[redacted]

STATISTICAL ANALYSIS PLAN

[redacted]

PROJECT 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
PRINCIPAL INVESTIGATOR:	[redacted]
SPONSOR	Boehringer Ingelheim
INSTITUTION:	UCSD/Rady Children's Hospital and the Children's Hospital-Acquired Thrombosis (CHAT) Consortium
SAP DATE:	July 23, 2024
DATA SOURCE:	Children's Hospital-Acquired Thrombosis (CHAT) Consortium
PREPARED BY:	[redacted] and [redacted]

SAP History:

Version Number	Version Date	Summary of Revisions Made:
1.00	23-Jul-24	[redacted] 1
Enter version # if applicable	Click or tap for drop down calendar to enter a date	Document editor

Table of Contents

1. STUDY OBJECTIVES

1.1. PRIMARY OBJECTIVE

To estimate the cumulative incidence of **clinically-relevant bleeding events (main safety outcome)** at 3 months, 6 months, and 1-year post-diagnosis of index venous thromboembolic event (VTE) while receiving or after discontinuing Pradaxa pellets, wherein clinically-relevant bleeding event is 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] [1]). MBE and CRNM bleeding detailed definitions are referenced in section 3.1 below.

1.2. SECONDARY OBJECTIVES

1.2.1. To estimate the cumulative incidence of **recurrent VTE (including both symptomatic and asymptomatic events) or VTE-related death (main efficacy outcome)** at 3 months, 6 months, and 1-year post-diagnosis of index VTE while receiving or after discontinuing Pradaxa pellets. Symptomatic and asymptomatic recurrent VTE are defined in section 3.2.1. below.

1.2.2. To estimate the cumulative incidence of **all bleeding events (secondary safety outcome)** at 3 months, 6 months, and 1-year post-diagnosis of index VTE while receiving or after discontinuing Pradaxa pellets, defined as the composite of major bleeding events, CRNM bleeding events, and minor bleeding events (according to recommendations from the ISTH Pediatric SSC [1]).

1.2.3. To estimate the prevalence of **post-thrombotic syndrome (PTS; secondary efficacy outcome)** among the study subpopulation of children with index deep vein thrombosis (DVT) of the upper extremity or lower extremity venous systems at 6 and 12 months post-diagnosis of the index DVT (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 [2,3]).

1.2.4. To estimate the incidence of **adverse events (AEs),** including AEs for which treatment was discontinued and **serious adverse events (SAEs**) (**tertiary safety outcome**).

1.2.5. To assess image-based **resolution status of the thrombus at end-of-treatment** relative to baseline, as follows: complete response, partial response, stable disease, progressive disease). This determination will be based on comparison of end-of-treatment imaging to baseline imaging of the study-qualifying VTE, using an end-of-

treatment imaging method that is the same as that which was performed for baseline evaluation, when appropriate [redacted]

[redacted]

2. STUDY DESIGN

This study is an observational and non-interventional national multi-center prospective cohort study based on newly collected data of pediatric patients (aged 3 months to less than 12 years) receiving anticoagulation with Pradaxa (i.e., dabigatran etexilate [DE]) Pellets for the treatment of VTE and/or for reduction in the risk of recurrence of VTE.

2.1. TREATMENT GROUPS

Single arm (DE)

2.2. STUDY POPULATION

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 criterion.
- Any contraindications to Pradaxa Pellets according to the US Prescribing Information.
- Previous participation in this study

2.3. EXPOSURES OF INTEREST

Pradaxa dose

3. OUTCOME VARIABLES

3.1. PRIMARY OUTCOME

Clinically-relevant bleeding events (main safety outcome), defined as the composite of major bleeding events and clinically relevant non-major (CRNM) bleeding events (according to recommendations from the ISTH Pediatric SSC [1]).

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

3.2. SECONDARY OUTCOMES

3.2.1. Recurrent VTE (including both symptomatic and asymptomatic events) or mortality related to thrombotic or thromboembolic events (main efficacy outcome), 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 (according to recommendations from the ISTH Pediatric SSC) 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 (according to recommendations from the ISTH Pediatric SSC [1]).

3.2.2. All bleeding events (secondary safety outcome), defined as the composite of major bleeding events, 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 [1]).

3.2.3 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.

3.2.4. Incidence of **adverse events (AEs)**, including AEs for which treatment was discontinued, and serious adverse events (SAEs).

3.2.5. **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.

3.2.6. Patient-important bleeding without intervention (according to the recommendations from the ISTH Pediatric SSC [1]) [redacted]**).**

[redacted]

3.3.1. Demographic [redacted]

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

[redacted]

[redacted]

3.3.2 Clinical measures at follow up

[redacted]

- Occurrence of AEs / SAEs

[redacted]

- Duration of Pradaxa Pellets administration and compliance with treatment
- Reason for discontinuation of Pradaxa Pellets if applicable

[redacted]

- PTS
- Lack of Efficacy (i.e., thrombotic burden at the end of the treatment period, recurrent VTE and VTE related deaths)

4. STATISTICAL METHODOLOGY

4.1. GENERAL METHODOLOGY

Data analyses for this study will be performed by the lead biostatistician and colleagues [redacted] at study completion, once the database has been locked and the Statistical Analysis Plan has been finalized and approved by the study team. All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.4 or higher ([redacted]).

