest estimate	2	20	1	3	26
Bleeding with hosp. - Average estimate	1	12	1	2	16
Recurrent VTE - Lowest estimate	0	1	0	0	1
Recurrent VTE - Highest estimate	0	4	0	1	6
Recurrent VTE - Average estimate	0	3	0	0	3

CRNM = Clinically relevant non-major; SIDIAP = Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària; SNDS = Système National Des Données De Santé; VTE = Venous thromboembolism
Counts in red are below disclosure threshold.

[a] Lowest estimate based on incidence rate of VTE of 0.14/10,000 and 20% of children under two years among children with VTE. Highest estimate based on incidence rate of VTE of 0.49/10,000 and 25% of children under two years among children with VTE. Average estimate is the mean of lowest and highest estimates.

[b] Based on respective estimate of patients' number and outcome incidence from EINSTEIN JR: 5.6% (rivaroxaban) and 5.9% (comparator) for bleeding with hospitalization (major + CRNM bleedings); 1.2% (rivaroxaban) and 3.0% (comparator) for recurrent VTE.

[C] Based on market share scenario for rivaroxaban oral suspension: 10% in 2021, 32% in 2022, 38% in 2023, 42% in 2024, 50% in 2025 and 30% in 2026.

9.5.3. Monitoring of actual patient counts

The number of patients for the study population that accrue in the data sources will be monitored over time in order to decide when to launch the analyses.

The strategy for this monitoring will depend on the two following data source conditions:

- In data sources where patient count and/or data extraction is feasible before the study conduct itself, the actual number of children with VTE receiving rivaroxaban oral suspension will be monitored annually, per calendar year and cumulatively.
- In data sources where this is not feasible, patient counts as estimated in Section 9.5.2 will be updated based on the actual sales data of rivaroxaban oral suspension.

These actual patient count estimates will be reported annually for each data source as part of progress reports.

Based on the patient count estimates (see Section 9.5.2) and the required number of patients for a precision level of 10% for the 95% CI of an outcome with a 5% incidence (see Section 9.5.1), it is anticipated that the study should last at least seven years (inclusion period from 2021 to 2026 with follow-up until end of 2027) to include at least 29 children under two years with VTE and receiving rivaroxaban oral suspension per data source. As explained above, the total of those patients in the four countries is expected to be approximately 280.

9.6. Data management

The processes for database management differ by country. Generally, the data are stored at the database level and analysed locally. High data quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. SAS Software or R language will be utilized for access to the raw data, to manage the analytic datasets and to conduct data analysis. If the study is conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures.

This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines for data management.

9.7. Data analysis

9.7.1. General considerations

A stand-alone statistical analysis plan (SAP) will be developed to describe the definitions of variables for exposures, outcomes, covariates, and subgroups of interest. The SAP will describe in detail the statistical analyses and include a full set of table shells. The SAP will be developed after final protocol approval and before data extraction.

The analyses will be conducted using the statistical software SAS Version 9.4 or above, or equivalent software.

Given the study objectives the analyses will be descriptive, with no intent for hypothesis generating or testing between exposure categories. Incidences in rivaroxaban and SOC exposure categories will be compared only in an exploratory sense and no confirmatory statistical tests will be performed. All analyses will be conducted separately by country and data source. Besides, combined analyses of aggregated data across data sources will be provided, as applicable.

Categorical variables will be presented as counts (n), and proportions (%), with 95% CI where relevant. Continuous variables will be presented as means with standard deviation and as medians with interquartile range, where appropriate.

Due to data protection regulations, and to avoid identification of individual patients, data cells with small numbers of patients (e.g., <5) may not be reported in the data sources. For the same reason, minimum and maximum values for individual variables may not be reported. The data will be presented in a format that complies with these regulations and prevents patient identification.

The planned analyses are summarized below.

9.7.2. Patient characteristics

The impact of inclusion and exclusion criteria on the number of patients in the study population will be described in an attrition diagram or table.

