Non-Interventional Study (NIS) Protocol

Document Number:	c36960571-02
BI Study Number:	1160-0309
BI Investigational Product(s):	dabigatran etexilate (DE)
Title:	Safety and effectiveness of Pradaxa oral pellet formulation for treatment of acute venous thromboembolic events (VTE) and/or for risk reduction of recurrence of VTE in pediatric patients aged 3 months to less than 12 years in a real world setting: a prospective non-interventional study conducted in the United States
Brief lay title:	A study in the United Sates that looks at the safety and effectiveness of Pradaxa Pellets in children aged 3 months to less than 12 years who need treatment of a blood clot or who have had a blood clot and are at risk of developing another blood clot.
Protocol version identifier:	Version 2.0
Date of last version of protocol:	Not applicable
PASS:	Yes
EU PAS register number:	EUPASS 104734
Active substance:	dabigatran etexilate
Medicinal product:	dabigatran etexilate oral pellet formulation
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	Boehringer Ingelheim Pharmaceuticals, Inc.
Joint PASS:	No
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Research question and objectives:	The main research question of this study is to obtain further safety and effectiveness data on Pradaxa Pellets in children aged 3 months to less than 12 years in a routine clinical practice setting. Primary objective: To estimate the cumulative incidence of clinically relevant bleeding events defined as the composite of Major bleeding events (MBE) and clinically relevant non-major (CRNM) bleeding events (according to recommendations from the Pediatric and Neonatal Thrombosis & Hemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [ISTH Pediatric SSC] (P24-01853). *Major bleeding defined as:* • fatal bleeding • clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL (20 g/L) in a 24-hour period • critical site bleeding such as retroperitoneal, pulmonary, pericardial, intracranial, or otherwise involved the central nervous system • bleeding that requires and intervention via invasive procedure such as surgery in an operating suite, interventional radiology, or endoscopy • overt bleeding for which a reversal agent is administered (i.e., vitamin K, plasma, prothrombin complex concentrate, protamine, andexanet alfa, or idarucizumab *CRNM bleeding defined as:* • overt bleeding for which a blood product was administered, and does not meet the criteria for major bleeding • bleeding that results in a medical or procedural intervention not meeting major bleeding criteria, including a medication change (reducing, holding, or changing anticoagulation or addition of new medication). Examples include: hormonal therapy, TXA, iron, nasal packing, nasal cautery, and LARC placement • bleeding that results in hospitalization or transfer to increased level of care Secondary objectives: 1. Efficacy defined as • occurrence of recurrent VTE including both symptomatic and asymptomatic events, wherein symptomatic recurrent VTE is defined as radiologically-confirmed new venous thrombotic or embolic burden ≥7 days post-diagnosis of the index VTE, accompanied by signs and/or symptoms

attributable to the new thromboembolism and asymptomatic VTE is defined by new thrombotic/embolic burden as disclosed by comparison of end-of-treatment imaging versus baseline imaging of the vascular region involved by the index VTE

- mortality related to thrombotic or thromboembolic events

2. Occurrence of all bleeding events defined as composite of major bleeding, CRNM bleeding events and minor bleeding events (defined as any overt or macroscopic evidence of bleeding that does not fulfil the criteria for major bleeding, CRNM bleeding, or patient important bleeding without intervention, defined as bleeding for which medical attention is sought (phone call, telehealth, clinic, or ED visit) but does not result in hospitalization, increased level of inpatient care, or an intervention by the medical team, according to recommendations from the ISTH Pediatric SSC (P24-01853).
3. Occurrence of post-thrombotic syndrome (PTS) as evaluated by the Villalta Scale Modified for Children, the Manco-Johnson instrument, or other validated pediatric PTS instrument employed in routine clinical care, in accordance with recommendations from the ISTH Pediatric SSC
4. Incidence of adverse events (AEs), including AEs for which treatment was discontinued, and serious adverse events (SAEs)
5. Thrombotic burden at the end of the treatment period vs baseline, i.e. image based resolution status of the thrombus (complete response, partial response, stable disease, progressive disease) using appropriate method and the same method as the baseline evaluations, when appropriate

[redacted]

In addition the following will be collected:

- Patient demographics, [redacted]

	[redacted] duration of use and compliance with treatment, [redacted]
Country of study:	United States
Author:	[redacted]
Marketing authorisation holder(s):	[redacted]
In case of PASS, add: **MAH contact person:**	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	Signature to be obtained electronically, will appear at end of document.
Date:	26 Apr 2024

1. TABLE OF CONTENTS

[redacted]

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
BMI	Body Mass Index
CA	Competent Authority
[redacted]	[redacted]
CI	Confidence Interval
CRF	Case Report Form
eCRF	Electronic Case Report Form
CRNM	Clinically Relevant Non-Major Bleeding Event
DE	Dabigatran Etexilate
DOAC	Direct Oral Anticoagulants
DVT	Deep Venous Thrombosis
EDC	Electronic Data Capture
EOS	End of Study
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FPI	First Patient In
GPP	Good Pharmacoepidemiology Practice
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LPI	Last Patient In
LPO	Last Patient Out
MAH	Marketing Authorization Holder
MBE	Major bleeding events
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
NIS-DMRP	NIS- Data Management and Review Plan
NLM	National Library of Medicine
PASS	Post-Authorization Safety Study
PE	Pulmonary Embolism
PDE	Paradoxical Embolism
PI	Principal Investigator
PTS	Post-thrombotic Syndrome
RCT	Randomized Clinical Trial
REP	Residual Effect Period
SAE	Serious Adverse Event
VTE	Venous Thromboembolic Event
SOP	Standard Operating Procedure

3. RESPONSIBLE PARTIES

Principal (Coordinating) Investigator	[redacted]
Team Member Medical Affairs (TMMA)	[redacted]
Asset Benefit Risk Team (ABRT)	[redacted]
BI NIS Lead	[redacted]
Project Statistician	[redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa Pellets			
Name of active ingredient: dabigatran etexilate			
Protocol date: 03 May 2023	**Study number:** 1160-0309	**Version/Revision:** 2.0	**Version/Revision date:** 26 Apr 2024
Title of study:	Safety and effectiveness of Pradaxa oral pellet formulation for treatment of acute venous thromboembolic events (VTE) and/or for risk reduction of recurrence of VTE in pediatric patients aged 3 months to less than 12 years in a real world setting: a prospective non-interventional study conducted in the United States.		
Rationale and background:	Pradaxa Pellets are a direct thrombin inhibitor that was recently approved by the Food and Drug Administration (FDA) in the United States for the treatment of VTE and to reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years. Pradaxa Pellets address the unmet need for an age-appropriate treatment option and are an alternative to other anticoagulation agents, such as heparin and Vitamin K antagonists that are frequently used in children and that present with many challenges [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 overall safety and efficacy of dabigatran in pediatric patients was established in 2 clinical trials; the data were consistent across all pediatric age groups and comparable to the clinical outcomes in adult patients with VTE who were treated with dabigatran [R13-3609, P19-11322, P20-07911, P13-16985]. However, further safety and efficacy data in a real world setting in the United States on Pradaxa Pellets in children aged 3 months to less than 12 years are requested by the US FDA.		