4.1.1. Population for analysis

The analytic population for all analyses will consist of all enrolled patients who received at least one dose of Pradaxa Pellets.

The primary, secondary, [redacted] will be evaluated based on the study observational period, defined as the period of time from initiation of Pradaxa Pellets administration through discontinuation of Pradaxa Pellets administration + 3 days of residual effect period (REP) or switch to other anticoagulation therapy or planned end of observation time, whichever occurs earlier.

4.1.2. Participant flow

The flow of patients, including the overall patients screened, excluded patients, patients enrolled, and patients retained in the analytic dataset will be presented [redacted]

[redacted]

4.1.5. Protocol deviations and patient withdrawals

All protocol deviations will be summarized using counts and frequencies. Similarly, reasons for early withdrawal from the study will be summarized using counts and frequencies.

4.2. SUMMARY OF DEMOGRAPHICS AND CLINICAL CHARACTERISTICS AT BASELINE

Demographic and baseline clinical characteristics of the study population (all enrolled participants) as well as the analytic population (see above, 4.1.1) will be summarized in Tables (Table 1a, Table 1b), overall [redacted]. Continuous variables will be summarized as means with standard deviations or medians with observed range or interquartile range [redacted]. Categorical variables will be summarized as counts with percentages [redacted]. All statistical analyses will be performed with SAS v 9.4 or latest version.

4.3. SUMMARY OF TREATMENT WITH PRADAXA PELLETS [redacted]

Pradaxa Pellet [redacted] duration, and adherence, as well as dosing and duration of any concomitant antithrombotic agents, will be summarized in the analytic population in Tables and Listings (Table 2, Listing 2), overall and by age group and DE dose.

4.4. ANALYSIS OF THE PRIMARY OUTCOME

The primary outcome, cumulative incidence of clinically-relevant bleeding events (main safety outcome) at 3 months, 6 months, and 1-year post-diagnosis of index VTE while receiving or after discontinuing Pradaxa pellets will be reported with the corresponding 95% CIs (using the Wilson method) in the analytic population during the exposure period as described in 4.1.1. The incidence will also be reported, by type (any, major, CRNM, minor), age group and DE dose, if numbers permit.

4.5. ANALYSIS OF THE SECONDARY OUTCOMES

The three secondary outcomes, described in sections 3.2.1 and 3.2.2, will each be summarized in the analytic population during the exposure period as described in 4.1.1 using proportions with the corresponding 95% CI (using the Wilson method) or medians and IQRs, overall and by age group and DE dose. Distributions will be

compared across age groups where appropriate, using Chi-Square or Fisher's exact test, for categorical variables, and Mann-Whitney U test for continuous variables, as appropriate.

4.6. ANALYSIS OF THE ADDITIONAL OUTCOMES OF INTEREST

The safety and effectiveness outcomes, including PTS (tertiary efficacy outcome) as described in sections 3.2.3 to [redacted], will be summarized as cumulative incidences with the corresponding Wilson 95% CIs. All AE/verbatim terms will be reported in accordance with Medical Dictionary for Regulatory Activities (MedDRA) coding. Concomitant medications will be reported according to World Health Organization Drug Dictionary (WHO-DD) coding.

[redacted]

4.8 SAMPLE SIZE JUSTIFICATION

The study is not powered to test a formal hypothesis; therefore, all statistical analyses will be exploratory [redacted] The anticipated study sample size is based on the request from the United States Food and Drug Administration to include a minimum of 300 patients aged 3 months to less than 12 years.

[redacted]

[redacted]

4.9 REFERENCES

1. 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.

2. Revel-Vilk S, Brandão LR, Journeycake J, Goldenberg NA, Monagle P, Sharathkumar A, Chan AK; Perinatal And Paediatric Haemostasis Subcommittee Of The Scientific And Standardization Committee Of The International Society On Thrombosis And Haemostasis. Standardization of post-thrombotic syndrome definition and outcome assessment following upper venous system thrombosis in pediatric practice. J Thromb Haemost. 2012 Oct;10(10):2182-5. doi: 10.1111/j.1538-7836.2012.04885.x. Erratum in: J Thromb Haemost. 2014 Nov;12(11):1948. Goldenberg, A [corrected to Goldenberg, N A]. PMID: 23193586.

3. Goldenberg NA, Brandão L, Journeycake J, Kahn S, Monagle P, Revel-vilk S, Sharathkumar A, Chan AK; Perinatal And Paediatric Haemostasis Subcommittee Of The Scientific And Standardization Committee Of The International Society On Thrombosis And Haemostasis. Definition of post-thrombotic syndrome following lower extremity deep venous thrombosis and standardization of outcome measurement in pediatric clinical investigations. J Thromb Haemost. 2012 Mar;10(3):477-80. doi: 10.1111/j.1538-7836.2011.04594.x. PMID: 22482118.