The study population will be described according to the descriptive variables mentioned in Section 9.3.2.1.1.

For each exposure category (rivaroxaban and SOC), analyses of patient characteristics will be described, with stratification on the status of exposure, i.e., initiators versus switchers.

Patient characteristics will also be described over time during the study period to identify potential time trends (secondary objective).

9.7.3. Drug utilization patterns

Drug utilization patterns will be described according to the variables mentioned in Section 9.3.2.1.2.

Exposure duration will be classified into two categories: ≤3 months and >3 months.

A Sankey diagram or equivalent will be used to describe at the patient-level the sequence over time of successive anticoagulant agents/classes.

Drug utilization patterns will also be described over time during the study period to identify potential time trends (secondary objective).

9.7.4. Safety and effectiveness outcomes

Analyses of outcomes will be conducted according to anticoagulation therapy received: rivaroxaban and SOC (including heparins, VKAs, and other DOACs).

Time at risk will consider the exposure of interest (rivaroxaban or SOC) according to the as-treated assumption. For each outcome, the first occurrence for that outcome during time at risk will be identified.

The primary analysis of major bleeding will be based on the outcome definition considering all bleedings at critical sites (or requiring transfusion or resulting in death). A secondary analysis will be based on an analysis per bleeding site if numbers permit.

For each exposure category:

- A crude incidence rate with corresponding 95% CI will be estimated for each outcome.
- The cumulative incidence with 95% CI of each outcome will be estimated at regular time intervals (e.g., at 3, 6, 9 and 12 months).
- Event-free survival of each outcome will be presented graphically with the Kaplan-Meier method.

9.7.5. Handling of missing data

As a general strategy, no data imputation strategies will be applied to supplement missing data. However, missing values may occur in a small proportion for some variables. In this case, individuals with missing values will be kept in the analysis and a separate category will be created for missing values of that variable.

9.7.6. Sensitivity analysis

9.7.6.1. Sensitivity analysis on exposure

In case of drug switch, the 30-day carry-over period will not be added at the end of the first treatment episode for the main analysis because patients will then contribute time at risk to the switched drug and can only contribute to one exposure category at any given point of time (see Section 9.3.1). However, patients may actually be using more than one anticoagulant agent at the same time, e.g., when converting from rivaroxaban to VKA. To account for the potential misclassification on exposure during transition and test the impact of the carry-over period, a sensitivity analysis will be conducted, whereby only the first treatment agent episode will be considered, with time at risk including a 30-day carry-over period at the end.

9.7.6.2. Sensitivity analysis on bleeding outcomes

A sensitivity analysis will be conducted by applying a more restrictive definition to the bleeding diagnoses reported only as main/primary diagnosis during hospitalization, excluding secondary diagnostic codes.

9.7.6.3. Sensitivity analysis on VTE outcome

A sensitivity analysis will be conducted by applying a more restrictive definition to the VTE outcome diagnoses reported only as main/primary diagnosis during hospitalization, excluding secondary diagnostic codes.

9.7.7. Subgroup analysis

A subgroup analysis for primary and secondary outcomes will be performed by age of children at index date (<6 months and 6 months to <2 years).

9.7.8. Combined analysis across data sources

In addition to separate analysis in each data source, descriptive analyses combining cumulative aggregated data of each individual data source will be conducted when possible.

According to GDPR, values must be suppressed whenever a patient count is less than a defined threshold: less than five cases/observations in the Nordic countries, less than six in Spain, and less than ten in France.

Therefore, combined analyses should be possible for characteristics of patients and drug use patterns. However, due to the small sample size and rarity of the outcomes bleedings and recurrent VTE, it is expected that these analyses should only be feasible in the SNDS, in which case combined analyses of outcomes across data sources would not be possible.

9.8. Quality control

The study will use existing databases in different countries, which are being used widely for research. The study will be executed in line with all applicable regulations and guidelines – such as best-practice guidelines applicable to non-interventional DUS, including but not limited to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP) as well as the specific Standard Operating Procedures of each contractor. All study programs, log files, and output files will be stored on a secure server. Where elements of the study are being conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures.