Research question and objectives:	The main research question of this study is to obtain further safety and effectiveness data on Pradaxa Pellets in children aged 3 months to less than 12 years in routine clinical practice setting. This study will include three types of patients: 1) Patients who need treatment of VTE and who have been treated with a parenteral anticoagulant for at least 5 days (hereinafter referred to "VTE treatment") 2) Patients who need treatment to reduce the risk of recurrence of VTE and who have been previously treated (hereinafter referred to "risk reduction of recurrence of VTE") 3) Patients who are taking Pradaxa Pellets for VTE treatment or to reduce the risk of VTE recurrence or in any manner not aligned with prescribing information (any off-label use) Primary objective: To estimate the cumulative incidence of clinically relevant bleeding events defined as the composite of Major bleeding events (MBE) and clinically relevant non-major (CRNM) bleeding events (according to recommendations from the Pediatric and Neonatal Thrombosis & Hemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [ISTH Pediatric SSC]) (P24-01853). *Major bleeding defined as:* • fatal bleeding • clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL (20 g/L) in a 24-hour period • critical site bleeding such as retroperitoneal, pulmonary, pericardial, intracranial, or otherwise involved the central nervous system • bleeding that requires and intervention via invasive procedure such as surgery in an operating suite, interventional radiology, or endoscopy • overt bleeding for which a reversal agent is administered (i.e., vitamin K, plasma, prothrombin complex concentrate, protamine, andexanet alfa, or idarucizumab *CRNM bleeding defined as:* • overt bleeding for which a blood product was administered, and does not meet the criteria for major bleeding • bleeding that results in a medical or procedural intervention not meeting major bleeding criteria, including a medication change (reducing, holding, or changing anticoagulation or addition of new medication). Examples include: hormonal therapy, TXA, iron, nasal packing, nasal cautery, and LARC placement • bleeding that results in hospitalization or transfer to increased level of care

Secondary objectives:

1. Efficacy defined as
    - occurrence of recurrent VTE including both symptomatic and asymptomatic events, wherein symptomatic recurrent VTE is defined as radiologically-confirmed new venous thrombotic or embolic burden ≥7 days post-diagnosis of the index VTE, accompanied by signs and/or symptoms attributable to the new thromboembolism and asymptomatic VTE is defined by new thrombotic/embolic burden as disclosed by comparison of end-of-treatment imaging versus baseline imaging of the vascular region involved by the index VTE
    - mortality related to thrombotic or thromboembolic events

2. Occurrence of all bleeding events defined as composite of major bleeding, CRNM bleeding events and minor bleeding events (defined as any overt or macroscopic evidence of bleeding that does not fulfil the criteria for major bleeding, CRNM bleeding, or patient important bleeding without intervention, defined as bleeding for which medical attention is sought (phone call, telehealth, clinic, or ED visit) but does not result in hospitalization, increased level of inpatient care, or an intervention by the medical team, according to recommendations from the ISTH Pediatric SSC (P24-01853).
3. Occurrence of post-thrombotic syndrome (PTS) as evaluated by the Villalta Scale Modified for Children, the Manco-Johnson instrument, or other validated pediatric PTS instrument employed in routine clinical care, in accordance with recommendations from the ISTH Pediatric SSC
4. Incidence of adverse events (AEs), including AEs for which treatment was discontinued, and serious adverse events (SAEs)
5. Thrombotic burden at the end of the treatment period vs baseline, i.e. image based resolution status of the thrombus (complete response, partial response, stable disease, progressive disease) using appropriate method and the same method as the baseline evaluations, when appropriate

[redacted]

In addition the following will be collected:

- The patient demographics, [redacted] recurrence of VTE while on treatment (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, DVT, PE and PDE, thrombus

	progression), duration of use and compliance with treatment, [redacted]

Study design:	This is an observational and non-interventional national multi-center study based on newly collected data of pediatric patients receiving anticoagulation treatment with Pradaxa Pellets for the treatment of VTE and/or for the reduction in the risk of recurrence of VTE. The study is designed to collect and evaluate Pradaxa Pellets safety and effectiveness in the context of routine anticoagulation care provided in the United States in children aged 3 months to less than 12 years. The overall duration of the study will be up to 5 years with the goal to enroll 300 patients under Pradaxa Pellets administration. Individual patients will be followed for 12 months after initiation of Pradaxa Pellets treatment. Collection of existing data back to the time point of therapy will be done for patients enrolled in the trial after the date of treatment onset. Safety and efficacy outcomes will be collected for a period of up to 12 months from the day of Pradaxa Pellets initiation. The overall duration of the study observational period for any patient will not exceed 12-month period of anticoagulation. Anticoagulation of more than 12-month duration, if required due to the presence of unresolved VTE risk factors, will not be covered in this study setting. Data collection timepoints are planned for both VTE treatment and risk reduction of recurrent VTE groups as follows: - Baseline: initiation of Pradaxa Pellets administration - Follow up: o At approximately 6 weeks, 3, 6, and 12 months of Pradaxa Pellets administration. o End of Study (EOS) visit is defined as a follow up 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. Patient contacts can be in person, remote or telephone contacts, with a remote consenting procedure used at time of enrollment if available at that site. If the patient is identified and enrolled after beginning treatment with Pradaxa Pellets, the past medical records may be used to obtain information from the date of treatment onset until the date of enrollment. Data will be collected at each time point via both patient questions and review of relevant medical records as appropriate. If additional information is needed after review of medical records by the PI and the PI is not the prescribing physician, the prescribing/treating physician will be contacted to provide the additional information if possible. This trial will be conducted as a hybrid of both a traditional registry trial, in conjunction with the [redacted]

	registry and prescribers not currently members of [redacted] will be invited to join this registry as well. In addition to the [redacted] patient recruitment, patient recruitment will be facilitated via the specialty pharmacy and distributor for Pradaxa Pellets. These entities may provide prescriber information to the sponsor (prescriber name and institution or only institution) and outreach will be conducted to notify the prescriber of the study and how to participate. The goal will be to attempt contact with every prescriber (or prescribing institution) to inform them of the study and provide information on enrollment for their patient(s). Prescribers can choose to join the registry trial as a study site or they will be provided with informational materials to provide to the patient with instructions on how to enroll in the trial at the metasite. In addition to multiple traditional study sites participating in the registry, one registry site will be set up as a metasite. If a prescriber is not interested in participating in the registry, they may refer the patient/caregiver to the metasite. The metasite will then consent and enroll the patient into the trial via remote consenting and remote study visits, and obtain medical records from the treating physician(s) and query the treating physician if needed to answer all registry questions. This outreach to all prescribers and the metasite option is intended both to facilitate enrollment and to limit selection bias by recruiting patients after Pradaxa Pellets treatment has been initiated and allowing patient participation even if the prescriber is not interested in trial participation.

Population:	Pediatric patients aged 3 months to less than 12 years, who may be considered for anticoagulation with Pradaxa Pellets due to VTE, are usually treated in neonatology, pediatric general surgery, cardiac surgery, general pediatric inpatient and hematology wards, or intensive care units. Pediatric patients with anticoagulation with DE for the prevention of recurrent VTE are usually evaluated by pediatric hematologists in pediatric hematology units.
	
	Inclusion criteria:
	
	- Pediatric patients aged 3 months to less than 12 years at the time of Pradaxa Pellets initiation
	- Written informed consent from parents/care givers and patient assent if age appropriate
	- Initiation of Pradaxa Pellets administration as either initial or subsequent treatment for:
	  o Treatment of VTE
	  o Treatment to reduce the risk of recurrence of VTE
	
	Exclusion criteria:
	
	- Participation in any randomized clinical trial or use of investigational product. Note: participation in any other observational study is not an exclusion
	- Any contraindications to Pradaxa Pellets according to the US Prescribing Information.
	- Previous participation in this trial
	
	Safety and efficacy outcomes will be collected from overall 300 patients anticoagulated with Pradaxa Pellets for VTE treatment and/or risk reduction of recurrent VTE due to presence of unresolved clinical VTE risk factor(s).
	
	The pediatric population will be accordingly recruited from three groups:
	
	1) Patients who need treatment of VTE and who have been treated with a parenteral anticoagulant for at least 5 days (hereinafter referred to “VTE treatment”)
	2) Patients who need treatment to reduce the risk of recurrence of VTE and who have been previously treated (hereinafter referred to “risk reduction of recurrence of VTE”
	3) Patients who are taking Pradaxa Pellets for VTE treatment or to reduce the risk of VTE recurrence and in a manner not aligned with prescribing information (off-label use)

Variables:	Detailed information on pediatric patients aged 3 months to less than 12 years and Pradaxa Pellets administration will be collected as follows: At Baseline: - Demographics (e.g. age, weight, Body Mass Index (BMI), gender, race, ethnicity) [redacted] At Follow up: - Occurrence of any bleeding event defined as Major bleeding events (MBE), clinically relevant non-major (CRNM) bleeding events, Patient important bleeding without intervention or minor bleeding events including location(s) - Characteristics of all non-contiguous thrombosis and all recurrent thrombosis, with any associated chronic or acute VTE risk factors [redacted]

	[redacted] - Occurrence of AEs / SAEs [redacted] - Duration of Pradaxa Pellets administration and compliance with treatment [redacted] The safety and efficacy data will be evaluated based on the study observational period defined as the initiation of Pradaxa Pellets administration onwards up until Pradaxa Pellets administration discontinuation + 3 days of residual effect period (REP) or switch to other anticoagulation therapy or planned end of observation time whatever occurs earlier.

