Boehringer Ingelheim

Non-Interventional Study (NIS) Protocol

Document Number:	***c35920658-03***
BI Study Number:	1160.307
BI Investigational Product(s):	Dabigatran etexilate
Title:	Safety of dabigatran etexilate (DE) for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: a prospective European non-interventional cohort study based on new data collection
Brief lay title:	A study in Europe based on medical records that looks at the safety of dabigatran in children below 2 years of age who have had a blood clot and are at risk of developing another blood clot
Protocol version identifier:	3.0
Date of last version of protocol:	11 January 2024
PASS:	Yes
EU PAS register number:	The study will be registered on ENCePP and clinicaltrials.gov before the study initiation
Active substance:	Dabigatran
Medicinal product:	Pradaxa®
Product reference:	BIBR 1048 MS
Procedure number:	NA
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	Limited safety data is available for DE in children from birth to < 2 years of age for the treatment of acute VTE treatment and prevention of recurrent VTE. The objective of this study is to evaluate the safety of DE for the treatment of VTE and prevention of recurrent VTE in children from birth to < 2 years of age in a routine clinical practice setting.

	Primary objective: • To estimate the incidence of any bleeding event defined as Major Bleeding Event (MBE) or Non- Major Bleeding Event (Non-MBE) among the children under 2 years of age on dabigatran etexilate (DE) administration. Secondary objective: • To estimate the incidence of AEs. • To estimate the incidence of SAEs. Further objective: • To assess acceptability and tolerability of paediatric formulation.
Country(-ies) of study:	European Economic Area (EEA) states: EU member states plus Norway, Iceland and Liechtenstein (depending on country regulations and requirements).
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Date:	29 November 2021
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
aRMM	Additional Risk Minimization Measure
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
DE	Dabigatran Etexilate
EEA	European Economic Area
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FSV	Final Study Visit
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
IEC	Independent Ethics Committee
ISF	Investigator Site File
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MBE	Major bleeding events
NIS	Non-Interventional Study
PTS	Post-thrombotic syndrome
REP	Residual Effect Period
SAE	Serious Adverse Event
TMF	Trial Master File
VTE	Venous thromboembolism

3. RESPONSIBLE PARTIES

[redacted] Investigator	[redacted] Tel: [redacted] Email: [redacted]
Country coordinating investigator	All investigators including country coordinating investigators with contact details are listed in a stand-alone document in Annex 1, Trial Master File (TMF) and Investigator Site File (ISF).
Therapeutic Area [redacted] CardioMetabolism Respiratory Med	[redacted]
[redacted] of Global Epidemiology Team CardioMetabolism and Respiratory	
Team Member Medical Affairs (TMMA)	
Team Member Epidemiology (TMEpi)	
Pharmacovigilance Working Group (PVWG) Chair	
BI NIS [redacted]	
Project Statistician (PSTAT)	
Contractor(s) involved	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Protocol date: *26 May 2021*	**Study number:** 1160.307	**Version/Revision:** 3.0/2.0	**Version/Revision date:** 3.0/11 January 2024
Title of study:	Safety of dabigatran etexilate (DE) for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: a prospective European non-interventional cohort study based on new data collection.		
Rationale and background:	Dabigatran is a direct thrombin inhibitor that is effective for treatment of VTE and prevention of recurrent VTE in adults. However, the concept of developmental hemostasis precludes complete extrapolation of adult efficacy and safety data to children, particularly those of the youngest age group of neonates and infants [R15-4967]. In hospitalized children, a significant increase of 70% in VTEs has been noted [R13-4251]. Anticoagulation agents commonly used in children present with frequent challenges, and there is a high unmet need for age-appropriate treatment options to manage VTEs in children [P19-00949, R14-1033, R19-2558, R20-3319]. For adequate anticoagulation, it is essential to balance the risk of thromboembolic events with the risk of bleeding. The clinical results of dabigatran anticoagulation in children with VTEs are based on a limited number of patients. However, the overall safety and efficacy of dabigatran in this population was supported by a remarkable consistency across all age groups and comparable to the clinical outcomes in adult patients with VTE who were treated with dabigatran [R13-3609, P19-11322, P20-07911]. However, limited evidence is available for safety of dabigatran anticoagulation in children from birth to < 2 years. This is also the age group that demonstrates the most marked differences from adults in haemostaseology. Thus, this post-authorization data collection is planned to collect more safety data of dabigatran in children under 2 years of age. The results from this PASS study will be interpreted in the context of the findings from the paediatric clinical development program.		