9.9. Limitations of the research methods

The use of secondary data that has not been primarily collected for research purposes comes with specific limitations.

Selection bias

- All patients fulfilling eligibility criteria will be included in the study. The data sources in the different countries differ in terms of contents and expected coverage. Most have a national coverage, while SIDIAP which only covers ~75% of Catalonia is also considered representative of the Spanish population. Therefore, the selection bias is considered to be low with respect to the target countries.

Information bias

- Exposure data
    - Anticoagulation therapy is expected to be initiated during hospital stay and renewed for outpatient use. According to its indication, rivaroxaban oral suspension should be used after at least five days of initial parenteral anticoagulation treatment. Thus, in theory, all patients receiving rivaroxaban should be switchers from parenteral anticoagulant treatment. In practice, the capacity to observe the actual initial parenteral anticoagulation treatment and its duration will depend on the availability of inpatient drug data in the selected data sources. This will be feasible when

inpatient drug data is captured, e.g., in the Danish SMR (soon available, with data collected since May 2018) and in SIDIAP through linkage with hospital dispensation medication. However, inpatient drug data is not captured in SNDS and in Swedish national registers, which represents a risk of exposure underestimation. In this latter situation, the information on anticoagulation therapy and its duration will be based on outpatient prescriptions only, at a time when patients may have already, or not yet, stopped the initial parenteral anticoagulation treatment, and switched to maintenance therapy like rivaroxaban. Hence, when patients will have switched to rivaroxaban during hospital stay in an unobservable period in the data source, they will appear as initiating anticoagulation therapy with rivaroxaban, and not switchers. To avoid immeasurable time bias, the index date will be the first observed record of anticoagulation therapy in each data source, whether it occurs during inpatient stay or afterwards.

  - Prescriptions may be issued but not dispensed or dispensed but not used. No information will be available to confirm if the medication is actually taken by patient When available, dispensing data will be preferred over prescription data to minimize the risk of exposure misclassification.
  - Patients may sometimes be exposed to more than one anticoagulant agent at the same time, e.g., when converting from rivaroxaban to VKA. However, at a given time, patients will contribute time at risk to a single exposure category, either rivaroxaban or SOC. In order to test the robustness of the main exposure assumption, a sensitivity analysis will be conducted, whereby only the first treatment agent episode will be considered, with a 30-day carry-over period added at the end of the time at risk.

- Outcomes
  - The definitions of bleeding outcomes are derived from definitions used in clinical trials and require some adaptation within the limitations that exist of available data captured in secondary data sources.
  - The ability to identify bleeding events and their severity will largely depend on the granularity of ICD-9 and ICD-10 codes (diagnoses and procedures), i.e., their sensitivity and specificity in identifying the events of interest. While this type of outcome has already been assessed among adults in previous studies on most data sources, the severity of bleeding might be difficult to determine accurately. Some of the bleedings among children might be more trivial, and will be evaluated as CRNM bleeding, while major bleeding will focus on the most severe events reported during hospitalization, either based on specific bleeding sites or reported with transfusion or as cause of death. Whenever available, prior knowledge on the algorithm to identify these outcomes will be used. The evaluation of these two co-primary bleeding outcomes (major bleeding and CRNM bleeding) with mutually exclusive definitions will allow to provide results with severity grading, thus facilitating the interpretation of study findings.
  - There is a risk of misclassification of the bleeding outcomes because of the uncertainty whether the bleeding event is the actual reason for the hospitalization. It

is also possible that a bleeding occurs while the child is already hospitalized for another reason being reported as the primary diagnosis. To mitigate this risk of misclassification, two definitions will be considered for the bleeding outcomes: in the main analysis, a sensitive approach considering all appropriate bleedings reported as primary, related, or associated diagnoses will be used as the primary definition to capture all bleedings that might represent a major bleeding or a CRNM bleeding. By increasing specificity, a sensitivity analysis restricted to those bleeding events reported as *primary* diagnoses during hospitalization will inform on the robustness of study findings.