Data sources:	Newly collected data and/or data collected from medical records will be entered by the site directly in an electronic data capture system (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 are trained for the program data collection.
Study size:	The study sample size is based on the request from the FDA to include a minimum of 300 patients aged 3 months to less than 12 years.
Data analysis:	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, [redacted] and incidences as appropriate for the nature of the variables (i.e. categorical or continuous)). Safety and effectiveness outcomes will be summarized as incidence [redacted] All AE/ verbatim terms will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA). [redacted] Since there is no control group, data will be contextualized by using data from the Dabigatran pediatric clinical development program and other available evidence. 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/First Patient In (FPI): 22 Sep 2023, Last Patient In (LPI): 28 Jun 2028, End of data collection / Last Patient Out (LPO): 28 Jun 2029 Final report: 30 Nov 2029.

5. AMENDMENTS AND UPDATES

Version 2.0 Changes

Protocol Section	v1.0	v2.0	Reason for Change
List of Abbreviations (2)		Added additional abbreviations.	Some abbreviations missing or new added with revision.
Abstract (4)		Updates made throughout the main protocol document were incorporated into the abstract section, where applicable.	Updated to conform with revisions in main protocol.
Research Questions and Objectives (8) and Outcomes (9.3.2)	The main research question of this study is to obtain further safety and effectiveness data on Pradaxa Pellets in children aged 3 months to less than 12 years in routine clinical practice setting. This study will include two types of patients: 4) Patients who need treatment of VTE and who have been treated with a parenteral anticoagulant for at least 5 days (hereinafter referred to "VTE treatment") 5) Patients who need treatment to reduce the risk of recurrence of VTE and who have been previously treated (hereinafter referred to "risk reduction of recurrence of VTE" Primary objective: To estimate the incidence of any bleeding events defined as Major bleeding events (MBE), clinically relevant non-major (CRNM) bleeding events or minor bleeding events (according to recommendations made by the Perinatal and Pediatric Hemostasis Subcommittee). *Major bleeding defined as:*	The main research question of this study is to obtain further safety and effectiveness data on Pradaxa Pellets in children aged 3 months to less than 12 years in routine clinical practice setting. This study will include three types of patients: 1) Patients who need treatment of VTE and who have been treated with a parenteral anticoagulant for at least 5 days (hereinafter referred to "VTE treatment") 2) Patients who need treatment to reduce the risk of recurrence of VTE and who have been previously treated (hereinafter referred to "risk reduction of recurrence of VTE") 3) Patients who are taking Pradaxa Pellets for VTE treatment or to reduce the risk of VTE recurrence or in any manner not aligned with prescribing information (any off-label use) Primary objective: To estimate the cumulative incidence of clinically relevant bleeding events defined as the	Third patient group added to capture patients that use Pradaxa Pellets off-label. Objectives and bleeding definitions updated to align with 2023 ISTH Pediatric SSC recommendations. Protocol v1.0 contained 2011 recommendations.

	• fatal bleeding • clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL (20 g/L) in a 24-hour period • bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the central nervous system • bleeding that required surgical intervention in an operating suite *CRNM bleeding defined as:* • overt bleeding for which a blood product was administered, and which was not directly attributable to the patient's underlying medical condition • bleeding that required medical or surgical intervention to restore hemostasis, other than in an operating suite. *Minor bleeding defined as:* • any overt or macroscopic evidence of bleeding that did not fulfil the criteria for either major bleeding or CRNM bleeding.	composite of Major bleeding events (MBE) and clinically relevant non-major (CRNM) bleeding events (according to recommendations from the Pediatric and Neonatal Thrombosis & Hemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [ISTH Pediatric SSC]) (P24-01853). *Major bleeding defined as:* • fatal bleeding • clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL (20 g/L) in a 24-hour period • critical site bleeding such as retroperitoneal, pulmonary, pericardial, intracranial, or otherwise involved the central nervous system • bleeding that requires and intervention via invasive procedure such as surgery in an operating suite, interventional radiology, or endoscopy • overt bleeding for which a reversal agent is administered (i.e., vitamin K, plasma, prothrombin complex concentrate, protamine,	

	Secondary objectives: 1. Lack of Effectiveness defined as • thrombotic burden at the end of the treatment period vs baseline, i.e. image-based resolution status of the thrombus (complete response, partial response, stable disease, progressive disease) using and appropriate method and the same method as the baseline evaluations, when appropriate • Mortality related to thrombotic or thromboembolic events 2. Occurrence of post-thrombotic syndrome (PTS) as chronic complication of VTE evaluated by appropriate instrument, e.g. the Villalta Scale Modified for Children after 3, 6 and 12 months of start of treatment Recurrence of VTE while on treatment (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, DVT, PE and PDE, thrombus progression) Whenever available, the events outlined above should be	andexanet alfa, or idarucizumab *CRNM bleeding defined as:* • overt bleeding for which a blood product was administered, and does not meet the criteria for major bleeding • bleeding that results in a medical or procedural intervention not meeting major bleeding criteria, including a medication change (reducing, holding, or changing anticoagulation or addition of new medication). Examples include: hormonal therapy, TXA, iron, nasal packing, nasal cautery, and LARC placement • bleeding that results in hospitalization or transfer to increased level of care Secondary objectives: 1. Efficacy defined as • occurrence of recurrent VTE including both symptomatic and asymptomatic events, wherein symptomatic recurrent VTE is defined as radiologically-confirmed new venous thrombotic	

	assessed by radiologists or other qualified clinicians using an appropriate method such as ultrasound, echocardiography, venography, or CT scan, based on the location of the thrombus and the test used to perform the baseline assessment. No adjudication committee will be involved in the assessment of the events. In addition the following will be collected: • Incidence of AEs and SAEs • Treatment discontinuation due to an AE The patient demographics, indication for therapy, underlying cause for VTE (provoked, such as indwelling central venous catheter (CVC), surgery, trauma, infection, immobilization, malignancy, vs unprovoked (no identifiable disorder or risk factor)), VTE anatomic site and extent, recurrence of VTE while on treatment (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, DVT, PE and PDE, thrombus progression), duration of use and compliance with treatment, prior antithrombotic therapy and results of blood coagulation tests when available.	or embolic burden ≥7 days post-diagnosis of the index VTE, accompanied by signs and/or symptoms attributable to the new thromboembolism and asymptomatic VTE is defined by new thrombotic/embolic burden as disclosed by comparison of end-of-treatment imaging versus baseline imaging of the vascular region involved by the index VTE • mortality related to thrombotic or thromboembolic events 2. Occurrence of all bleeding events defined as composite of major bleeding, CRNM bleeding events and minor bleeding events (defined as any overt or macroscopic evidence of bleeding that does not fulfil the criteria for major bleeding, CRNM bleeding, or patient important bleeding without intervention, defined as bleeding for which medical attention is sought (phone call, telehealth, clinic, or ED visit) but does not result in hospitalization, increased level of inpatient care, or an intervention by the medical team, according to recommendations from the ISTH Pediatric SSC (P24-01853). 3. Occurrence of post-thrombotic syndrome (PTS) as evaluated	

		by the Villalta Scale Modified for Children, the Manco-Johnson instrument, or other validated pediatric PTS instrument employed in routine clinical care, in accordance with recommendations from the ISTH Pediatric SSC 4. Incidence of adverse events (AEs), including AEs for which treatment was discontinued, and serious adverse events (SAEs) 5. Thrombotic burden at the end of the treatment period vs baseline, i.e. image based resolution status of the thrombus (complete response, partial response, stable disease, progressive disease) using appropriate method and the same method as the baseline evaluations, when appropriate [redacted] In addition the following will be collected: [redacted], recurrence of VTE while on treatment (including symptomatic and asymptomatic, contiguous progression or non-contiguous new	