5. REVIEWERS AND APPROVAL SIGNATURES

Position: Data Coordinating Center PI	**Name:** [redacted]	**Signature:** DocuSigned by: [redacted]	**Date:** 02-Nov-2024
Position: ONIS Lead	**Name:** [redacted]	**Signature:** DocuSigned by: [redacted]	**Date:** 29-Oct-2024
Position: ONIS Statistician	**Name:** [redacted]	**Signature:** DocuSigned by: [redacted]	**Date:** 29-Oct-2024

DocuSign

Certificate Of Completion

Envelope Id: [redacted]
Status: Completed
Subject: Complete with Docusign: SAP_BI_Pradaxa_Pellet_FINAL_v1.pdf
Source Envelope:
Document Pages: 13 Signatures: 3
Certificate Pages: 4 Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna

Envelope Originator:
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
10/29/2024 5:29:36 PM
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] CTL Boehringer Ingelheim Security Level: Email, Account Authentication (None) **Electronic Record and Signature Disclosure:** Accepted: 10/29/2024 5:38:33 PM ID: [redacted]	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 10/29/2024 5:31:44 PM Viewed: 10/29/2024 5:38:33 PM Signed: 10/29/2024 5:38:40 PM
[redacted] TSTAT Security Level: Email, Account Authentication (None) **Electronic Record and Signature Disclosure:** Accepted: 10/29/2024 5:43:22 PM ID: [redacted]	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: 1[redacted]	Sent: 10/29/2024 5:38:42 PM Viewed: 10/29/2024 5:43:22 PM Signed: 10/29/2024 7:22:55 PM
[redacted] Security Level: Email, Account Authentication (None) **Electronic Record and Signature Disclosure:** Accepted: 11/2/2024 4:05:04 PM ID: [redacted]	DocuSigned by: [redacted] Signature Adoption: Drawn on Device Using IP Address: [redacted] Signed using mobile	Sent: 10/29/2024 7:22:58 PM Viewed: 11/2/2024 4:05:04 PM Signed: 11/2/2024 4:05:24 PM

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	10/29/2024 5:31:44 PM
Certified Delivered	Security Checked	11/2/2024 4:05:04 PM
Signing Complete	Security Checked	11/2/2024 4:05:24 PM
Completed	Security Checked	11/2/2024 4:05:24 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Attention Boehringer employees: If you are signing from a country that is not your country of employment, you are not allowed to sign binding agreements with external parties (e.g. speaker agreements, sponsoring agreements or consultancy agreements. Workaround: Please forward the envelope to an authorized signatory in your country of employment). This rule does not apply to the following groups: i) All employees for country combination Germany / USA. ii) AH + Group Function employees for country combination Germany / France.

Boehringer Ingelheim

Consent to Proceed with Electronic Signatures

This document describes the frame conditions with regard to the use of the DocuSign® system by the authorized user ('you') for electronic signing and/or processing of documents concerning the business with Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany or any of its affiliated companies ('we, us or Company').

Via the DocuSign® system, you will be able to complete, review, and even print documents you will electronically sign using only your web browser via the link sent to you by e-mail. Before using the DocuSign® system, please make sure that you are able to meet the technical system requirements, which can be accessed via the DocuSign® website. Please read the information below carefully and thoroughly.

Contractual documents and notices may be sent to you electronically

If not otherwise agreed in a given contract between you and us, we will provide electronically to you through your DocuSign® user account all contractual documents, notices and other documents that are required to be provided or made available to you during the course of our business relationship with you. To reduce the chance of you inadvertently not receiving any notice or document, we will provide all of the required notices and documents to you by the contractually agreed method(s) and to the address(es) provided therein. Subject to the provisions of the given contract you may receive documents and notices electronically or in paper format.

Getting paper copies

As long as you are an authorized user of the DocuSign® system, you will have the ability to download and print any documents we send to you through your DocuSign® user account for a limited period of time (usually 30 calendar days) after such documents are first sent to you. In case a mandatory local legal requirements exists, we will provide paper copies of the contractual documents upon your request which has to be sent to the respective Company contact nominated in the contract.

Consequences of changing your mind

In exceptional cases (f.e. contractually agreed option, mandatory local legal requirement) you may be entitled to elect to receive required notices and disclosures only or additionally in paper format. If you decide to exercise a given option you have to liaise with your respective Company contact nominated in the contract by using the address(es) in accordance with the process contractually foreseen.

Changing your e-mail address

If your e-mail address changes please arrange for your new e-mail address to be reflected in your DocuSign® account by following the process for changing e-mail in the DocuSign® system.

Acknowledging your access and consent to receive materials electronically

To confirm to us that you can access this information electronically, please verify that you were able to read this electronic consent and that you (i) also were able to print on paper or electronically save this disclosure for your future reference and access or that you (ii) were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access.

By checking the 'I Agree' box, I confirm that:

- I can access and read this CONSENT TO PROCEED WITH ELECTRONIC SIGNATURES document; and
- I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and

- Until or unless I have notified my respective Company contact as described above, I consent to receive through electronic means all contractual documents, notices and other documents that are required to be provided or made available to me by the Company during the course of the business relationship with you.