- Recurrent symptomatic VTE. Children are likely to come to a specialist/hospital for a control visit or something related to their first VTE. On this occasion they might be recorded with a diagnosis of VTE even if this does not represent a recurrent VTE event. In order to minimize this risk of misclassification, the outcome of recurrent VTE will be restricted to VTE diagnoses recorded in inpatient setting, thus excluding control visits for VTE which most likely occur in secondary outpatient care. However, a risk of misclassification remains for children hospitalized for a long period or for other reasons than the index VTE, where it might be difficult to distinguish a recurrent VTE event from the index VTE. For this reason, the use of a primary definition of VTE diagnoses, including all primary/main and secondary diagnoses codes, and a secondary more specific definition restricted to primary VTE diagnoses reported through hospitalization will allow to test the robustness of the findings.

Other limitations

- **Impact of the small sample size**

The number of available children aged under two years with VTE is expected to be very low in most data sources due to VTE being a rare event in this population. For this reason, all analyses will be descriptive and no confirmatory comparison between exposure categories will be performed.

To comply with GDPR, cell suppression is required to mitigate the risk of re-identification in most countries. Consequently, this is a major limitation for analyses in most data sources, except SNDS in France. Besides, due to the small sample size and low frequency of the safety and efficacy outcomes, it is expected that these analyses should only be feasible in the SNDS.

- **Missing data**

Some variables, e.g., daily dosage or prescription length may have missing data. Commonly used assumptions for this type of analysis will be used to approximate values. Other variables such as duration of oral or gastric feeding or bodyweight might not be captured or only partially captured in some data sources. However, these aspects are important to describe patient characteristics, but missing data will not impact overall results of this study.

9.10. Other aspects

Not applicable

10. Protection of human subjects

The analysis for this study is based on secondary data use. No identifying data will be collected in any of the planned approaches.

The study will be conducted in agreement with the regulation (EU) 2016/679 of the European Parliament on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR).

Regulatory and ethical requirements will be followed in each country where the respective countries databases are used. The study will comply with the module VIII of the good pharmacovigilance practices (GVP).

Although EU Pharmacovigilance Directive (DIR 2010/84/EU) is a legal act, it does not carry the same binding force of a regulation; each Member State can determine how best to transpose the Directive into local legislation. As a result, the submission requirements for PASS vary throughout the EU, with some countries being more onerous than others. The project team will include experts that are dedicated to the review and advisement on the regulations and guidelines applicable to this study in the participating countries.

The study will be submitted to ethical review boards (ERBs) for approval wherever required by local laws. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Annual progress reports will be submitted to ERBs, and regulatory authorities as required by local laws and regulations.

11. Management and reporting of adverse events/adverse reactions

This study is based on the secondary use of data from the country-specific databases.

As per the EMA Guideline on GVP (Module VI–Management and reporting of adverse reactions to medicinal products [Revision 1]), individual reporting of adverse reactions is not required for non-interventional study designs that are based on secondary use of data (20).

12. Plans for disseminating and communicating study results

This study will be registered at “www.clinicaltrials.gov” and in the EU PAS register at “http://www.encepp.eu/encepp_studies/indexRegister.shtml”.

Annual progress reports and – at study completion – a final report will be sent to the EMA.

The final report will follow the structure recommended in the EMA template “Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies”(21).

The results of this non-interventional study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the Marketing Authorization Holder (MAH). Current guidelines and recommendation on good publication practice will be followed (e.g., GPP3 Guidelines, Strengthening the Reporting of Observational Studies in Epidemiology) (22, 23).

Furthermore, authorities in the countries where the data source was selected (like Sweden) demand that the results need to be made publicly available (e.g., as a conference abstract or in a scientific manuscript).