		thrombus, DVT, PE and PDE, thrombus progression), duration of use and compliance with treatment, [redacted]	
Study Design (9.1)	This is a non-interventional national multi-center study based on newly collected data of pediatric patients anticoagulated with Pradaxa Pellets for treatment of VTE and/or for risk reduction of recurrence of VTE.	This is an observational and non-interventional national multi-center study based on newly collected data of pediatric patients receiving anticoagulation treatment with Pradaxa Pellets for the treatment of VTE and/or for reduction in the risk of recurrence of VTE.	Updated to align with BI ONIS definition and rest of protocol.
	Two types of patients can be considered for inclusion into the study: 1) Patients who need treatment of VTE and who have been treated with a parenteral anticoagulant for at least 5 days (hereinafter referred to "VTE treatment") – at least 50% of the patients will be recruited for this group. 2) Patients who need treatment to reduce the risk of recurrence of VTE and who have been previously treated (hereinafter referred to "risk reduction of recurrence of VTE")	Three types of patients can be considered for inclusion into the study: 1) Patients who need treatment of VTE and who have been treated with a parenteral anticoagulant for at least 5 days (hereinafter referred to "VTE treatment") 2) Patients who need treatment to reduce the risk of recurrence of VTE and who have been previously treated (hereinafter referred to "risk reduction of recurrence of VTE") 3) Patients who are taking Pradaxa Pellets for VTE treatment or to reduce the risk of VTE recurrence and in a manner not aligned with prescribing information (off-label use)	Third patient group added to capture patients that use Pradaxa Pellets off-label.
	Information on enrolled patients will be collected as follows: At Baseline: - Demographics (e.g. age, weight, BMI, gender, race, ethnicity) [redacted]	Information on enrolled patients will be collected as follows: At Baseline: - Demographics (e.g. age, weight, BMI, gender, race, ethnicity) [redacted]	Updated to include menstrual history and patient important bleeding without intervention. Also updated to align data collection timepoints.

	[redacted] At Follow up: - Occurrence of any bleeding event defined as defined as Major bleeding events (MBE), clinically relevant non-major (CRNM) bleeding events or minor bleeding events including location(s)	[redacted]	

		[redacted] At Follow up: - Occurrence of any bleeding event defined as Major bleeding events (MBE), clinically relevant non-major (CRNM) bleeding events, Patient important bleeding without intervention, or minor bleeding events including location(s) - Characteristics of all non-contiguous thrombosis and all recurrent thrombosis, with any associated chronic or acute VTE risk factors [redacted] - Occurrence of AEs / SAEs [redacted]	

		[redacted] ets administration and compliance with treatment [redacted]	
Study Population (9.2.2)	Inclusion criteria: - Written informed consent from parents/care givers and patient assent if age appropriate - Initiation of Pradaxa Pellets administration either as initial or subsequent therapy: o Treatment of VTE o Treatment to reduce the risk of recurrence of VTE	Inclusion criteria: - Pediatric patients aged 3 months to less than 12 years at the time of Pradaxa Pellets initiation - Written informed consent from parents/care givers and patient assent if age appropriate - Initiation of Pradaxa Pellets administration either as initial or subsequent therapy: o Treatment of VTE o Treatment to reduce the risk of recurrence of VTE	Updated to include age as an inclusion criterion.
Study Visits (9.2.3 – Figure 1)	Table Headers • Trial Periods • Consent • Observation Period/Data Collection Timepoints Weeks (row) • Up to 12 weeks after treatment initiation • 6 • 12 • 26 • 52 Footnotes	Table Headers • Trial Periods • Pradaxa Pellets Initiation • Observation Period/Data Collection Timepoints Weeks (row) • 6 • 12 • 26 • 52 (EoS) • Unscheduled Months (row) • 3 • 6	Updated to align with observation period and data collection timepoints referenced throughout the document. Visit windows added to guide sites on patient follow-up procedures.

	(1) All assessments except post thrombotic syndrome and SAEs will end at date of last Pradaxa dose plus 3 days or at week 52 plus 3 days, whichever is earlier. Post thrombotic syndrome and SAEs will be assessed through 12 months for all patients. (2) End of Study (EoS). (3) Patients may be consented up to 12 weeks after the initiation of treatment with Pradaxa Pellets. Medical records will be requested and data recorded for all relevant study questions back to the date of treatment initiation. (4) Medication status will included dose modifications, dates of treatment and compliance to treatment.	• 12 (EoS) • Unscheduled Observation Period Visit Windows • 6 weeks ±2 weeks • 3 months ±2 weeks • 6 months ±4 weeks • 12 months -8 weeks Unscheduled Visit Assessments • Informed consent • Post-thrombotic syndrome assessment • Bleeding-related events • Medication status • All AEs/SAEs • Concomitant therapy Informed Consent Assessment • As needed for the 6 week and 3 month visits Footnotes (1) All assessments will be assessed through 12 months for all patients unless patient withdraws their participation. (2) End of Study (EoS). (3) Patients may be consented up to 12 weeks after the initiation of treatment with Pradaxa Pellets. Medical records will be requested, and data recorded for all relevant study questions back to the date of treatment initiation. All Visit 1 procedures will be completed at the consent visit. The consent visit may be combined with Visit 2 if patient is consented at 6 weeks (±2 weeks) or with Visit 3 if patient is consented at 12 weeks. Visit 2 may be skipped if timing of consent is close to 12 weeks (4) Medication status will include dose modifications, dates of treatment and compliance to treatment. (5) Patient contact that occurs in between scheduled study visits should be recorded as an Unscheduled visit.	

		(6) If a patient withdraws their participation in the study prior to the EoS visit, the "Completion of patient population" information must be collected at their final study visit. A reasonable effort will be made to collect the reason for early termination. (7) Visit windows are provided as guidance for study implementation. All effort should be made to adhere to visit windows as instructed as patient/caregivers memories of some events may be less accurate over time. Therefore divergence from the visit window will not be captured as an important protocol deviation but only a point of discussion with the patient caregiver	
[redacted]			
	Concomitant medications will be recorded according to World Health Organisation Drug Dictionary (WHO-DD).	Concomitant medications will be recorded according to [redacted] a standardized nomenclature for clinical drugs for humans, produced by the U.S. National Library of Medicine (NLM).	Trial is utilizing the Ontology services available in [redacted] which does not currently support WHO-DD. If required by the sponsor, [redacted] will be converted to WHO-DD.
[redacted]			

[redacted]

[redacted]			
	Concomitant medications will be recorded according to World Health Organisation Drug Dictionary (WHO-DD).	Concomitant medications will be recorded according to [redacted], a standardized nomenclature for clinical drugs for humans, produced by the U.S. National Library of Medicine (NLM).	Trial is utilizing the Ontology services available in [redacted] which does not currently support WHO-DD. If required by the sponsor, [redacted] coding will be converted to WHO-DD.
Published References (13.1)		Removed: R11-4225 - Mitchell LG, Goldenberg NA, Male C, Monagle P, Nowak-Goettl U. et al. Definition of clinical efficacy and safety outcomes for clinical trials in deep vein thrombosis and pulmonary embolism in children. J Thromb Haemost 2011; 9; 1856-1858. Added: P24-01853 Whitworth H, Amankwah EK, Betensky M, Castellucci LA, Cuker A, Goldenberg NA, Male C, Rinzler E, Zia A, Raffini L. Updated guidance for efficacy and safety outcomes for clinical trials in venous thromboembolism in children: communication from the ISTH SSC Subcommittee on Pediatric and Neonatal Thrombosis and Hemostasis. J Thromb Haemost. 2023 Jun;21(6):1666-1673.	Updated to include the 2023 ISTH Pediatric SSC recommendations publication replacing the 2011 recommendations

All		Spelling and grammatical updates made throughout the document. Updates made to timelines and trial personnel.	For clarity and to provide current information.