Research question and objectives:	The objective of this study is to evaluate the safety of DE for the treatment of VTE and prevention of recurrent VTE in children from birth to < 2 years of age in a routine clinical practice setting. Primary objective: • To estimate the incidence of any bleeding event defined as Major Bleeding Event (MBE) or Non- Major Bleeding Event (Non-MBE) among the children under 2 years of age on DE administration. Secondary objective: • To estimate the incidence of AEs, • To estimate the incidence of SAEs. Further objective: • To assess acceptability and tolerability of paediatric formulation.
Study design:	This is a prospective, non-interventional European multinational multi-centre cohort study based on newly collected data of paediatric patients anticoagulated with DE for acute VTE treatment or prevention of recurrent VTE. The study is designed to collect and evaluate DE safety in the context of routine anticoagulation care provided in the EU/EEA for children under 2 years of age. The duration of the study will be up to 2 years from the date of study initiation with the goal to enrol 50 evaluable patients under DE administration. Approximately 10 EU/EEA countries are planned to engage in this study. After informed consent patients will be screened for enrolment into the study. A screening log to ensure consecutive screening and enrolment will be used so that all eligible patients under 2 years with an indication for anticoagulation are identified. If a patient completes all study entry criteria, a baseline part of the Screening / Baseline visit will be conducted, and the patient will enter an observational study period. Safety outcomes will be collected for a period of up to 3 months from the day of DE initiation defined as the index date for the treatment of acute VTE and up to 6 months from the index date for prevention of recurrent VTE. DE acute VTE treatment may be followed by the secondary VTE prevention due to unresolved VTE risk factors. Overall duration of the study observational period for any patient will not exceed 6-month period of anticoagulation. If acute treatment is followed by anticoagulation for prevention of recurrent VTE, the maximal period in the study is 6 months. In this situation, the index date for start of anticoagulation for prevention of recurrent VTE is based on investigator judgement or after 3 months of treatment for acute VTE, whichever occurs earlier. Anticoagulation of more than 6-month duration, if required due to the presence of unresolved VTE risk factors, will not be covered in this study setting. Patients who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors will be considered as one unique patient. However, safety outcomes of each anticoagulation period will be evaluated within the corresponding cohort. The study observational period for a patient is defined as the time period

	from the index date (initiation of DE administration) onwards up until DE administration discontinuation + 3 days of Residual Effect Period (REP) or switch to other anticoagulation therapy + 3 days of REP or planned end of 6-month observation time, whatever occurs earlier. Patients will not be followed outside the observational period. Data collection visits are planned for both VTE treatment and prevention of recurrent VTE groups as follows: • Baseline part of Screening/Baseline visit: index date (initiation of DE administration). • Follow up visit(s): - At approx. 6 weeks or 3 months after initiation of DE administration for children treated for acute VTE, based on investigator judgment. - At approx. 3 or 6 months of DE administration, for prevention of recurrent VTE group based on investigator judgment. Patients who continued secondary VTE prevention after acute VTE treatment will conduct two follow up visits: at the end of DE treatment for acute VTE, at discontinuation of DE for secondary VTE prevention or after total 6 months of DE administration, whichever occurs first. Final Study Visit is defined as a follow up visit conducted after the end of the observational period. The study is observational and does not entail any change in prescribing pattern or management strategies which are left to the discretion of the treating physician. According to NIS concept no special evaluation procedure is required.

Population:	Paediatric patients under 2 years of age, who may be considered for anticoagulation with DE due to acute VTE, are usually treated in neonatology, paediatric general surgery, cardiac surgery, or intensive care units. Paediatric patients with anticoagulation with DE for the prevention of recurrent VTE are usually evaluated by paediatric haematologists in paediatric haematology units. Inclusion criteria: • Written informed consent from parents/care givers, • Children from birth to less than 2 years of age, • Initiation of DE administration according to the EU DE SmPC: - for treatment of acute VTE or/and - prevention of recurrent VTE due to presence of an unresolved clinical VTE risk factor(s). Exclusion criteria: • Participation in any RCT or use of investigational product, • Any contraindications to DE according to the EU SmPC. Safety outcomes will be collected from overall 50 patients anticoagulated with DE for acute VTE treatment and/or prevention of recurrent VTE due to presence of unresolved clinical VTE risk factor(s). Paediatric population will be accordingly stratified into two cohorts: • children anticoagulated with dabigatran due to acute VTE treatment • children anticoagulated with dabigatran for prevention of recurrent VTE due to the presence of an unresolved VTE clinical risk factor. • Patients who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors will be considered as one unique patient. However, each anticoagulation period will be evaluated within the corresponding cohort.

Variables:	Detailed information on paediatric patients under 2 years of age and DE administration will be collected as follows: At Screening/Baseline: • Demographics (e.g., age, weight, gender, race, country), • Hospitalisation details, type of paediatric department (e.g., neonatology, cardio-surgery, ICU, haematology, etc.) and procedures related to VTE diagnostic modalities, • Medical history including concomitant medications history (administered within 14 days prior to informed consent), • Baseline conditions, • Acute VTE characteristics as type of VTE, symptomatic / asymptomatic, location; VTE characteristics obtained according to standard diagnostic modalities and local protocols, • Available characteristics of the most recent VTE event (as specified above) for prevention of recurrent VTE group, • Presence of post-thrombotic syndrome (PTS); if PTS present, used diagnostic scale and score should be indicated, • VTE clinical risk factor(s), • Initial DE dosage and formulation if a patient initiated DE treatment. At Follow up: • Incidence of any bleeding event defined as Major Bleeding Events (MBE) or Non- Major Bleeding Events (Non-MBE) including location(s), • Incidence of AEs / SAEs, • Concomitant treatment and procedures, • Any changes in DE dosage(s) and formulation with corresponding age and weight • Duration of DE administration, • Acceptability and tolerability of paediatric DE formulation; acceptability is defined as the overall ability and willingness of the patient to use the medicinal product as intended; tolerability is measured as premature treatment discontinuation, and adherence to trial medication. The safety data will be evaluated based on the study observational period, i.e., from the index date (initiation of DE administration) onwards up until DE administration discontinuation + 3 days of REP or switch to other anticoagulation therapy + 3 days or planned end of 6-month observation time whichever occurs earlier. Patients who continued secondary VTE prevention after acute VTE treatment will conduct two follow up visits: at the end of DE treatment for acute VTE, at discontinuation of DE for secondary VTE prevention or after total 6 months of DE administration, whatever occurs first. All data will be obtained by qualified clinicians according to the standard medical practice.

Data sources:	Newly collected data and/or data collected from medical records will be entered by the site directly in an electronic data capture (EDC) system via an Internet portal. All sites will be fully trained for using the EDC system and BI AE/SAE reporting procedure. It is the Principal Investigator's responsibility to ensure for his/her site the accuracy of the data provided to the program by any site staff that is trained for the program data collection.
Study size:	The study sample size is based on the anticipated usage of DE for VTE treatment and prevention. An overall 50 patients under 2 years of age will be enrolled in the study. Approximately 30 paediatric study sites with experience in VTE anticoagulation treatment and prevention will be selected for the PASS in EU/EEA states. Approximately 10 EU/EEA countries are planned to engage in this study.
Data analysis:	Safety outcomes from this single-arm study will be interpreted in the context of findings from the paediatric developmental program, i. e., acute VTE treatment (DIVERSITY) and secondary VTE prevention studies. As this is a descriptive non-interventional study, no hypotheses will be tested, rather, all variables will be presented using descriptive statistics (absolute and relative frequencies, means, standard deviations, medians, ranges, minimum and maximum values, 95% confidence intervals [CI] and incidences as appropriate for the nature of the variables (i.e., categorical or continuous)). Safety outcomes will be summarized as incidence with 95% CIs using Wilson method. All AE/ verbatim terms will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be recorded according to World Health Organisation Drug Dictionary (WHO-DD). All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.4 or higher ([redacted]).
Milestones:	Start of data collection: Q4 2022, Last Patient In (LPI): Q2 2024, End of data collection: Q3 2024, Final report: Q2 2025.

5. MILESTONES

Milestone	Planned Dates
First IRB/IEC approval	Q3 2022
Last IEC approval	Q4 2022
Start of data collection	Q4 2022
End of data collection	Q3 2024
<Registration in the EU PAS register>	Q2 2022
Final report of study results:	Q2 2025

6. RATIONALE AND BACKGROUND

Dabigatran is a direct thrombin inhibitor demonstrated to be effective for treatment of VTE and prevention of VTE in adults. However, the concept of developmental haemostasis precludes complete extrapolation of adult efficacy and safety data to children, particularly those of the youngest age group of neonates and infants [R15-4967]. In hospitalised children, a dramatic increase of 70% in VTEs has been noted [R13-4251]. Anticoagulation agents commonly used in children present frequent challenges. Current paediatric standard of care (SOC) with heparins or vitamin K antagonists is limited by parenteral administration and frequent monitoring, respectively. Therefore, there is a high unmet need for age-appropriate treatment options to manage VTEs in paediatric patients [P19-00949, R14-1033, R19-2558, R20-3319]. For adequate anticoagulation, it is essential to balance the risk of thromboembolic events with the risk of bleeding. Dabigatran has been shown to overcome SOC limitations in children with VTE, as its action is independent of antithrombin, it has an immediate onset and offset of action, has minimal interactions with commonly used drugs or diet, and is excreted mainly via the kidneys. [P08-05411, R13-3609].

The overall safety and efficacy of DE in children are supported by remarkable consistency within all age groups and with the clinical outcomes in adult patients with VTE who are treated with DE, despite the smaller number of children enrolled in paediatric trials. [P13-16985, P19-11322, P20-07911]. The results of the DIVERSITY study conducted in 267 children from birth to < 18 years of age show that DE was non-inferior to SOC for thrombus resolution and VTE recurrency with similar bleeding rates [P20-07911]. DE showed a favourable safety profile for prevention of recurrent VTE in children aged from >3 months to <18 years with persistent VTE clinical risk factor(s) evaluated in a long-term secondary VTE prevention study [P19-11322]. Overall, the DE clinical program for paediatric patients showed an acceptable benefit-risk ratio and supports treatment of VTE and prevention of recurrent VTE in children from birth to less than 18 years.

However, limited evidence is available in early age children (from birth to < 2 years) for treatment of VTE and prevention of recurrent VTE. This age group also demonstrate the most marked differences from adults in hemostaseology [R15-4967]. The results of acute VTE treatment in this age group were evaluated in 35 cases of the DIVERSITY study, where 22

patients received DE and 13 received SOC [P20-07911]. The long-term secondary VTE prevention study evaluated 9 children in this early age group [c29754273-01]. The limited number of neonates and infants evaluated in the DE paediatric program was connected with multiple challenges, including the relatively rare condition, a critically ill population with life-threatening comorbidities, use of aggressive treatments, limited blood volumes that can be drawn for study purposes and, finally, parental consent that is often difficult to obtain in young children with acute serious conditions [R11-4524, P17-11774, P19-00949, R20-3318]. Thus, post-authorization data collection is planned to characterize the safety profile of dabigatran in children under 2 years of age. The aim of this PASS is to evaluate the safety of all paediatric patients under 2 years of age receiving DE in a routine clinical practice setting.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to evaluate the safety of DE for VTE treatment and prevention of VTE recurrency in children from birth to < 2 years of age in a routine clinical practice setting.

Primary objective:

- To estimate the incidence of any bleeding event defined as Major Bleeding Event (MBE) or Non- Major Bleeding Event (Non-MBE) among the children under 2 years of age on DE administration.

Secondary objective:

- To estimate the incidence of AEs.
- To estimate the incidence of SAEs.

Further objective:

- To assess acceptability and tolerability of paediatric formulation.

8. RESEARCH METHODS

8.1 STUDY DESIGN

The DE Post-Authorization Safety Study (PASS) for VTE treatment and prevention of recurrent VTE in children under 2 years of age is designed as a prospective, non-interventional European multinational multi-centre, single-arm cohort study based on newly collected data of patients anticoagulated by DE for acute VTE treatment or prevention of recurrent VTE.

The study is designed to collect and evaluate DE safety in the context of routine anticoagulation care provided in the EU/EEA for children under 2 years of age. The duration of the study will be up to 2 years with the goal to enrol 50 evaluable patients under DE administration. Approximately 10 EU/EEA countries are planned to engage in this study.

The study will be conducted in paediatric hospitals or paediatric departments of *European Economic Area* member states where VTE patients of the evaluated age group are treated, depending on country regulations and requirements.

In order to assure assessment of representativeness of the PASS, all patients under 2 years who required anticoagulation and sign informed consent will be screened for potential participation in the study. Screening details will be entered in the Screening Log, which will contain final conclusion on study eligibility with clarification of screening failure if not enrolled in the PASS. If a patient completes all study entry criteria, a baseline part of the Screening / Baseline visit will be conducted, and the patient will enter an observational study period.

During the observational period safety outcomes, which comprise all specific clinical safety data connected with anticoagulation management of the children under 2 years of age, will be collected.

The study observational period is defined as a time period from the index date (i.e., initiation of DE administration) onwards up until DE administration discontinuation + 3 days of Residual Effect Period (REP) or switch to other anticoagulation therapy + 3 days of REP or planned end of 6 month observation time, whatever occurs earlier. Overall duration of the study observational period for any

patient will not exceed 6-month period of anticoagulation. Patients will not be followed outside the observational period.

Duration of the observational period will be as follows:

- up to 3 months from the day of DE initiation defined as index date for the treatment of acute VTE and
- up to 6 months from index date for prevention of recurrent VTE.

Patients after completion of acute VTE treatment may continue anticoagulation due to unresolved VTE risk factors. The duration of the VTE treatment and secondary VTE prevention periods will be based on investigator judgement. Total duration of the observational period for this group will be performed until DE administration discontinuation + 3 days of REP or planned end of 6-month observation time, whatever occurs earlier.
Patient who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors will be considered as one unique patient. However, safety outcomes of each anticoagulation period will be evaluated within the corresponding cohort.
Anticoagulation of more than 6-month duration, if required due to the presence of unresolved VTE risk factors, will not be covered in this study setting.

The duration of anticoagulation outlined in this PASS study is in accordance with international guidelines for management of VTE paediatric patients [P19-00949], results and experience of the previous DE registrational studies, and reflect routine VTE paediatric care. The recommended duration of anticoagulation treatment is up to 3 months for children above one year of age. For neonates and infants (children under 1 year), the usual recommended treatment duration is 6 weeks. However, it may be extended, if the VTE clinical risk factors are unresolved at the end of the 6-week treatment period. Recommendations on the duration of anticoagulation for prevention of VTE recurrence depend on the presence of unresolved VTE clinical risk factors and may continue for an indefinite period of time. Final decision on the duration of VTE treatment and /or secondary prevention periods will be based on investigator's judgment.

Safety data collection will be conducted at Screening/Baseline and Follow up visits for both VTE treatment and prevention of recurrent VTE groups. Visit details provided in the Section 8.2.3. "Study visits".

The study is observational and does not entail any change in prescribing pattern or management policies which are left to the discretion of the treating physician. No special evaluation procedure is required.

8.2 SETTING

8.2.1 Study sites

The PASS is intended to be available to paediatric hospitals and paediatric departments of European Economic Area member states, where VTE paediatric patients under 2 years of age are treated, depending on country regulations and requirements. Approximately 30 paediatric study sites with experience in VTE anticoagulation treatment and prevention will be selected and initiated by Q4 2022. Every effort will be made to identify sites where paediatric use of DE is available.

The selection of study sites for the 1160.307 study will be focused on specialised paediatric units treating neonates, infants, and young children.

Previous experience from the DIVERSITY and prevention of secondary VTE studies support the assumption that approximately 30 specialised paediatric sites focusing on treatment of neonates and infants with VTE risk factors will be able to enrol and collect safety data from overall 50 evaluable children administered DE for VTE treatment and prevention. In addition, experience from the previous dabigatran VTE paediatric program indicates on a potential varying enrolment rate in the selected sites and variations in the clinical management mainly in terms of duration of anticoagulation based on investigator's judgment. However, these variations related to the baseline clinical conditions underline acute VTE event or VTE risk factors that affect safety outcomes, e.g., bleeding events rate in patients with thrombophilia is usually lower than in unselected VTE population under anticoagulation [R21-0986]. The collected safety data from a variety of paediatric units with early age children will reflect routine medical care in EU/EEA when receiving DE anticoagulation.

Based on the previous BI VTE program experience, neonates and infants with acute VTE requiring DE administration are localised in the following paediatric units:

- neonatology departments, where target conditions are umbilical thrombosis, cerebral vein thrombosis, central line related-VTE, etc.
- paediatric surgery, paediatric cardiology, paediatric cardio- surgery, intensive care units, and paediatric haematology departments where target conditions are central line / implantable devices related-VTE, cyanotic congenital heart disease, venous malformations, leukaemias etc.

Patients who require anticoagulation for secondary VTE prevention are evaluated mostly in paediatric haematology, paediatric cardiology, and paediatric cardio-surgery departments.

During the approximate 1.5-year enrolment period every effort will be made to support investigators to include the paediatric patients requiring dabigatran anticoagulation in this study. These efforts will include communications with investigators using digital resources and face to face communications, presentation of the results and enrolment strategies of the previous published studies on DE, focused on early age children [P20-07911].

8.2.2 Study population

Paediatric patients from birth to < 2 years of age considered by investigator after screening as eligible for DE treatment of acute VTE or secondary prevention of recurrent VTE will be enrolled in the PASS and evaluated for up to 3 months in case of acute VTE treatment, and up to 6 months in case of prevention of recurrent VTE.

Patients after completion of acute VTE treatment may continue anticoagulation as secondary VTE prevention due to unresolved VTE risk factors in accordance with investigator's judgment. Total observational period for this group, which include VTE treatment and prevention will be also up to 6 months duration. Further anticoagulation, if required due to unresolved VTE risk factors, will be continued outside the study setting.

Inclusion criteria:

- Written informed consent from parents/care givers,
- Children from birth to less than 2 years of age,
- Initiation of DE administration:
  - for treatment of VTE or/and
  - prevention of recurrent VTE due to presence of unresolved clinical VTE risk factor(s).

Exclusion criteria:

- Participation in any Randomised Clinical Trial or use of any investigational product,
- Any contraindications to DE according to the EU SmPC.

Paediatric population will be stratified into two groups according to the EU DE SmPC:

- children anticoagulated with dabigatran due to acute VTE treatment
- children anticoagulated with dabigatran for prevention of recurrent VTE due to the presence of an unresolved VTE clinical risk factor.

Patients who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors will be considered as one unique patient. However, safety outcomes of each anticoagulation period will be evaluated within the corresponding cohort.

The target sample size for the study is considered to be 50 evaluable patients enrolled from approx. 30 paediatric sites over an approximate 1.5-year period with a total approximate 2-year study duration.

The enrolment period is planned from Q4 2022 (FPI) to the Q2 2024 (LPI) depending on the availability of DE paediatric formulation (granules) on the market.

8.2.3 Study visits

The study is designed as a non-interventional study based on newly collected data and no study related visits are planned. New data collection will reflect routine medical care standards in the EU/EEA paediatric units.

The safety data will be collected during the study observational period defined in the Section 8.1 "Study design". Patients will not be followed outside the observational period.

In order to assure assessment of representativeness of the PASS, all patients under 2 years who required anticoagulation and sign informed consent will be screened for potential participation in the study. During the screening part of the Screening/Baseline visit, screening details will be entered in the Screening Log, which will contain demography, baseline conditions which required anticoagulation and final conclusion on study eligibility with comments on screening failure if not enrolled in the PASS. If a patient completes all study entry criteria, the investigator will proceed with conduction of a baseline part of the Screening/Baseline visit and the patient will enter an observational study period.

Registration of the safety data will be performed at the following visits of both VTE treatment and secondary VTE prevention cohorts:

- Baseline part of Screening / Baseline visit: index date (initiation of DE administration).

- Follow up visits:
  - At approx. 6 weeks or 3 months after initiation of DE administration for acute VTE treatment based on investigator judgment.
  - At approx. 3 or 6 months of DE administration for prevention of recurrent VTE based on investigator judgment.

Patients who continued secondary VTE prevention after acute VTE treatment will conduct two follow up visits: at the end of DE treatment for acute VTE, at discontinuation of DE for secondary VTE prevention or after 6 months of DE administration, whichever occurs first.

Safety data for these patients will be registered for this cohort at the following visits:

- Baseline part of the Screening / Baseline visit: index date (initiation of DE administration).
- Follow up visit(s).

Duration of the observational period for this group. will be performed until DE administration discontinuation + 3 days of REP or planned end of 6-month observation time, whatever occurs earlier. Patient who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors will be considered as one unique patient. However, safety outcomes of each anticoagulation period will be evaluated within the corresponding cohort.

Final Study Visit is defined as a follow up visit conducted after the end of the observational period.

8.2.4 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any effectiveness/safety information that could significantly affect continuation of the study, or any other administrative reasons
3. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator, or research collaborator, disturbing the appropriate conduct of the study

The investigator/the study site/research collaborator will be reimbursed for reasonable expenses incurred in case of study/site termination (except in case of the third reason).

8.3 VARIABLES

8.3.1 Exposures

As per inclusion criteria, all patients in this single arm study will receive DE and will be evaluated as such unless there is no documentation of DE administration as per CRF.
Dabigatran exposure is defined as from start of DE administration (index date) up to the DE administration discontinuation + 3 days of REP or switch to other anticoagulation therapy + 3 days of REP or planned end of observation time whichever occurs earlier.
Dabigatran exposure for the VTE treatment group planned up to a 3-month period and for the prevention of recurrent VTE group up to 6 months (see Section 8.1 “Study design”).

8.3.2 Outcomes

All outcome events collected in this PASS are considered as safety outcomes.

8.3.2.1 Primary outcomes

- The incidence of any bleeding events defined as Major Bleeding Events (MBE) or Non-Major Bleeding Events (Non-MBE).

Bleeding assessment

In accordance with routine medical care patients on anticoagulation will be carefully assessed for signs and symptoms of bleeding.
In context of this clinical practice study with no blinded adjudication of outcome events it is planned to record bleeding events, as documented in the patient files. Thus, it is planned to differentiate bleeding events as a Major Bleeding Event (MBE) and a Non- Major Bleeding Event (Non-MBE) using the clearly defined criteria for MBEs and Non-MBEs by the Perinatal and Paediatric Haemostasis Subcommittee of the SSC of the ISTH.

Major bleeding defined as,
- Fatal Bleeding,
- Clinically overt bleeding associated with a decrease in haemoglobin of at least 2 g/dL (20 g/L) in a 24-hour period,
- Bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system,
- Bleeding that requires surgical intervention in an operating suite.

Non- Major bleeding defined as,
- Any overt or macroscopic evidence of bleeding that does not fulfil the criteria for major bleeding.

8.3.2.2 Secondary outcomes

- Incidence of AEs.
- Incidence of SAEs (see Sections 10.1 and 10.2).

8.3.2.3 Further outcome

- To assess acceptability and tolerability of paediatric formulation.

Acceptability is defined as the overall ability and willingness of the patient and/or parent (legal guardian) to use the medicinal product as intended.
Tolerability is measured as premature treatment discontinuation, treatment interruption, and adherence to trial medication.

Assessment of acceptability and tolerability.
The overall clinical assessment of acceptability and tolerability will be performed by the parent / legal guardian and investigators by completing a standardized questionnaire. In between baseline and study final visits, the parent /legal guardian will be asked to document any failed or missed intake of medication (e.g., the patient did not swallow the medication, or doses missed, etc.) and provide this documentation to the investigator. The parent / legal guardian will be instructed to inform the

investigator immediately if two or more consecutive doses of study medication are missed or not taken correctly.

Assessment of the representativeness of the study cohort.
Screening Log with details of all patients requiring anticoagulation due to acute VTE treatment and/or secondary VTE prevention will be used for assessment of the representativeness of the study cohort, when all required anticoagulation patients will be compared with patients enrolled in the PASS.

All parents/legal guardians will be asked to sign informed consent before the screening procedures.
Screening Log will contain demography, details of conditions that require anticoagulation, conclusion on entry in the PASS or comments on reasons for screening failure.

The safety outcomes will be evaluated based on the on-treatment period, i.e., from start of DE administration (index date) up to DE administration discontinuation + 3 days of REP or switch to other anticoagulation therapy + 3 days of REP or planned end of observation time, whatever occurs earlier.

8.3.3. Covariates

Detailed information on paediatric patients under 2 years of age and DE administration will be collected as follows:

At Screening/Baseline:

- Demographics (e.g., age, weight, gender, race, country),
- Hospitalisation details, type of paediatric department (e.g., neonatology, cardio-surgery, ICU, haematology, etc.) and procedures related to VTE diagnostic modalities,
- Medical history including concomitant medications history (administered within 14 days prior to informed consent),
- Baseline conditions,
- Acute VTE characteristics as type of VTE, symptomatic / asymptomatic, location; VTE characteristics obtained according to standard diagnostic modalities and local protocols,
- Available characteristics of the most recent VTE event (as specified above) for prevention of recurrent VTE group,
- Presence of post-thrombotic syndrome (PTS); if PTS present, used diagnostic scale and score should be indicated,
- VTE clinical risk factor(s),
- Initial DE dosage and formulation.

At Follow up:

- Concomitant treatment and procedures,
- Any changes in DE dosage(s) and formulations with corresponding age and weight
- Duration of DE administration,

The safety outcomes will be evaluated based on the study observational period defined above (Section 8.1 “Study design” and Section 8.3.2 “Outcomes”).

8.4 DATA SOURCES

Newly collected data and/or data collected from medical records will be entered by the site directly in an electronic data capture (EDC) system via an Internet portal.

All data will be obtained by qualified clinicians by an appropriate objective method used in standard practice.
All sites will be fully trained for using the EDC system and the BI AE/SAE reporting procedure. It is the Principal Investigator's responsibility at each study site to ensure the accuracy of the data provided to the program by any site staff that is trained for the program data collection.

8.5 STUDY SIZE

The study sample size is based on the anticipated usage of dabigatran for acute VTE treatment and prevention of recurrent VTE.

The target sample size of 50 evaluable patients is planned to be enrolled from approximately 30 paediatric sites over a 2-year period. Patients who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors will be considered as one unique patient Approximately 10 EU/EEA countries are planned to engage in this study.

The feasibility to reach this target sample size is based on the previous experience in the DE paediatric VTE clinical trial program (see Section 8.2) and data from existing registries [R11-4525].

In the DIVERSITY study with acute VTE study population from 99 globally initiated sites, 65 were active. However, only 15 of these sites enrolled 35 children under 2 years of age with acute VTE within an approximate one-year enrolment period. In the long-term secondary VTE prevention study, from 62 active sites, 6 sites enrolled 9 patients under 2 years of age within approximately one year. Most of the young patients were enrolled from the sites outside EEA. However, in contrast to the current PASS, selection of the sites in these studies was not initially focused on their ability to enrol children under 2 years of age.

8.6 DATA MANAGEMENT

Newly collected data and/or data collected from medical records will be entered by the site directly in an electronic data capture (EDC) system via an Internet portal. All participating sites will have access to the data entered regarding the individual site of its own enrolled subjects. All sites will be fully trained on using the online data capture system, including the electronic case report form completion guidelines. A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection and validation. Real time data cleaning will be performed through EDC. The eCRFs will include programmable edit checks to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous at the time of data entry. The selected vendor will coordinate the data collection and data management including the necessary quality measures, according to the vendor standard operating procedures (SOPs).

Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).

8.7 DATA ANALYSIS

The statistical analysis plan for the study is summarized below. Full details of the statistical analysis will be documented in the SEAP, which will be finalized before the end of data collection.
Safety outcomes from this single-arm study will be interpreted in the context of findings from the paediatric clinical developmental program, i.e., acute VTE treatment (DIVERSITY) and secondary VTE prevention studies.
All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.4 or higher ([redacted]).

8.7.1 Main analysis

As this is a descriptive non-interventional, single-arm study, no hypotheses will be tested, rather all variables will be presented in summary using descriptive statistics (absolute and relative frequencies, means, standard deviations, medians, ranges, minimum and maximum values, 95% confidence intervals [CI] and incidences as appropriate for the nature of the variables (i.e., categorical, or continuous))

Safety outcomes will be summarized as incidence with 95% CIs (using Wilson method). All AE/ verbatim terms will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Analysis of AEs and other outcomes will be based on treatment emergent events and on all patients, who were treated with dabigatran at least once. Treatment-emergent events are defined as events occurring from start of DE administration (index date) up to DE administration discontinuation + 3 days of Residual Effect Period (REP) or switch to other anticoagulation therapy or planned end of observation time, whatever occurs earlier.
Concomitant medications will be coded according to the World Health Organisation Drug Dictionary (WHO-DD).

8.7.2 Further analysis

To assess the representativeness of the study cohort, the screening log will be summarized for screening failures and eligible patients who enter the study.

8.7.3 Safety Analysis

Analysis of AEs is described in Section 8.7.1 as incidence of AEs constitute secondary endpoints of this study.
Occurrence of recurrent VTE, Post-Thrombotic Syndrome, VTE related death and all cause of death will be identified from the study database via AE/preferred term-based search strategies and will be descriptively summarized.

8.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the NIS-DMRP.

High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

A quality assurance audit/inspection of this study may be conducted by the Sponsor or Sponsor's designees or by IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records for the consenting paediatric patients, the investigator's study-related files and correspondence, and the informed consent documentation of the paediatric cohort study only.

8.9 LIMITATIONS OF THE RESEARCH METHODS

Potential limitations of the study design and measures proposed to address them include the following:

- Descriptive analysis and absence of a comparator group due to feasibility reasons.
- Recruitment time is strongly dependent on the market uptake of DE pediatric formulations and on market availability in each country). The VTE treatment/secondary VTE prevention patient population is heterogeneous, and composition of this population might limit the interpretation of the study result (generalizability and comparability to other VTE population might be limited).
- Some limitations with regard to data completeness may occur in relation with the type and completeness of the information captured in the medical records. Measures to ensure the completion of the eCRF is conducted in a systematic, professional, and unbiased manner include:
    - eCRF completion guidelines will provide consistent instructions on completion of the eCRF,
    - missing data will be followed up on during remote or on-site monitoring contacts.

8.10 OTHER ASPECTS

Not applicable.

8.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

8.10.2 Study records

Electronic Case Report Forms (eCRFs) for individual patients will be provided by the sponsor via remote data capture.

8.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are contained in the patient's medical record and filed at the investigator's site.

Data reported on the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Sponsor before any destruction of medical records of study participants.

For eCRFs all data must be derived from source documents.

8.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g., US FDA). BI study staff and auditor may review all CRFs/eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.10.2.1.

8.10.3 Completion of study

The EC/competent authority in each participating EU/EEA member state needs to be notified about the end of the study (last patient/patient out, unless specified differently in Section 8.2) or early termination of the study.

8.10.4 Protocol deviations

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, the ICH Good Clinical Practice (GCP) guidelines (May 9, 1997) as they apply to post-marketing, observational studies; the Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol.

9.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and

Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from the patient's legally accepted representative per GCP, GPP and according to the regulatory and legal requirements of the participating country, if applicable.

The study will be registered on ENCePP and clinicaltrials.gov before the study initiation.

9.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1 DEFINITIONS OF ADVERSE EVENTS

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

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any

suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)
The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g., the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

10.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator should document any AEs, irrespective of causal relationship to DE intake into the EDC system for each patient throughout full study period. The investigator should maintain and keep detailed records of all AEs in their patient files.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases, and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**
- A **plausible time to onset of the event** relative to the time of drug exposure
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g., preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g., Stevens-Johnson syndrome).
- An indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g., after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

Not applicable.

Collection of AEs

The study design is of a non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason, the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF from signing the informed consent onwards until the end of the study:

- all AEs and SAEs,

All AEs including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

Expedited Reporting of AEs to Pharmacovigilance

The following must be reported by the investigator on the NIS AE form from signing the informed consent onward until the end of study and provided to BI unique entry point:

Type of Report	Timeline
All **SAEs** in patients exposed to dabigatran etexilate	immediately within 24 hours
All **non-serious AEs** in patients exposed to dabigatran etexilate	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate eCRF page and the NIS AE form.

10.3 REPORTING TO HEALTH AUTHORITIES

Adverse Event reporting to regulatory agencies will be done by the Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The protocol summary, study status, and report(s) will be included in regulatory communications in line with regulations in respective countries with the EU dabigatran RMP, Periodic Safety Update Reports, and other regulatory milestones and requirements, including communications with the Committee for Medicinal Products for Human Use.
In the case of communications in other settings (such as conferences or publications), abstracts, presentations, and manuscripts will be prepared in accordance with the guidelines of the International Society for Pharmacoepidemiology (2007) and the International Committee of Medical Journal Editors (2013).

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

12. REFERENCES

12.1 PUBLISHED REFERENCES

P08-05411 Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet 2008; 47: 285–95

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12.2 UNPUBLISHED REFERENCES

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

All investigators including country coordinating investigators with contact details will be kept in Trial Master File and Investigator Site File.

Stand-alone documents are not applicable.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

A copy of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study protocols available at website: encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

“Study start” means “Start of data collection”
“Study progress” means “Progress report(s)”
“Study completion” means “End of data collection”
“Reporting” means “Final report of the study results”

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	**Local NIS**
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMMA	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X

** After review by Global TM for function*

Study Title: Safety of dabigatran etexilate (DE) for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: a prospective European non-interventional cohort study based on new data collection.

Study Number: 1160.307

Protocol Version: 3.0

APPROVAL / SIGNATURE PAGE

Document Number: c35920658 **Technical Version Number:3.0**

Document Name: non-interventional-study-protocol-1160-307

Title: Safety of dabigatran etexilate (DE) for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: a prospective European non-interventional cohort study based on new data collection

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	[redacted]	16 Jan 2024 11:42 CET
Approval-Therapeutic Area [redacted]		16 Jan 2024 11:45 CET
Approval		17 Jan 2024 08:18 CET
Approval-Biostatistics		17 Jan 2024 15:13 CET
Approval-[redacted] Safety Evaluation Therapeutic Area		05 Feb 2024 10:20 CET
Approval-On behalf of [redacted] or VP or Director		06 Feb 2024 11:41 CET
Approval-Team Member Medical Affairs		06 Feb 2024 14:20 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**