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Annex 1: List of stand-alone documents

Document Name

- *22195_Feasibility Report, v 1.0, 15-APR-2022*
- *22195_Steering Committee Charter, v 0.1, 03-MAR-2022*
- *22195_Study timelines and milestones tracker:* Study tracked in Mont Blanc
- *22195_Detailed list of variables*: Not yet available, additional information in Annex 3
- *22195_SAP*: Not yet available

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

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title: Xarelto Paediatric VTE PASS Drug Utilization Study: An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS)

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

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1, 9.2.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	

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

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.5

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.2
4.2.2 Age and sex	☒	☐	☐	9.2.1,9.2.3
4.2.3 Country of origin	☒	☐	☐	9.1
4.2.4 Disease/indication	☒	☐	☐	9.2.1, 9.2.3
4.2.5 Duration of follow-up	☒	☐	☐	9.2.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.4

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	9.2.3, 9.9
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.1, 9.3.1
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1, 9.3.1

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2, 9.4, 9.9
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.3.2.1.1

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.1, 9.9

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.6
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.5
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.6

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.4.1, 9.5.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.4, 10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____ Date: dd/Month/year

Signature:

Annex 3: Additional information

ATC codes for anticoagulant drugs

Class	Drug name	ATC code
1. Parenteral anticoagulants	Heparin	B01AB01
	Enoxaparin	B01AB05
	Dalteparin	B01AB04
	Nadroparin	B01AB06
	Tinzaparin	B01AB10
	Reviparin	B01AB08
	Parnaparin	B01AB07
	Bemiparin	B01AB12
	Fondaparinux	B01AX05
	Danaparoid	B01AB09
	Bivalirudin	B01AE06
	Argatroban	B01AE03
2. Vitamin K antagonists		B01AA
	Warfarin	B01AA03
	Phenprocoumon	B01AA04
	Acenocoumarol	B01AA07
	Dicoumarol	B01AA01
	Tioclomarol	B01AA11
	Ethyl biscoumacetate	B01AA08
	Fluindione	B01AA12
	Phenindione	B01AA02
	Chlorindione	B01AA09
	Diphenadione	B01AA10
3. Direct oral anticoagulants	Rivaroxaban	B01AF01
	Dabigatran	B01AE07
	Apixaban	B01AF02
	Edoxaban	B01AF03

ATC = Anatomical Therapeutic Chemical (Classification System)

Codes for VTE (preliminary list)

Condition	ICD-10 or procedure code beginning with
VTE (composite)	I26, I801-802

ICD = International Classification of Diseases; VTE = Venous Thromboembolism

Codes for bleeding (preliminary list)

Condition	ICD-10 or procedure code beginning with
Intracranial bleeding	I60-62, S064, S065, S066, S067, S068
Gastrointestinal bleeding	I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922
Urogenital bleeding	N02, R319, N95
Other bleeding	H431, R04, R58, D629, procedure code DR029

ICD = International Classification of Diseases

Further details to the data sources

France - SNDS

SNDS contains information on beneficiaries age, sex, region of residence, death date, complementary universal health coverage status, and all outpatient healthcare consumption including all reimbursed prescription drugs identified by their ATC code, the date of delivery, quantity, and brand name. Medical procedures performed on an outpatient basis or in a healthcare institution are identified by the *classification commune des actes médicaux* (CCAM, or common classification of medical procedures), laboratory procedures are identified by the *nomenclature des actes de biologie médicale* (NABM, clinical pathology test nomenclature), and paramedical or medical visits are identified by the *nomenclature générale des actes professionnels* (NGAP, General nomenclature of professional procedures).

SNDS informs about the presence of long-term chronic disease (LTD) status, eligible for 100% reimbursement of healthcare expenditure; the date of the LTD diagnosis; and its nature, coded according to the International Classification of Diseases, 10th edition (ICD-10). Registration for LTD is requested by the patient's general practitioner, and diagnoses are approved by the health insurance medical consultant. Registration is not mandatory. It may be missing, for instance, if the medical expenses are already covered by another chronic disease or the treatment is not expensive.