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	22 Sep 2023
Start of data collection	31 Oct 2023
End of data collection	28 Jun 2029
Final report of study results:	30 Nov 2029

7. RATIONALE AND BACKGROUND

The FDA approval of the Pradaxa Pellets NDA includes the request for a prospective observational study to characterize the safety and effectiveness of dabigatran oral pellet formulation for the treatment of VTE and to reduce the risk of VTE in pediatric patients <12 years of age. A minimum of 300 patients were requested, with outcomes of interest to include all major and clinically relevant non-major and minor bleeding events, post-thrombotic syndrome and lack of efficacy. The FDA has requested this study as they have determined that an analysis of spontaneous post-marketing adverse events will not be sufficient to assess a signal.

8. RESEARCH QUESTION AND OBJECTIVES

The main research question of this study is to obtain further safety and effectiveness data on Pradaxa Pellets in children aged 3 months to less than 12 years in routine clinical practice setting.

Primary objective:

To estimate the cumulative incidence of clinically relevant bleeding events defined as the composite of Major bleeding events (MBE) and clinically relevant non-major (CRNM) bleeding events (according to recommendations from the Pediatric and Neonatal Thrombosis & Hemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [ISTH Pediatric SSC]) (P24-01853).

Major bleeding defined as:

- fatal bleeding
- clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL (20 g/L) in a 24-hour period
- critical site bleeding such as retroperitoneal, pulmonary, pericardial, intracranial, or otherwise involved the central nervous system
- bleeding that requires and intervention via invasive procedure such as surgery in an operating suite, interventional radiology, or endoscopy
- overt bleeding for which a reversal agent is administered (i.e., vitamin K, plasma, prothrombin complex concentrate, protamine, andexanet alfa, or idarucizumab

CRNM bleeding defined as:

- overt bleeding for which a blood product was administered, and does not meet the criteria for major bleeding
- bleeding that results in a medical or procedural intervention not meeting major bleeding criteria, including a medication change (reducing, holding, or changing anticoagulation or addition of new medication). Examples include: hormonal therapy, TXA, iron, nasal packing, nasal cautery, and LARC placement
- bleeding that results in hospitalization or transfer to increased level of care

Secondary objectives:

1. Efficacy defined as
    - occurrence of recurrent VTE including both symptomatic and asymptomatic events, wherein symptomatic recurrent VTE is defined as radiologically-confirmed new venous thrombotic or embolic burden ⩾7 days post-diagnosis of the index VTE, accompanied by signs and/or symptoms attributable to the new thromboembolism and asymptomatic VTE is defined by new thrombotic/embolic burden as disclosed by comparison of end-of-treatment imaging versus baseline imaging of the vascular region involved by the index VTE
    - mortality related to thrombotic or thromboembolic events

2. Occurrence of all bleeding events defined as composite of major bleeding, CRNM bleeding events and minor bleeding events (defined as any overt or macroscopic evidence of bleeding that does not fulfil the criteria for major bleeding, CRNM bleeding, or patient important bleeding without intervention, defined as bleeding for which medical attention is sought (phone call, telehealth, clinic, or ED visit) but does not result in hospitalization, increased level of inpatient care, or an intervention by the medical team, according to recommendations from the ISTH Pediatric SSC (P24-01853).
3. Occurrence of post-thrombotic syndrome (PTS) as evaluated by the Villalta Scale Modified for Children, the Manco-Johnson instrument, or other validated pediatric PTS instrument employed in routine clinical care, in accordance with recommendations from the ISTH Pediatric SSC
4. Incidence of adverse events (AEs), including AEs for which treatment was discontinued, and serious adverse events (SAEs)
5. Thrombotic burden at the end of the treatment period vs baseline, i.e. image based resolution status of the thrombus (complete response, partial response, stable disease, progressive disease) using appropriate method and the same method as the baseline evaluations, when appropriate

In addition the following will be collected:

- The patient demographics, indication for therapy, underlying cause for VTE (provoked, such as indwelling central venous catheter (CVC), surgery, trauma, infection, immobilization, malignancy, vs unprovoked (no identifiable disorder or risk factor)), VTE anatomic site and extent, recurrence of VTE while on treatment (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, DVT, PE and PDE, thrombus progression), duration of use and compliance with treatment, prior antithrombotic therapy and results of blood coagulation tests when available.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is an observational and non-interventional national multi-center study based on newly collected data of pediatric patients receiving anticoagulation treatment with Pradaxa Pellets for the treatment of VTE and/or for reduction in the risk of recurrence of VTE. The study is designed to collect and evaluate Pradaxa Pellets safety and effectiveness in the context of routine anticoagulation care provided in the United States in children aged 3 months to less than 12 years.

The duration of the study will be up to 5 years with the goal to enroll 300 patients under Pradaxa Pellets administration. Collection of existing data back to the time point of therapy will be done for patients enrolled in the trial after the date of treatment onset. Patients may be enrolled who are switching from another antithrombotic therapy of any type, including a different Direct Oral Anticoagulant (DOAC).

Safety and effectiveness outcomes will be collected for a period of up to 12 months from the day of Pradaxa Pellets initiation.

Three types of patients can be considered for inclusion into the study:

1) Patients who need treatment of VTE and who have been treated with a parenteral anticoagulant for at least 5 days (hereinafter referred to “VTE treatment”)
2) Patients who need treatment to reduce the risk of recurrence of VTE and who have been previously treated (hereinafter referred to “risk reduction of recurrence of VTE”)
3) Patients who are taking Pradaxa Pellets for VTE treatment or to reduce the risk of VTE recurrence and in a manner not aligned with prescribing information (off-label use)

The overall duration of the study observational period for any patient will not exceed 12-month period of anticoagulation. Anticoagulation of more than 12-month duration, if required due to the presence of unresolved VTE risk factors, will not be covered in this study setting.

Data collection timepoints are planned for both VTE treatment and risk reduction of recurrent VTE groups as follows (see Flow Chart also):

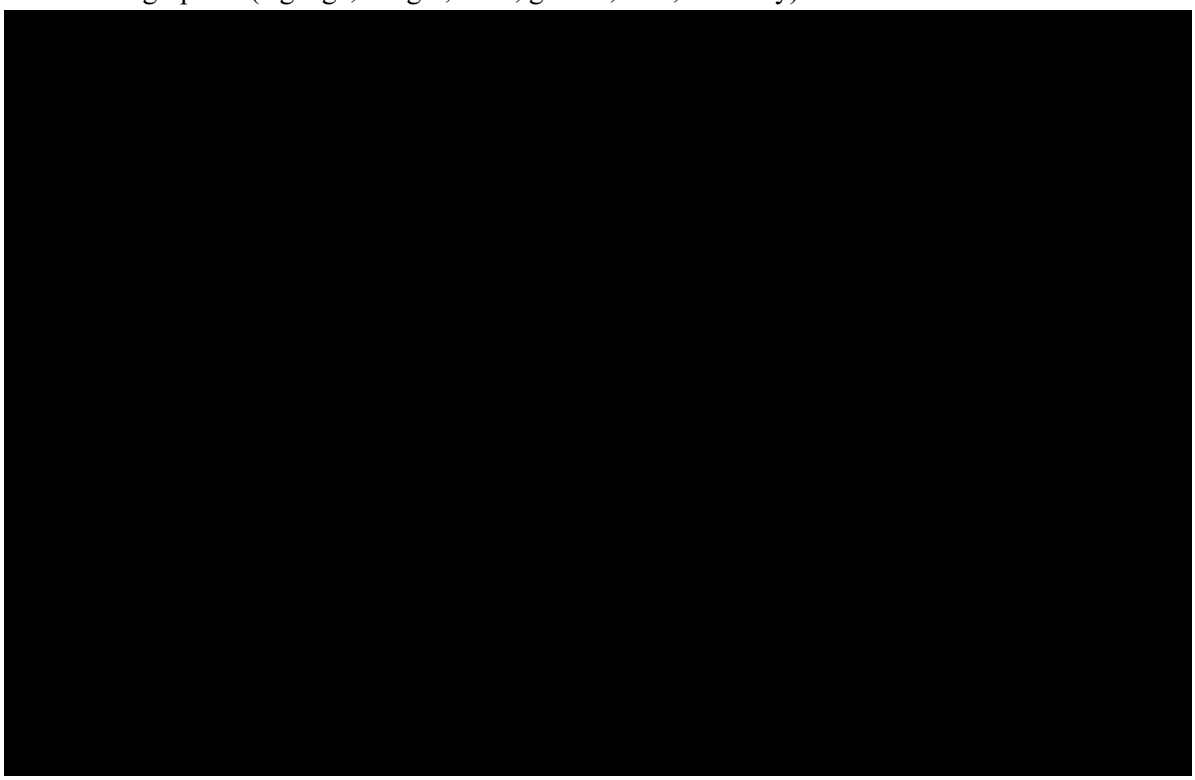
- Baseline: initiation of Pradaxa Pellets administration
- Follow up:
    - At approximately 6 weeks, 3, 6, and 12 months of Pradaxa Pellets administration.
    - End of Study (EOS) visit is defined as a follow up conducted after the end of the observational period. The study is observational and does 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.

