Boehringer Ingelheim

Observational and Non-Interventional Study (ONIS) Report

Global ID:	206893_10940773
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
Version identifier of the interim/final study report:	1.0
Date of last version of the final study report:	NA
PASS:	Yes
EU PAS register number:	EUPAS47909
Active substance:	Dabigatran
Medicinal product:	Pradaxa®
Product reference:	BIBR 1048 MS
Procedure number:	NA
Joint PASS:	No
Research question and objectives:	Limited safety data are 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 was 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 Adverse Events (AEs). • To estimate the incidence of SAEs. Further objective: • To assess acceptability and tolerability of paediatric formulation.
Countries of study:	European Economic Area (EEA) member states
Author:	[redacted] Tel.: [redacted] Fax: Email: [redacted]
Marketing authorisation holder:	[redacted]
MAH contact person:	[redacted] Tel.: [redacted] Fax: Email: [redacted]
Date	25 Nov 2024

1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Report date: 25 Nov 2024	**Study number:** 1160.307	**Version/Revision:** 1.0/NA	**Version/Revision date:** 1.0/NA
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.		
Keywords:	Dabigatran etexilate, paediatric formulation, anticoagulant drugs, venous thromboembolism in children, paediatric patients from birth to less than 2 years of age, non-interventional cohort study.		
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 haemostasis precludes complete extrapolation of adult efficacy and safety data to children, particularly those of the youngest age group of neonates and infants. In hospitalised children, a significant increase of 70% in VTEs has been noted. 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. 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. However, limited evidence is available for the 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 non-interventional cohort study was planned to obtain more safety data of dabigatran in children under 2 years of age. The results from this Post-Authorisation Safety Study (PASS) were planned to be interpreted in the context of the findings from the paediatric clinical development program.		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Report date: 25 Nov 2024	**Study number:** 1160.307	**Version/Revision:** 1.0/NA	**Version/Revision date:** 1.0/NA
Research question and objectives:	Limited safety data are 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 was 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 Adverse Events (AEs). • To estimate the incidence of Serious Adverse Events (SAEs). Further objective: • To assess acceptability and tolerability of paediatric formulation.		
Study design:	This was 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 was designed to collect and evaluate DE safety in the context of routine anticoagulation care provided in the European Economic Area (EEA) member states for children under 2 years of age. The duration of the study was planned to be up to 2 years from the date of study initiation with the goal to enrol 50 evaluable patients under DE administration. Approximately 10 EEA member states were planned to engage in this study. Safety outcomes were planned to 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 could have been followed by secondary VTE prevention due to unresolved VTE risk factors. The overall duration of the study observational period for any patient was not to exceed a 6-month period of anticoagulation. If acute treatment was		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Report date: 25 Nov 2024	**Study number:** 1160.307	**Version/Revision:** 1.0/NA	**Version/Revision date:** 1.0/NA
	followed by anticoagulation for prevention of recurrent VTE, the maximal period in the study was planned to be 6 months. In this situation, the index date for start of anticoagulation for prevention of recurrent VTE was to be based on investigator judgment or after 3 months of treatment for acute VTE, whichever occurred earlier. Anticoagulation of more than 6 months' duration, if required due to the presence of unresolved VTE risk factors, was not planned to be covered in this study setting. The study was observational and did not entail any change in prescribing pattern or management strategies, which were left to the discretion of the treating physician. According to the Non-Interventional Study concept no special evaluation procedure was required.		
Setting:	**<u>Study periods</u>** After informed consent patients were planned to be screened for enrolment into the study. A Screening Log to ensure consecutive screening and enrolment was planned to be used so that all eligible patients under 2 years with an indication for anticoagulation were identified. If a patient met all study entry criteria, a baseline part of the Screening/Baseline visit was planned to be conducted, and the patient was to enter an observational study period. The observational study period for a patient was 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 the 6 months' observation time, whichever occurred earlier. It was not planned to follow patients outside the observational period. A patient who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors was to be considered as one unique patient. However, safety outcomes of each anticoagulation period were planned to be evaluated within the corresponding cohort. Data collection visits were 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):		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Report date: 25 Nov 2024	**Study number:** 1160.307	**Version/Revision:** 1.0/NA	**Version/Revision date:** 1.0/NA

- 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 were planned to have 2 follow-up visits: the first at the end of DE treatment for acute VTE, and the second at discontinuation of DE for secondary VTE prevention or after a total of 6 months of DE administration, whichever occurred first. The Final Study Visit was defined as a follow-up visit conducted after the end of the observational period.

Study sites

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

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

Neonates and infants with acute VTE requiring DE administration were localised in the following paediatric units:

- neonatology departments, where target conditions were 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 were central line/implantable devices related-VTE, cyanotic congenital heart disease, venous malformations, leukaemias etc.

Patients who required anticoagulation for secondary VTE prevention were expected to be evaluated mostly in paediatric haematology, paediatric cardiology, and paediatric cardio-surgery departments.