Through the PMSI, the SNDS also includes medical summaries of all hospitalizations from all private or public hospitals, including the date of stay, medical procedures and costly innovative drugs (medicaments liste en sus) or implantable devices during the hospital stay, the primary diagnosis (main reason for admission), related diagnosis (specifies the disease context of the primary diagnosis), and diagnoses related to other conditions, all encoded according to the ICD-10. Information on occupational diseases, sick leaves are also available.

Denmark – National health registers

In Denmark several registers with different content exist on national level.

- Danish Register of Medicinal Products Statistics (RMPS)

The Danish RMPS contains patient-level data on all prescription drugs filled by patients at community pharmacies, but not medication administered at hospitals (24, 25). The register contains information on the date of purchase, item number, product name, ATC code, strength per unit, quantity of World health Organization (WHO)'s defined daily doses per package and number of packages filled.

Data is available from 1995 and onwards. Since April 2004, information on medical indication for prescription and daily prescribed dose by physician has also been available, but completeness and validity are affected by a non-compulsory obligation to record this information.

At Danish Health Care Authority, the register is updated once a month, typically with a lag of approximately 2 months. But if the project requires that data are stored at Statistics Denmark because of link to socio-economic registers, the register is updated twice a year after end of June and December with a lag of approximately 5-6 months.

- The Hospital Patient Medication Register (SMR)

The register will contain information on drugs administered to patients while admitted to hospital or during outpatient visits: the date and time of administering the drug, the dose administered via number of units and strength per unit, product name, ATC code, and department information. Thus, this register will complement the RMPS. Data has been captured since May 2018.

It is expected that the register will be updated monthly with a lag of approximately 2 months. However, the register is not yet released for research. Current expectations are that it will be released during 2022.

- Danish National Patient Register (DNPR)

The DNPR contains information on the Danish population's encounters at hospitals (secondary care) (26, 27). Data on activities and diagnoses in primary care at general physicians and specialists in private practice is not included. The register contains information on date and type of admissions and outpatient visits, discharge date and diagnoses, treatments, examinations, surgeries and procedures, including Diagnosis Related Group (DRG) costs.

Data is available from 1977 and onwards for inpatient somatic admissions. Since 1995, outpatient visits, emergency room visits, and encounters at psychiatric wards are included, too. DRG costs have been available since 2002. At Danish Health Care Authority, the register is updated once a month, typically with a lag of approximately 2 months. But if the project requires that data are stored at Statistics Denmark because of link to socio-economic registers, the register is updated once a year after end of December with a lag of approximately 10 months.

Since 1994, ICD-10 has been used as classification system. ICD-8 was used between 1977 and 1993.

- Danish Medical Birth Register (MBR)

The Danish MBR is an enrichment of data already recorded in the National Patient Register (NPR) and compiles relevant information of pregnancies that has led to childbirth in Denmark at home or in a hospital. It contains information on characteristics of mother and child, pregnancy, and delivery characteristics including induction procedures and gestational age, outcomes of pregnancy and delivery, and the mother's history of previous abortions and/or deliveries. MBR includes linkage between infant, mother and father.

- Danish Register of Causes of Death

The Danish Cause of Death Register contains information on date and cause of death (28). When a person dies in Denmark, a death certificate is filled by a medical doctor. The information from the death certificate, including place of death, information about any autopsy, and municipality of residence is transferred to the Cause of Death Register.

Causes of death recorded from 2002 and onwards have been post-processed with the Automated Classification of Medical Entities system to further ensure a uniform recording of the underlying cause of death over time.

Data is available from 1970 and onwards. The register is updated once a year after end of December with a lag of approximately 13 months. Since 1994, ICD-10 has been used as classification system. ICD-8 was used before 1994.

- Danish Civil Registration System (CPR)

CPR introduced in 1968 is a national register containing basic personal information on all who have a civil registration number. Information on demographics (age, sex, geographical region), migration and vital statistics data has been registered electronically on a daily basis for all Danish residents. Every individual in Denmark is provided with a unique PIN at birth or upon immigration which allows for follow-up until death or emigration. The database contains variables on civil registration number, name, address, birth registration, citizenship, church membership, parentage, marital status as well as information on the status of the individual registration. The PIN also allows for family linkage of data.

Sweden – National health registers

In Sweden several registers with different content exist on national level.

- Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register was established in July 2005 and contains all prescribed drugs dispensed at pharmacies. About 67 percent (6.8 million) of the population were prescribed a pharmaceutical at least once in 2019. The register contains information about patient, product (ATC code, strength, pack size), the prescription (prescribed quantity/number of packages, strength, date of prescription, date of purchase) and the prescriber.

- Swedish NPR

The NPR is managed by the National Board of Health and Welfare. The register includes inpatient care with complete coverage since 1987 (ICD-10 from 1998) and specialized outpatient care from 2001 onwards. However, primary care is not yet covered in the NPR. The register contains information on, e.g., admission and discharge, main and secondary diagnosis (ICD-9 or -10 codes) and performed medical procedures, as well as patient demographics. The register is updated annually with around 7-9-month lag time to data access. The register has aimed at updating frequency to monthly updated, and thus more frequent updates and faster access can be expected in the future. Access to the register data for scientific research is decided by the National Board of Health and Welfare through a standard application procedure.

- Swedish MBR

The Swedish MBR contains information about all pregnancies resulting in delivery in Sweden and is frequently used for quality improvement work and for research. The register contains detailed information about mothers and births.

- Swedish Cause of Death Register

The Swedish Cause of Death Register has captured death information for residents of Sweden since 1952. The information recorded includes hometown, sex, date of death, cause of death (ICD-9/10 codes), time of death, and intention in cases of injury or poisoning. The Cause of Death Register is updated annually. Complete data for the previous year is normally available in August, however dates of death are available in the register earlier.

Annex 4: Description of updates and amendments

None

Annex 5: Signature pages

A. Electronic Signature

Signature Page

This protocol is electronically signed in the study management system

Title	Xarelto Paediatric VTE PASS Drug Utilization Study: An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS)
Protocol version and date	v 2.1 16 NOV 2022
IMPACT study number	22195
Study type / Study phase	Observational ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
NCT number	Study not yet registered
Medicinal product	Xarelto® 1mg/1mL granules for oral suspension
Comparator / Reference therapy	Standard of care (heparins, vitamin K antagonists, other direct oral anticoagulants)
Study Initiator and Funder	Bayer AG

The signatories agree that the study will be conducted under the conditions described in the protocol.

Signatories

Name: PPD OS Conduct Responsible

Name: PPD OS Medical Expert

Name: PPD OS Statistician

Name: PPD OS Epidemiologist

Name: PPD OS Safety Lead

Name: PPD Qualified Person responsible for Pharmacovigilance (QPPV)

Name: PPD Global Regulatory Strategist

Name: PPD OS Health Economics and Outcomes Research (HEOR) responsible

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Reason for signing: Approved	Name: PPD Role: OS Conduct Responsible Date of signature: 21-Nov-2022 13:59:15 GMT+0000
Reason for signing: Approved	Name: PPD Role: GRS/EPM Date of signature: 24-Nov-2022 09:06:16 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Medical Expert Date of signature: 24-Nov-2022 09:20:31 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Statistician Date of signature: 24-Nov-2022 10:24:15 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Content Owner Date of signature: 25-Nov-2022 10:27:13 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Safety Lead Date of signature: 25-Nov-2022 16:46:52 GMT+0000
Reason for signing: Approved	Name: PPD Role: QPPV Date of signature: 29-Nov-2022 12:56:12 GMT+0000

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Reason for signing: Approved	Name: PPD Role: HEOR Project Lead Date of signature: 29-Nov-2022 20:52:17 GMT+0000

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