Patient contacts can be in person, remote or telephone contacts, with a remote consenting procedure used at time of enrollment if available at that site. If the patient is identified and enrolled after beginning treatment with DE, the past medical records may be used to obtain information from the date of treatment onset until the date of enrollment. Data will be collected at each time point via both patient questions and review of relevant medical records as appropriate. If additional information is needed after review of medical records by the PI and the PI is not the prescribing physician, the prescribing/treating physician will be contacted to provide the additional information if possible.

Information on enrolled patients will be collected as follows:

At Baseline:

- Demographics (e.g. age, weight, BMI, gender, race, ethnicity)



At Follow up:

- Occurrence of any bleeding event defined as Major bleeding events (MBE), clinically relevant non-major (CRNM) bleeding events, Patient important bleeding without intervention, or minor bleeding events including location(s)

- Occurrence of AEs / SAEs

- Duration of Pradaxa Pellets administration and compliance with treatment

[redacted]

9.2 SETTING

9.2.1 Study sites

This study will be conducted as a prospective cohort study, in conjunction with the existing [redacted] This trial will be a new cohort, not a substudy or addition to any existing study. Sites will be recruited and managed by [redacted] The number of sites is not predetermined, sites may be initiated into the study at the time of study launch through the Consortium or may be initiated via outreach after they are identified as having prescribed Pradaxa Pellets to a patient. Outreach will be done by the Consortium to inform pediatric hematologists about the trial and invite participation in the registry. Existing [redacted] Consortium members can join this registry and prescribers not currently members of [redacted] will be invited to join this study as well.

In addition to the [redacted] outreach to physicians, site and patient recruitment will be facilitated via the specialty pharmacy and distributor for Pradaxa Pellets. These entities may provide prescriber information to the sponsor (prescriber name and institution or only institution) and outreach will be conducted to notify the prescriber of the study and how to participate. The goal will be to attempt contact with every prescriber (or prescribing institution) to inform them of the study and provide information on enrollment opportunities for their patient(s). Prescribers can choose to join the registry trial as a study site or they will be provided with informational materials to provide to the patient with instructions on how to enroll in the trial at the metasite.

In addition to traditional study sites participating in the prospective cohort study, one Consortium site will be set up as a metasite. If a prescriber is not interested in participating in the registry, they may refer the patient/caregiver to the metasite. The metasite will then consent and enroll the patient into the study via remote consenting and remote study visits, and obtain medical records from the treating physician(s) and/or the participants parent/legally authorized representative and query the treating physician if needed to address data clarifications.

This outreach to all prescribers and metasite option is intended both to facilitate enrollment and to limit selection bias by recruiting patients after Pradaxa Pellets treatment has been initiated, allowing patient participation even if the prescriber is not interested in study participation as a site investigator.

9.2.2 Study population

Pediatric patients aged 3 months to less than 12 years, who may be considered for anticoagulation with Pradaxa Pellets due to VTE, are usually treated in neonatology, pediatric general surgery, cardiac surgery or intensive care units. Pediatric patients with anticoagulation with Pradaxa Pellets for the prevention of recurrent VTE are usually evaluated by pediatric hematologists in pediatric hematology units. Any of these patients that are prescribed Pradaxa Pellets may be considered for inclusion into this study.

Inclusion criteria:

- Pediatric patients aged 3 months to less than 12 years at the time of Pradaxa Pellets initiation
- Written informed consent from parents/care givers and patient assent if age appropriate
- Initiation of Pradaxa Pellets administration either as initial or subsequent therapy:

- Treatment of VTE
- Treatment to reduce the risk of recurrence of VTE

Exclusion criteria:

- Participation in any randomized clinical trial or use of investigational product, participation in any other observational study is not an exclusion
- Any contraindications to Pradaxa Pellets according to the US Prescribing Information.
- Previous participation in this study.

A subject screening log must be kept at the site or in the study electronic portal, recording basic information (e.g. initials, gender, date of birth, reason for not enrolling the patient etc.) on all patients who were invited to participate in the study, with information on the eligibility (or reasons for non-eligibility) and date of signed informed consent, if applicable. In the case of refusal, reasons for refusal should be given. In addition, a log of all patients included into the study (i.e. having given informed consent) will be maintained in the main study file at the study site.

9.2.3 Study visits

There will be up to 5 study visits, refer to Figure 1 Flow Chart for the scheduling and activities at each visit. Patient participation will last up to approximately 52 weeks. All visits consist of data collection only, and may be either in person or virtual remote. Visit timepoints may have some flexibility due to scheduling, however every attempt should be made to conduct the visit as close to the scheduled timepoint as possible. If the consent has occurred after the 6 week visit, that visit information will be obtained at the time of consent and from medical records. Remote consent is allowed as long as procedures are in place at the study site and approved by the institutional review board (IRB).

Figure 1 Flow Chart of Contacts

Trial Periods	**Pradaxa Pellets Initiation**	**Observation Period/Data Collection Timepoints**[1]				
Visit	**1 Consent**	**2**	**3**	**4**	**EoS**	**Unscheduled**
Weeks		6	12	26	52 (**EoS**[2])	**Unscheduled**[5]
Months			3	6	12 (**EoS**[2])	
Visit Window[7]		±2 weeks	±2 weeks	±4 weeks	-8 weeks	
Informed consent	X[3]	X[3]	X[3]			X
Demographics	X					
Medical history	X					
Review of in-/ exclusion criteria	X					
Indication for Pradaxa	X					
Effectiveness assessment		X	X			
Post-thrombotic syndrome assessment			X	X	X	X
Bleeding-related events		X	X	X	X	X
Medication status[4]		X	X	X	X	X
All AEs/SAEs	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X
Completion of patient participation					X[6]	

Figure 1 Flow Chart of Contacts continued

(1) All assessments will be assessed through 12 months for all patients unless patient withdraws their participation.
(2) End of Study (EoS).
(3) Patients may be consented up to 12 weeks after the initiation of treatment with Pradaxa Pellets. Medical records will be requested, and data recorded for all relevant study questions back to the date of treatment initiation. All Visit 1 procedures will be completed at the consent visit. The consent visit may be combined with Visit 2 if patient is consented at 6 weeks (±2 weeks) or with Visit 3 if patient is consented at 12 weeks. Visit 2 may be skipped if timing of consent is close to 12 weeks
(4) Medication status will include dose modifications, dates of treatment and compliance to treatment.
(5) Patient contact that occurs in between scheduled study visits should be recorded as an Unscheduled visit.
(6) If a patient withdraws their participation in the study prior to the EoS visit, the "Completion of patient population" information must be collected at their final study visit. A reasonable effort will be made to collect the reason for early termination.
(7) Visit windows are provided as guidance for study implementation. All effort should be made to adhere to visit windows as instructed as patient/caregivers memories of some events may be less accurate over time. Therefore divergence from the visit window will not be captured as an important protocol deviation but only a point of discussion with the patient caregiver

9.2.4 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, such as change to the study request from the FDA.
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).