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Report date: 25 Nov 2024	**Study number:** 1160.307	**Version/Revision:** 1.0/NA	**Version/Revision date:** 1.0/NA
	During the approximate 1.5-year enrolment period every effort was made to support investigators to enrol paediatric patients requiring dabigatran anticoagulation in this study. These efforts taking into account the non-interventional character of the study included communications with investigators using digital resources and face to face communications, and presentation of the results and enrolment strategies of the previous published studies on DE, focused on early age children.		
Subjects and study size, including dropouts:	The study sample size was based on the anticipated usage of DE for VTE treatment and prevention. Overall, 50 patients under 2 years of age were planned to be enrolled in the study. Approximately 30 paediatric study sites with experience in VTE anticoagulation treatment and prevention were planned to be selected for the PASS in EEA member states. Approximately 10 EEA member states were planned to engage in this study. Paediatric patients under 2 years of age, who could have been considered for anticoagulation with DE due to acute VTE, were expected to be treated in neonatology, paediatric general surgery, cardiac surgery, or intensive care units. Paediatric patients with anticoagulation with DE for the prevention of recurrent VTE were expected to be evaluated mostly by paediatric haematologists in paediatric haematology units. Inclusion criteria: • Written informed consent from parents/care givers, • Children from birth to < 2 years of age, • Initiation of DE administration according to the EU DE Summary of Product Characteristics (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 randomised controlled trial or use of investigational product, • Any contraindications to DE according to the EU SmPC.		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Report date: 25 Nov 2024	**Study number:** 1160.307	**Version/Revision:** 1.0/NA	**Version/Revision date:** 1.0/NA
	Safety outcomes were planned to be collected from 50 patients overall anticoagulated with DE for acute VTE treatment and/or prevention of recurrent VTE due to presence of unresolved clinical VTE risk factor(s). The paediatric population was planned to be accordingly stratified into 2 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 were to be considered as one unique patient. However, each anticoagulation period was planned to be evaluated within the corresponding cohort.		
Variables and data sources:	Detailed information on paediatric patients under 2 years of age and DE administration was planned to 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, Intensive Care Unit, 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, diagnostic scale used and score should be indicated, • VTE clinical risk factor(s),		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Report date: 25 Nov 2024	**Study number:** 1160.307	**Version/Revision:** 1.0/NA	**Version/Revision date:** 1.0/NA

- Initial DE dosage and formulation if a patient initiated DE treatment.

At Follow up:

- Incidence of any bleeding event defined as 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 was defined as the overall ability and willingness of the patient to use the medicinal product as intended; tolerability was measured as premature treatment discontinuation, and adherence to trial medication.

The safety data were planned to 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 of REP or planned end of the 6 months' observation time, whichever occurred earlier.

Patients who continued secondary VTE prevention after acute VTE treatment were planned to have 2 follow-up visits: the first at the end of DE treatment for acute VTE, and the second at discontinuation of DE for secondary VTE prevention or after a total of 6 months of DE administration, whatever occurred first.

All data were to be obtained by qualified clinicians according to the standard medical practice.

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

All sites were to be fully trained for using the EDC system and BI AE/SAE reporting procedure. It was to be the PI's responsibility to ensure for his/her

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Report date: 25 Nov 2024	**Study number:** 1160.307	**Version/Revision:** 1.0/NA	**Version/Revision date:** 1.0/NA
	site the accuracy of the data provided to the program by any site staff that were trained for the program data collection.		
Results:	This study aimed to enrol 50 patients under 2 years of age with VTE across 30 specialised sites in 10 European countries. After major efforts to identify appropriate sites who were willing to participate in the study 19 sites across 9 countries finally agreed and were selected. The study enrolment was finally discontinued at the end of the pre-defined enrolment period on 31 May 2024; no patients could be screened/enrolled.		
Discussion:	The study encountered significant recruitment challenges for site identification and patient enrolment: 1) Lack of availability of the oral solution (OS) formulation particularly important for population of infants and neonates. This formulation was never introduced to the markets due to a negative outcome of a human factor study as reported with the procedure EMEA/H/C/000829/II/0144. The OS formulation was subsequently deregistered in December 2023 following the approval of procedure EMEA/H/C/000829/II/0147/G. The absence of the OS led to the exclusion of neonates and young infants, who have the highest rate of VTE, which narrowed significantly the target patient population of this study. 2) Insufficient scientific interest among potential investigators in light of the availability of an alternative paediatric treatment, namely Xarelto® (rivaroxaban), for the target population. 3) An overall low incidence of VTE in paediatric patients. Additionally, some PIs expressed hesitation in prescribing DE due to limited clinical experience with the drug. These factors collectively contributed to challenges in site selection and investigator engagement, and potentially affected the study's ability to recruit the target patient population negatively. Pre-screening was conducted at 16 sites; however, patient enrolment was primarily impeded by 1) dosage issues (no suitable dosage was available for low-weight patients); 2) swallowing difficulties (no OS formulation was		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate			
Report date: 25 Nov 2024	**Study number:** 1160.307	**Version/Revision:** 1.0/NA	**Version/Revision date:** 1.0/NA
	available); 3) financial considerations, including treatment costs and reimbursement issues in some countries. The study enrolment was finally discontinued on 31 May 2024, at the end of the pre-defined enrolment period; no patients could be screened/enrolled. Considering the multi-factorial reasons leading to the infeasibility of conducting this study, a further prolongation of the screening/enrolment phase would not have been productive. In conclusion, the objective of this PASS which was 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 could not be accomplished for feasibility reasons. The availability of alternative paediatric treatments on the market, current clinical practices, investigator preferences, and the non-availability of the DE OS formulation collectively presented significant obstacles. Given these challenges, any future attempt to conduct a similar study is highly likely to encounter similar feasibility issues.		
Marketing Authorisation Holder(s):	[redacted]		
Names and affiliations of principal investigators:	[redacted] Tel: [redacted] Email: [redacted]		