9.3 VARIABLES

9.3.1 Exposures

Exposure to Pradaxa Pellets will be collected via medication status questions at the study visits, including dose prescribed, compliance with treatment and dates of treatment.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Primary objective:

To estimate the cumulative incidence of clinically relevant bleeding events defined as the composite of Major bleeding events (MBE) and clinically relevant non-major (CRNM) bleeding events

(according to recommendations from the Pediatric and Neonatal Thrombosis & Hemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [ISTH Pediatric SSC] (P24-01853).

Major bleeding defined as:

- fatal bleeding
- clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL (20 g/L) in a 24-hour period
- critical site bleeding such as retroperitoneal, pulmonary, pericardial, intracranial, or otherwise involved the central nervous system
- bleeding that requires and intervention via invasive procedure such as surgery in an operating suite, interventional radiology, or endoscopy
- overt bleeding for which a reversal agent is administered (i.e., vitamin K, plasma, prothrombin complex concentrate, protamine, andexanet alfa, or idarucizumab

CRNM bleeding defined as:

- overt bleeding for which a blood product was administered, and does not meet the criteria for major bleeding
- bleeding that results in a medical or procedural intervention not meeting major bleeding criteria, including a medication change (reducing, holding, or changing anticoagulation or addition of new medication). Examples include: hormonal therapy, TXA, iron, nasal packing, nasal cautery, and LARC placement
- bleeding that results in hospitalization or increased level of care

9.3.2.2 Secondary outcomes

1. Efficacy defined as
    - occurrence of recurrent VTE including both symptomatic and asymptomatic events, wherein symptomatic recurrent VTE is defined as radiologically-confirmed new venous thrombotic or embolic burden ≥7 days post-diagnosis of the index VTE, accompanied by signs and/or symptoms attributable to the new thromboembolism and asymptomatic VTE is defined by new thrombotic/embolic burden as disclosed by comparison of end-of-treatment imaging versus baseline imaging of the vascular region involved by the index VTE
    - mortality related to thrombotic or thromboembolic events
2. Occurrence of all bleeding events defined as composite of major bleeding, CRNM bleeding events and minor bleeding events (defined as any overt or macroscopic evidence of bleeding that does not fulfil the criteria for major bleeding, CRNM bleeding, or patient important bleeding without intervention, defined as bleeding for which medical attention is sought (phone call, telehealth, clinic, or ED visit) but does not result in hospitalization, increased level of inpatient care, or an intervention by the medical team, according to recommendations from the ISTH Pediatric SSC (P24-01853).

3. Occurrence of post-thrombotic syndrome (PTS) as evaluated by the Villalta Scale Modified for Children, the Manco-Johnson instrument, or other validated pediatric PTS instrument employed in routine clinical care, in accordance with recommendations from the ISTH Pediatric SSC
4. Incidence of adverse events (AEs), including AEs for which treatment was discontinued, and serious adverse events (SAEs)
5. Thrombotic burden at the end of the treatment period vs baseline, i.e. image based resolution status of the thrombus (complete response, partial response, stable disease, progressive disease) using appropriate method and the same method as the baseline evaluations, when appropriate

[redacted]

In addition the following will be collected:

- [redacted] recurrence of VTE while on treatment (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, DVT, PE and PDE, thrombus progression), duration of use and compliance with treatment, [redacted]

9.3.3 Covariates

Not applicable

9.4 DATA SOURCES

Data will be collected at study visits via both patient/caregiver questioning and medical records if applicable. Data will be entered into a secure [redacted] database managed by the [redacted] Data will be managed by BI according to SOPs once transferred to BI.

9.5 STUDY SIZE

The requested sample size from the FDA is 300 patients. The number of study sites required will be determined by both existing [redacted] member institutions should they choose to participate, as well as additional sites recruited from prescribers of Pradaxa Pellets identified via the specialty pharmacy and distributors. There is no planned minimum or maximum number of study sites, sites will be allowed to join the registry until the 300 patients are enrolled.

9.6 DATA MANAGEMENT

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

Data will be collected using an electronic data capture (eDC) system, [redacted]. Details regarding the data management system will be provided in the [redacted] documents and site training materials.

All study documentation will be entered by the site personnel into the eDC system, with the exception of SAE/ADR reporting where paper/fax forms may be required in addition to eDC entry. Site personnel will be provided with appropriate instructions for data entry.

9.7 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.

9.7.1 Main analysis

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, [redacted] All AE/ verbatim terms will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA). [redacted]

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.4 or higher [redacted]

[redacted]

9.7.3 Safety Analysis

All adverse events and adverse drug reactions collected per study protocol will be included and summarised in the interim safety analyses and in the final study report.

Safety outcomes will be summarized as incidence with [redacted]. All AE/ verbatim terms will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA). [redacted]

[redacted]

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.4 or higher ([redacted]

9.8 QUALITY CONTROL

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

[redacted] will facilitate the data management activities of this study. [redacted] will be the data management system. Data will be reviewed in an ongoing basis during the study, with programmed edit checks, dependency checks and manual review if required. Sites will be queried to resolve discrepancies.

Data will be transferred to BI at the end of the study, and managed via BI SOPs for storage and archiving.

The [redacted] will facilitate the conduct of the study including site management. A site training plan will be developed and implemented. No on-site monitoring or source document verification is planned for this trial.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Study enrolment will be dependent upon actual prescribing of Pradaxa Pellets and the ability to recruit those patients into the study. As this is an observational and non-interventional study, the study design does not encourage prescribing of Pradaxa Pellets or outreach to potential patients/caregivers other than to inform them of the study.

To avoid selection bias, patients must be enrolled within 12 weeks of beginning treatment with Pradaxa Pellets.

In addition, attempts will be made to identify all prescribers of Pradaxa Pellets using information obtained from the specialty pharmacy and distributor. Outreach to those prescribers will be made to ensure that as many prescribers as possible are informed of the study and to encourage enrolment of their patient(s).

9.10 OTHER ASPECTS

Not applicable.

9.10.1 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.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by [redacted], either on paper or via remote data capture, if applicable.

9.10.2.1 Source documents

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

Data reported on the CRFs *or* entered in the Electronic CRFs (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. Current medical records must be available.

For eCRFs **all** data must be derived from source documents.

9.10.2.2 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 Food and Drug Administration (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 9.10.2.1

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant [redacted] Consortium and 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.

10.1 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 each patient caregiver and assent must be obtained from the patient if appropriate per GPP and according to the regulatory and legal requirements of the participating country, if applicable.

10.2 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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 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.

Adverse drug reaction
An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

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.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

All AEs will be recorded in the eCRFs. Bleeding events, symptoms related to VTE reoccurrence, and symptoms related to post-thrombotic syndrome will be recorded on the Clinical Follow-up, Bleeding Events, and VTE Information pages of the eCRF. If these events are deemed to be either serious or related to Pradaxa Pellets (serious or non-serious), they must in addition be recorded on the Adverse Events eCRF.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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:

In rare cases, pregnancy might occur in a NIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The ISF will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying serious ADR and/or SAE, only the Pregnancy Monitoring Form and not the NIS AE form is to be completed. If there is a serious ADR and/or SAE associated with the pregnancy a NIS AE form must be completed in addition.

The study design is of an observational and 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 (e)CRF from signing the informed consent onwards until the end of the study:

- all adverse events (serious and non-serious),

All SAEs 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 ADRs, AEs and Drug Exposure during Pregnancy to BI Pharmacovigilance

The investigator carefully assesses whether an AE constitutes an ADR and/or a SAE using the information above. If a non-serious AE is considered related then follow the reporting process below in addition to entering the information into the eCRF. If an AE is considered serious, follow the reporting process below in addition to entering the information into the eCRF.

The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form from signing the informed consent onwards until the end of the study and provided to BI unique entry point. After signing informed consent, the following must also be collected if identified during the course of medical chart review beginning with the index date.

Type of Report	Timeline
All SAEs in patients exposed to dabigatran etexilate	Immediately within 24 hours
All **non-serious ADRs** in patients exposed to dabigatran etexilate	7 calendar days
Drug exposure during pregnancy	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 and fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF page and the NIS AE form if applicable according to the table above.

11.3 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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.

As this is a PASS (Post Authorization Safety Study), periodic reports will be provided to the FDA.

13. REFERENCES

13.1 PUBLISHED REFERENCES

P13-16985	Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, et al. RE-COVER II Trial Investigators. Treatment of acute venous thromboembolis with dabigatran or warfarin and pooled analysis. Circulation, published online December 16, 2013, doi: 10.1161/CIRCULATIONHA.113.004450; 2014. P. 764-772.
P19-00949	Monagle P, Cuello CA, Augustine C, Bonduel M, Brandao LR, Capman T, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood Adv 2018; 2(22); 3292-3316.
P19-11322	Brandao L, Albisetti M, Halton J, Bomgaars L, Chalmers E, Mitchell L, et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. Blood, December 5, 2019, doi: 10.1182/blood.2019000998; 2020. P. 491-504.
P20-07911	Halton J, Brandao L, Luciani M, Bomgaars L, Chalmers E, Mitchell L, et al. Efficacy and safety of dabigatran etexilate for treatment of venous thromboembolism in paediatric patients aged from birth to <2 years – results of the DIVERSITY trial. ISTH 202, 28th Cong of the International Society on Thrombosis and Haemostatis (ISTH) (Virtual), 12-14 Jul 2020. Res Pract Thromb Haemost 2020; 4(Suppl 1); 35.
R13-3609	Pradaxa 75 mg, 110 mg, 150 mg hard capsules (Boehringer Ingelheim Pharma) (summary of product characteristics, manufacturer(s) responsible for batch release, conditions or restrictions regarding supply and use, other conditions and requirements of the marketing authorization, labelling and package leaflet, last updated: 07/02/1013). 2013.
R14-1033	Nowak-Goettl U, Bindlingmaier C, Kruempel A, Goettl L, Kenet G. Pharmacokinetics, efficacy and safety of LMWHs in venous thrombosis and stroke in neonates, infants and children. Br. J Pharmacol 2008; 153(6); 1120-1127.
R19-2558	Klaassen ILM, Sol JJ, Suijker MH, Fijmvamdraat K, Wetering MD van de, Ommen CH van. Are low-molecular weight heparins safe and effective in children? A systematic review. Blood Rev 2019; 33; 33-42.
R20-3319	Romantsik O, Brusschettini M, Zappettini S, Ramenghi LA, Calevo MG. Heparin for the treatment of thrombosis in neonates (review). Cochrane Database Syst Rev 2016 (11).
P24-01853	Whitworth H, Amankwah EK, Betensky M, Castellucci LA, Cuker A, Goldenberg NA, Male C, Rinzler E, Zia A, Raffini L. Updated guidance for efficacy and safety outcomes for clinical trials in venous thromboembolism in children: communication from the ISTH SSC

	Subcommittee on Pediatric and Neonatal Thrombosis and Hemostasis. J Thromb Haemost. 2023 Jun;21(6):1666-1673.

13.2 UNPUBLISHED REFERENCES

None

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.

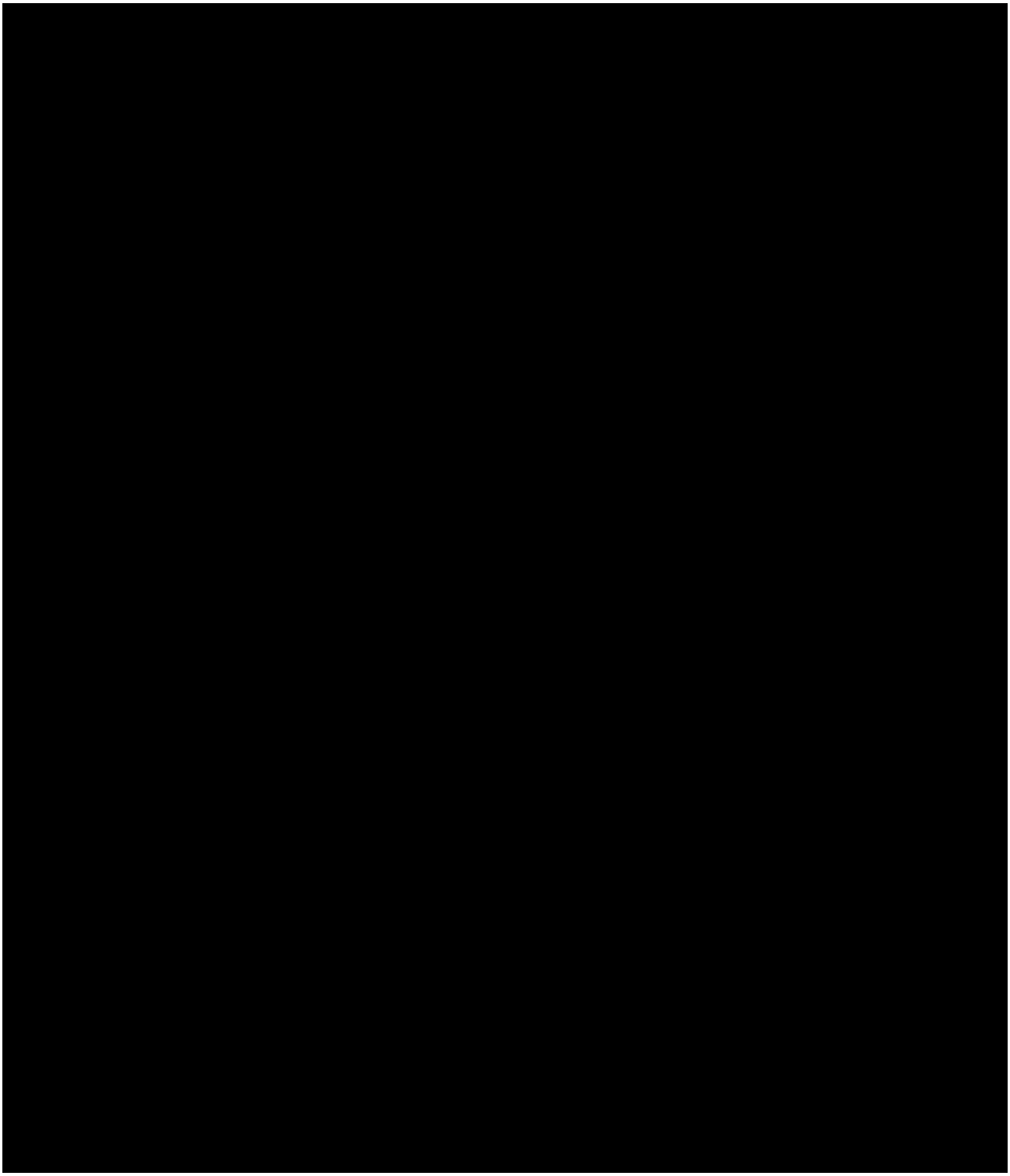
Stand-alone documents are not applicable.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable, this is a US only study.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.



APPROVAL / SIGNATURE PAGE

Document Number: c36960571 **Technical Version Number:2.0**

Document Name: protocol

Title: Safety and effectiveness of Pradaxa oral pellet formulation for treatment of acute venous thromboembolic events (VTE) and/or for risk reduction of recurrence of VTE in pediatric patients aged 3 months to less than 12 years in a real world setting: a prospective non-interventional study conducted in the United States

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area Head	[redacted]	26 Apr 2024 14:23 CEST
Approval-Clinical Trial Leader	[redacted]	26 Apr 2024 14:27 CEST
Approval-EU Qualified Person Pharmacovigilance	[redacted]	26 Apr 2024 15:15 CEST
Approval-Team Member Medical Affairs	[redacted]	26 Apr 2024 15:18 CEST
Approval	[redacted]	29 Apr 2024 05:33 CEST
Approval-Regulatory Affairs	[redacted]	29 Apr 2024 09:47 CEST
Approval-On behalf of Head or VP or Director	[redacted]	29 Apr 2024 14:56 CEST
Verification-Paper Signature Completion	[redacted]	14 May 2024 20:46 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed