Received: 13 October 2017 | Accepted: 18 February 2018

DOI: 10.1002/rth2.12093

ORIGINAL ARTICLE

rpth research & practice in thrombosis & haemostasis

Phase 3, single-arm, multicenter study of dabigatran etexilate for secondary prevention of venous thromboembolism in children: Rationale and design

Matteo Luciani MD[1] | Manuela Albisetti MD[2] | Branislav Biss MD[3] | Lisa Bomgaars MD[4] | Martina Brueckmann MD[5,6] | Elizabeth Chalmers MD[7] | Savion Gropper MD, PhD[5] | Jacqueline M. L. Halton MD[8] | Ruth Harper PhD[9] | Fenglei Huang PhD[10] | Ivan Manastirski MD[3] | Lesley G. Mitchell MD, PhD[11] | Igor Tartakovsky MD[5] | Bushi Wang PhD[12] | Leonardo R. Brandão MD, MSc[13]

[1]OncoHematology Department, Bambino Gesù Children's Hospital, Rome, Italy

[2]Hematology Department, University Children's Hospital, Zürich, Switzerland

[3]Department of Clinical Development, Boehringer Ingelheim RCV GmbH & Co. KG, Vienna, Austria

[4]Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA

[5]Clinical Development and Medical Affairs, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

[6]Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany

[7]Royal Hospital for Children, Glasgow, UK

[8]Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada

[9]Boehringer Ingelheim Ltd, Bracknell, Berkshire, UK

[10]Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA

[11]University of Alberta, Edmonton, AB, Canada

[12]Biostatistics and Data Sciences, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA

[13]Department of Pediatrics, Division of Hematology/Oncology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Correspondence
Leonardo R. Brandão, Department of Pediatrics, Division of Hematology/Oncology, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, ON, Canada.
Email: leonardo.brandao@sickkids.ca

Funding information
Boehringer Ingelheim Pharma GmbH & Co. KG

Abstract

Background: Anticoagulant therapy for venous thromboembolism (VTE) in children is largely based on treatment recommendations for adults. However, differences in both physiology (ie, renal maturation and drug excretion) and developmental hemostasis must be considered when treating children, as such differences could affect dose appropriateness, safety and efficacy.

Objectives: To address these concerns, a study was designed to evaluate the safety of dabigatran etexilate in children requiring secondary thrombus prevention in whom an initial VTE was associated with an identified risk factor that persisted after the acute VTE treatment period. We report herein the rationale and design of the study.

Patients/Methods: This phase 3, open-label, single-arm, multicenter, multinational, prospective cohort study will be conducted in ≥100 children aged 0 to <18 years at

~100 specialist sites worldwide. Children will be treated with dabigatran etexilate for 12 months, or for a shorter duration if their identified VTE risk factor resolves, as per current American College of Chest Physicians recommendations. A nomogram will be used to determine starting doses for each patient.

Results: The primary outcomes of the study will be VTE recurrence, bleeding events, overall mortality, and VTE-related mortality. Secondary outcomes will include occurrence of post-thrombotic syndrome, the pharmacokinetics of dabigatran, and the need for dose adjustments during treatment. Data on adverse events during the study will also be collected.

Conclusion: This study will evaluate the safety of dabigatran etexilate for the secondary prevention of VTE in children, in addition to providing further data to guide pediatric dosing with dabigatran.

KEYWORDS

anticoagulant, dabigatran, pediatrics, secondary prevention, venous thromboembolism

Essentials

- Treating pediatric venous thromboembolism (VTE) based upon adult guidelines may be inappropriate.
- This phase 3 trial will assess the safety of dabigatran for secondary VTE prevention in children.
- A dosing algorithm will be used to determine individualized dabigatran doses.
- The study will provide key data on dabigatran safety and guide pediatric dosing recommendations.

1 | INTRODUCTION

Venous thromboembolism (VTE) in children is typically secondary to underlying diseases and/or their treatment, or to acquired thrombosis risk factors.[1] In pediatric patients, VTE has an annual incidence of approximately 0.07-0.14 events per 10 000 children,[2] but the number of cases appears to be rising.[3] Raffini et al. reported a 70% increase in VTE cases among neonates, infants, children, and adolescents in tertiary pediatric institutions in the United States between 2001 and 2007.[4] The increased incidence could be due to a heightened level of awareness towards pediatric VTE among healthcare professionals, better diagnostic techniques leading to more frequent identification, improved survival of children with more complex or catastrophic conditions, and more frequent use of interventions such as central venous catheters, which is the most common risk factor for pediatric VTE.[4]

The current standard of care for pediatric patients with acute VTE is anticoagulant treatment with unfractionated heparin or low-molecular-weight heparin (LMWH) followed by several weeks or months of treatment with LMWH, or oral vitamin K antagonists (VKAs).[1,5] Estimates of the rate of pediatric VTE recurrence vary widely,[6,7] ranging between 2% and 21%.[8] Post-thrombotic syndrome (PTS), another long-term consequence of VTE, has been reported in 12-65% of children following an initial VTE.[1,7,9–12] Risk factors associated with VTE recurrence include underlying chronic conditions associated with a prothrombotic tendency, such as malignancies, cardiac/vascular abnormalities, short bowel syndrome with total parenteral nutrition dependency, or congenital disorders (eg, severe inherited thrombophilias). In addition, chronic conditions with interim disease flares such as in inflammatory disorders (eg, systemic lupus erythematosus, bowel disorders, systemic sclerosis, or vasculopathies), infections (eg, infective endocarditis or bone infections), and nephrotic syndrome can be accompanied by intermittent prothrombotic periods. Lastly, acquired risk factors are typically exemplified by the presence of central venous catheters.[1,2,4,6,8,13–15]

When a risk factor is present, anticoagulant therapy, usually with LMWH or oral VKAs, may be extended beyond the acute period to prevent VTE recurrence until the risk factor has resolved, or be administered lifelong in selected cases.[1] While both treatments yield acceptable clinical results, their use in pediatric VTE presents challenges.[1] For instance, parenteral administration of LMWH, the need for regular monitoring of the international normalized ratio (INR) with VKAs, as well as risks due to VKA-related food–drug and drug–drug interactions, may represent a burden to children and their families, directly affecting treatment feasibility and compliance, and ultimately, efficacy. There is an unmet need for therapies that can overcome these challenges.[14]

The efficacy and safety of dabigatran etexilate have been demonstrated in a number of indications in adults. These include the acute

treatment of VTE,[16–18] the acute treatment of VTE in the presence of cancer,[19] and extended treatment for secondary prevention of VTE,[20] for which dabigatran etexilate was shown to be non-inferior to well-controlled warfarin, with an overall reduced risk of bleeding, and superior in efficacy compared with placebo.

Anticoagulant therapy for pediatric VTE is based mostly on extrapolations from recommendations for the treatment of adults.[1,14,21] There are, however, important differences between adults and children that must be considered. For example, unprovoked VTE is rarer in the pediatric population[6,22]: in children, up to 95% of VTEs are secondary to an identifiable risk factor,[1] whereas there is no readily identifiable risk factor in approximately 25-50% of adults with VTE.[23] The continued presence of a risk factor in pediatric patients is therefore an important consideration when making decisions about continued anticoagulation. Adults and children also have differences in their coagulation systems, the maturation of which is not complete until adolescence. Developmental differences in coagulation maturation are exemplified by lower circulating levels of both procoagulant and natural anticoagulant proteins in children versus adults,[24,25] particularly in infants,[26] which may affect the way children respond to anticoagulant drugs. In the case of dabigatran, which is primarily renally excreted,[27,28] differences in maturation of renal function are considered important in determining safe and effective pediatric dosages.[29] Guidance from the US Food and Drug Administration (FDA) notes that if the course of a disease and the effects of a particular drug treatment are similar in adults and children, findings on drug effectiveness might be extrapolated from adults to children.[30] This same FDA guidance and corresponding guidance from the European Medicines Agency, however, states that extrapolation of findings on drug safety from adults to pediatric populations is not appropriate.[30,31]

Findings from studies of dabigatran etexilate in children have been promising (Table 1). In an in vitro study, fibrin clot generation and lysis assay responses to dabigatran in children aged 0 to <18 years were consistent and comparable with those of adults.[32] A three-day, phase 2a, open-label study in adolescent patients who had successfully completed planned treatment for VTE showed similar pharmacokinetic (PK)/pharmacodynamic (PD) relationships in children and adults; dabigatran was also generally well tolerated.[33] The PK and PD of dabigatran administered as oral liquid formulation were evaluated in 2 phase 2a, open-label, safety and tolerability studies in pediatric patients with VTE. One study included patients aged 1 to <2 years and the other study included patients aged <1 year. In both studies, the projected steady-state trough concentrations of dabigatran were largely comparable with those in adults with VTE. A linear relationship was observed between PK and PD for diluted thrombin time (dTT) and ecarin clotting time, and a non-linear relationship was observed between PK and PD for activated partial thromboplastin time. These PK/PD findings are largely comparable with those observed in adults with VTE. There were no bleeding events or other adverse events (AEs) during the studies.[34,35] Furthermore, dabigatran etexilate is also being compared with LMWH or oral VKAs for the treatment of acute VTE in an open-label, randomized, active-controlled,

TABLE 1 Key findings with dabigatran etexilate in pediatric patients[32–35]

Phase	Number of patients	Objective	Findings
In vitro	41	To determine the optimum coagulation assays for dabigatran in children and the anticoagulant effect of dabigatran across pediatric age groups	• Diluted thrombin time was the most suitable assay for indirect assessment of dabigatran concentrations in children • Fibrin clot generation and lysis assay responses to dabigatran across the pediatric age range were consistent with and comparable to those in adults
2a	9	To investigate the tolerability and safety of dabigatran etexilate in adolescents who had completed either LMWH or oral anticoagulation for primary VTE, and to explore PK and PD in this age group	• Dabigatran etexilate was generally well tolerated • The dabigatran PK/PD relationship in adolescent patients was similar to that in adults
2a	18	To examine the PK and PD of an oral liquid formulation of dabigatran etexilate and to evaluate its tolerability and safety in patients ages 1 to <12 years	• The oral liquid formulation was well tolerated • Projected steady-state dabigatran trough concentrations were largely comparable with those in adults with VTE • The PK/PD relationship in this age group was similar to that seen in adults and adolescents with VTE
2a	8	To examine the PK and PD of an oral liquid formulation of dabigatran etexilate and to evaluate its tolerability and safety in patients aged <1 year	• The oral liquid formulation was well tolerated • Projected steady-state dabigatran trough concentrations were largely comparable with those in adults with VTE • The PK/PD relationship in this age group was similar to that seen in adults and adolescents with VTE

LMWH, low-molecular-weight heparin; PD, pharmacodynamics; PK, pharmacokinetic; VTE, venous thromboembolism.

multicenter, phase 3 study in children aged 0 to <18 years (NCT01895777).

2 | OBJECTIVES

The aim of this study is to provide information regarding the safety (with efficacy criteria considered safety-related) of extended anticoagulant therapy with dabigatran etexilate when used for the secondary prevention of VTE in children aged 0 to <18 years. Primary outcomes include VTE recurrence, bleeding events, and mortality. Secondary outcomes include PTS, the PK and PD of dabigatran etexilate, and the number of patients who require a dose adjustment during treatment. Findings from the study will complement those from NCT01895777, which is to assess dabigatran in the acute VTE setting.

3 | METHODS

3.1 | Study design and timeline

This is a phase 3, open-label, single-arm, multicenter, multinational, prospective cohort study that will include ≥100 patients. The study will be conducted worldwide at approximately 100 trial sites, most of which will be specialized referral centers experienced in the management of pediatric VTE. Patients will be treated with dabigatran etexilate for up to 12 months, or less if the identified clinical risk factor for VTE resolves. A post-treatment follow-up visit will be conducted 28 days after the last intake of the study drug. A timeline for the study with details of study visits and assessments is shown in Table 2. Patients who stop treatment before 12 months, either as a result of VTE risk factor resolution or early treatment discontinuation, will be invited for an end-of-treatment visit and then followed according to the remainder of the visit schedule. At the end of their participation in the study, all patients will discontinue dabigatran etexilate; if there is an ongoing risk factor, they will be required to switch to standard of care. The end of the trial will be defined as the date of completion of the last study visit by the last patient.

3.2 | Oversight

Figure 1 outlines the administrative and oversight structure of the trial. A steering committee comprising academic and sponsor members will provide scientific leadership and has final responsibility for the trial design, the development of the protocol and the conduct and oversight of the study. The study sponsor is Boehringer Ingelheim (Ingelheim, Germany). The study protocol will be submitted for approval by the national competent authority and the institutional review board or ethics committee for each participating center. Written informed consent, and assent if applicable, will be obtained before study commencement from the patient's parent(s) or legal guardian, and/or the patient, in accordance with local legislation.

An independent data monitoring committee (DMC) will review safety on an ongoing basis and will advise the sponsor on continuation, modification, or termination of the study, according to a detailed DMC charter. The DMC will also review the study results and monitor the overall dabigatran etexilate pediatric study program. An independent adjudication committee will evaluate all primary outcome events. All laboratory samples for the planned safety assessments will be analyzed centrally, although local laboratories may be employed if needed and when feasible to evaluate some assays, such as dTT, for the evaluation of dabigatran anticoagulant activity and corresponding plasma levels, INR, serum creatinine, and hemoglobin. Samples for PK and PD evaluations will be analyzed at contract research organization laboratories.

3.3 | Patients

Participants will be males and females aged <18 years who require anticoagulant therapy for secondary prevention of VTE because of the presence of an ongoing clinical risk factor for VTE recurrence (Table 3). The VTE risk factor must be specified for each patient during pretrial screening and will then be reevaluated at each visit to determine the need for continuing treatment. The key inclusion and exclusion criteria for study participants are summarized in Table 3. Eligible patients must have completed at least 3 months of initial anticoagulant treatment for acute VTE (eg, with LMWH or an oral VKA) or have completed the treatment period in an open-label study comparing the efficacy and safety of dabigatran etexilate versus standard of care in children with acute VTE (study NCT01895777), although those who switched from dabigatran etexilate to standard of care during the latter study will be excluded.

Recruitment will be phased according to age group; adolescents aged 12 to <18 years will be recruited first and, based on ongoing evaluation of study data and data from other ongoing dabigatran etexilate pediatric studies by the DMC, recruitment will be opened to children aged 2 to <12 years. Based on consideration of these data, the DMC will recommend if and when it is appropriate to open recruitment to 0 to <2-year-old study participants.

3.4 | Study intervention

After written consent has been obtained, and if the patients meet all inclusion criteria and none of the exclusion criteria, they will initiate dabigatran etexilate treatment or continue treatment if already receiving the drug as part of a prior study. Where patients have been receiving treatment with LMWH or oral VKAs, guidance will be provided to investigators on how to manage switching to dabigatran etexilate. Patients will be assigned twice-daily dabigatran etexilate as capsules if they are able to swallow them (eg, patients aged ≥8 years); otherwise the drug will be administered as pellets sprinkled on food (eg, ages 6 months to, in general, <8 years, but also allowed up to 12 years), or as an oral liquid formulation (eg, from birth to, in general, age <6 months, but also allowed up to 12 months).

TABLE 2 Overview of the study assessments. The table shows the assessments to be carried out at each visit during the study

Trial period/procedure	Screening[a]	Treatment period (open-label) with dabigatran etexilate													Follow-up[b]
Visit number	1	2	3	4	5	6	7	8	9	10	11	Titration visit[c]	Unscheduled visit[d]	eEOT[d]	Visit 11 + 28 days (±7)
Study week	−1	1	1	3	6	12	18	26	34	42	52				
Study day (visit window, days)	−7 to −1	1	4 (+3)	22 (±7)	43 (±7)	85 (±7)	127 (±7)	183 (±7)	239 (±7)	295 (±7)	365 (±7)				
Evaluate signs/symptoms of recurrent VTE and clinical risk factor	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Evaluation of PTS	–	–	–	–	–	–	–	✓	–	–	✓	–	–	–	–
Evaluation of bleeding events	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Objective diagnosis of recurrent VTE or bleeding	–	At any time in cases of suspected recurrent VTE, PTS, or bleeding events													
PK blood sample	–	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	–
PD blood sample (aPTT and ECT)	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	–
dTT (or alternative method) blood sample	–	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	–
First administration of dabigatran etexilate	–	✓	–	–	–	–	–	–	–	–	–	–	–	–	–
Dispense dabigatran etexilate	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	–	✓	–	–
Adverse events and concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medication compliance	–	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	–
Vital signs, body weight, blood samples for laboratory tests	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination, 12-lead ECG, height measurement[e]	✓	–	–	–	–	–	–	✓	–	–	✓	–	–	✓	–

aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECG, electrocardiogram; ECT, ecarin clotting time; eEOT, early end of treatment; PD, pharmacodynamic; PK, pharmacokinetic; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.

[a]Index of VTE and clinical risk factor were assessed at the screening visit.

[b]Patient participation was concluded at the follow-up visit.

[c]If required.

[d]Required for all patients who have taken a dose of dabigatran etexilate but discontinued the study medication early for any reason before visit 11.

[e]Pregnancy testing will also be conducted at these visits for female adolescents of childbearing potential.

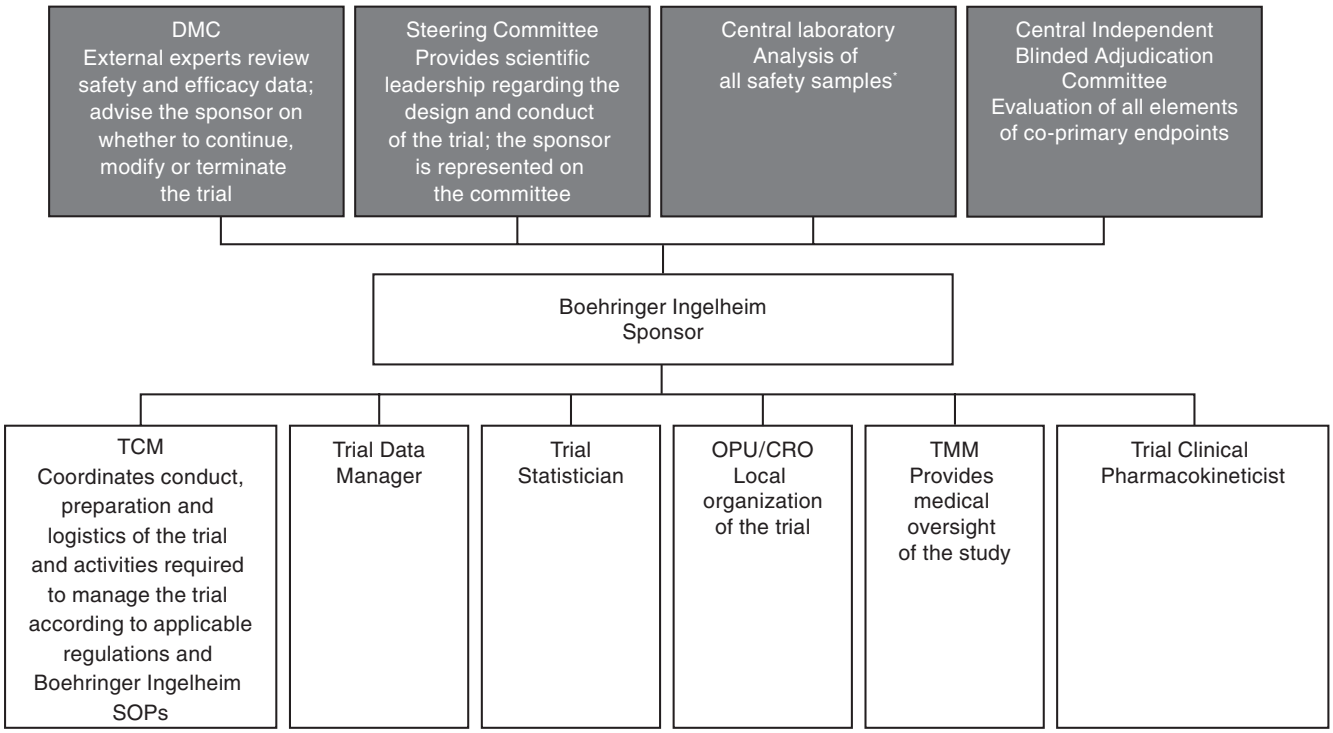

FIGURE 1 Trial administrative and oversight structure. The figure shows the organization and relationships of the roles and committees involved in the administration, oversight of the trial, and the trial sponsor. CRO, contract research organization; DMC, data monitoring committee; OPU, local Boehringer Ingelheim operating unit; SOP, standard operating procedure; TCM, trial clinical monitor; TMM, team member medicine. *Local laboratories may be employed after consultation with the sponsor to evaluate some assays, such as diluted thrombin time for the evaluation of dabigatran activity, international normalized ratio, serum creatinine and hemoglobin

The starting dose for each participant will be determined based on individual body weight and age using a specially developed nomogram, with the aim of attaining a target steady-state plasma concentration of dabigatran comparable with the observed plasma dabigatran concentration in adult VTE patients.[20,36] As dabigatran is predominantly (approximately 80%) renally excreted,[27,28] and its PK/PD relationship in children appears to be similar to that in adults,[33,34] the doses in the nomogram were estimated using a scaling method developed by Hayton et al.[29] that is considered applicable for drugs that are predominantly renally excreted. Using this method, the dose for an adult reference subject is scaled down according to a child's expected maturation of renal function, which is defined based on age and weight assuming that there is no renal impairment.[29] Dosing based on the Hayton formula results in a more individualized dosing algorithm in children. During the study, the suitability of the dosage determined for each patient will be confirmed by measuring steady-state trough plasma concentrations of dabigatran by high-pressure liquid chromatography–tandem-mass spectrometry (HPLC-MS/MS), dTT (calibrated for determining dabigatran plasma concentrations), or an alternative registered assay. Concentrations will be measured as the predose steady-state plasma concentration ($C_{pre,ss}$) in samples from visits 3-11 (Table 2), 10-16 h after the previous dose. The first opportunity to evaluate and adjust dosage will therefore be after six consecutive doses have been taken, during the first week of treatment. If necessary, the dose will be adjusted. If the dabigatran concentration is not within the required range after one dose adjustment, the patient will be withdrawn from study treatment. The dosing regimen will be reviewed on an ongoing basis by the DMC and may be revised during the study as PK, safety, and efficacy data are obtained.

3.5 | Outcome measures

All efficacy criteria in this study are considered safety-related.

3.6 | Primary outcomes

The primary study outcomes are shown in Table 4. For the VTE outcome, all new or recurrent suspected episodes will be evaluated using appropriate imaging modalities following local guidelines or as deemed necessary by the investigator and classified according to the recommendations for perinatal and pediatric patients of the International Society on Thrombosis and Haemostasis (ISTH).[13] These recommendations will also be used to classify bleeding events as major bleeding, minor bleeding, or clinically relevant non-major bleeding.

3.7 | Secondary outcomes

Secondary outcomes are shown in Table 4. PTS will be evaluated using the modified Villalta score, one of the two pediatric PTS scores

TABLE 3 Summary of key inclusion and exclusion criteria for the study

Inclusion criteria	Exclusion criteria
• Males or females aged 0 to <18 years at time of informed consent/assent • Previously documented objective diagnosis of VTE (eg, DVT, PE, central line thrombosis, sinus vein thrombosis), initially treated for ≥3 months (if treated with oral VKA at an intended INR of 2.0-3.0) or • Completed the treatment period in an open-label study comparing the efficacy and safety of dabigatran etexilate vs. standard-of-care in pediatric patients VTE (NCT01895777)[a] and who also require continuation of anticoagulation for secondary prevention of VTE • Have an unresolved clinical risk factor for VTE that requires further anticoagulation for secondary prevention Risk factors include having a central venous line, presence of underlying disease (eg, cancer), antiphospholipid antibodies, systemic lupus erythematosus, diagnosis of thrombophilia	• Conditions associated with an increased risk of bleeding • Renal dysfunction (eGFR <80 mL/min/1.73m^2 using the Schwartz formula) or requirement for dialysis • Active infective endocarditis • Heart valve prosthesis requiring anticoagulation • Hepatic disease (including active liver disease [eg, hepatitis A, B, or C], or persistent ALT/AST/AP >3 X ULN within 3 months of screening) • Pregnant or breast-feeding females • Females who have reached menarche and are not using an acceptable method of birth control, or who do not plan to continue using this method throughout the study and/or do not agree to adhere to pregnancy testing required by the protocol • Patients in age group 0 to <2 years with gestational age at birth <37 weeks or with body weight lower than the third percentile (according to the WHO child growth standards) • Anemia (hemoglobin <80 g/l) or thrombocytopenia (platelet count <80 × 10^9/l) at screening. Transfusions during the screening period are allowed, provided a satisfactory hemoglobin or platelet level is attained prior to visit 2 • Allergy or sensitivity to any component of the study medication or its solvent

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate transaminase; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; PE, pulmonary embolism; ULN, upper limit of normal; VKA, vitamin K antagonist; VTE, venous thromboembolism; WHO, World Health Organization.

[a]Except for those who switched from dabigatran etexilate to standard care during this study.

recognized by the ISTH.[10,37] For the PK evaluations, dabigatran exposure will be evaluated by HPLC-MS/MS as $C_{pre,ss}$ at visit 3 and/or at future visits if required.

3.8 | Additional outcomes

Compliance will be calculated as a percentage from the actual number of dabigatran etexilate doses taken since the last count versus the number of dabigatran etexilate doses that should have been taken in the same period, based on the amounts of medication returned and verbal report. Parents or guardians will be requested to bring all remaining trial medication to every clinic visit. Empty capsule containers, pellets boxes, or solution vials will also be requested for compliance evaluations and disposal. Parents or guardians will be requested to document failed or missed medication intake and provide information at the next study visit, and also to inform the investigator immediately if two or more consecutive doses are missed.

3.9 | Adverse event reporting

All AEs during the study will be recorded as on-treatment AEs, as will any that occur during the residual effect period for dabigatran (defined as 3 days after the last dose). Events will not have to have a causal relationship with treatment to be considered on-treatment AEs. Hepatic toxicity, defined as elevations of aspartate transaminase and or alanine transaminase ≥3 times the upper limit of normal (ULN) combined with elevated total bilirubin ≥2 × ULN found in the same blood sample, or renal dysfunction defined as an increase in creatinine of ≥2-fold from baseline to above the ULN, are considered AEs of special interest in this study. These events, and also serious AEs and non-serious AEs relevant to a serious AE, must be reported to the sponsor within 24 h.

3.10 | Determination of sample size

As discussed and agreed with the European Medicines Agency's Paediatric Committee, a sample size of 100 patients is considered adequate to capture any safety signal for the primary safety endpoints defined in the study (at least one recurrent VTE, major bleed, or thromboembolic event–related death during the 12-month study), with 99% probability if the true composite event rate is 5%, or with 63% probability if the true event rate is 1%. Although the follow-up periods of the various studies of VTE recurrence have varied from several months to several years,[6,8] based on these results, such predicted event rates during the 12-month study period are realistic. However, should the proposed sample size of 100 patients prove to be insufficient and the DMC decides that additional safety data are required, recruitment will be kept open beyond 100 patients.

TABLE 4 Study primary and secondary endpoints

Primary endpoints
• Recurrence of VTE at 6 and 12 months, defined as[13]: o All recurrent VTE, as either contiguous progression or non-contiguous new thrombus including DVT, PE, paradoxical embolism • Mortality overall and related to thrombotic or thromboembolic events at 6 and 12 months • Major and minor (including clinically non-relevant bleeding events) at 6 and 12 months, defined as[13]: o Major bleeding ■ Fatal bleeding ■ Clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dl (20 g/l) in a 24-hour period ■ Bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system ■ Bleeding that requires surgical intervention in an operating suite o Clinically relevant non-major bleeding ■ Overt bleeding for which a blood product is administered and that is not directly attributable to the patient's underlying medical condition ■ Bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite o Minor bleeding ■ Any overt or macroscopic evidence of bleeding that does not fulfil the criteria for either major bleeding or clinically relevant, non-major bleeding • Overall mortality and thrombotic or thromboembolism-related mortality
Secondary endpoints
• Occurrence of post-thrombotic syndrome at 6 and 12 months • PD evaluations (ie, aPTT and ECT) at visit 4 • Number of dabigatran etexilate dose adjustments required during the treatment period

aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; ECT, ecarin clotting time; PD, pharmacodynamics; PE, pulmonary embolism; VTE, venous thromboembolism.

3.11 | Data and statistical analysis

Findings for the primary outcomes and for the secondary PTS outcome will be presented as time-to-event values and summarized as Kaplan–Meier estimates with rates of occurrence at 6 and 12 months; descriptive rates for each outcome will also be calculated. Subgroups may be explored when appropriate, including but not limited to age groups, and type and duration of standard of care treatment at study entry. Patients with early withdrawal or lost to follow-up will be deemed non-events for the descriptive analyses; patients who withdraw early or who are lost to follow-up, as well as those who do not have VTE or bleeding episodes, will be censored from the survival analyses.

PK results will be summarized descriptively and compared with exposure data from previous studies in adult patients and healthy volunteers. Data on dose adjustments during the treatment period will be summarized descriptively. The PD findings will be evaluated using descriptive statistics and ratios to baseline (ie, visit 2), also determined to explore the dose-coagulation response relationship in this pediatric population. PK and PD and PK/PD relationships will be further explored using graphical analyses. All patients with ≥1 post-baseline measurement will be included in the PK/PD full analysis set. Descriptive statistics will be utilized for overall assessments of safety and AEs.

4 | DISCUSSION

This study has been designed (as agreed with the European Medicines Agency's Paediatric Committee) to evaluate the safety of extended anticoagulant therapy with dabigatran etexilate for the secondary prevention of VTE in ≥100 children aged 0 to <18 years. An open-label design will enable ongoing DMC review of outcomes within this study, as well as of other related studies. This will not only ensure the safety of participating patients but will also enable modification of the study design and decisions on the inclusion of the 0 to <2-year-old age group and, if emerging data warrant, recruitment of additional participants. The single-arm design and patient sample size are considered appropriate for a safety study such as this. However, the study should be considered as part of the wider pediatric dabigatran development program, which includes the phase III study NCT01895777, which is to provide efficacy and safety data for dabigatran compared with standard-of-care for the acute treatment of VTE in 180 patients. Although the two trial populations differ (acute and secondary VTE) they are considered to be similar enough to allow bleeding outcome data from the comparator arm of study NCT01895777 to be compared to bleeding outcomes in the current study. When considered as a study program, the two studies combined will provide VTE data for over 280 patients.

The additional central adjudication of VTE and bleeding events by an independent panel will allow for accurate and consistent classification of events, which should enable comparison with data from other sites and other studies. Use of recognized pediatric-specific VTE and bleeding-event classification criteria[13] and of a pediatric PTS scoring system[10,37,38] will also aid such comparisons.

Orally administered dabigatran etexilate may overcome some of the compliance-related challenges presented by currently available treatments; for example, LMWH requires subcutaneous injection,[1] and the physiologically age-appropriate lower circulating levels of antithrombin (eg, in newborns and infants aged ≤6 months or due to underlying disease),[1,6,24] may affect its activity in some patients. Dosing according to the nomogram has led to comparable exposure between pediatric and adult VTE patients and, in addition, the PK/PD relationship is found to be similar between these two patient populations in phase 2a studies.[33,34] Routine coagulation monitoring is not required during its use for the treatment and secondary prevention of VTE in adults.[16–20] The available PK and PD data from this study along with study NCT01895777 will be used to refine the nomogram procedure for determining pediatric dabigatran etexilate dosages. Data on compliance, as well as the availability of different

types of oral formulations, will provide further information on the suitability of dabigatran etexilate for pediatric use and also aid formulation selection.

Estimates of the risks of VTE recurrence after an initial event in children vary[8,9]; however, in children, as in adults, recurrence is associated with increased morbidity and mortality,[1,2,6,7] hence extended anticoagulant therapy may be warranted until VTE risk factors are resolved.[1] Further, although estimates of rates of PTS in children vary considerably,[7,9–11] it has been found to be associated with increased morbidity and cost.[39] There have been far fewer studies on the natural history, treatment, and secondary prevention of VTE in children than in adults.[1,9,40] Collaborative efforts between industry and academia, as in this study, are needed to enable the implementation of well-designed, adequately powered trials that can address this lack of data and investigate potentially advantageous new anticoagulant options. Although this study is focused on the safety of dabigatran etexilate, additional data will be collected to evaluate the rates of VTE recurrence in children with persisting risk factors for VTE, on anticoagulant-related bleeding risk, and on PTS after an initial VTE episode.

The in vitro and clinical investigation plan for dabigatran etexilate in children is in agreement with ISTH SCC recommendations regarding the key components of a pediatric investigation plan for an anticoagulant drug.[41] As per the ISTH recommendations, the evaluation of dabigatran in pediatric patients has followed a stepwise approach, beginning with adolescents and then proceeding to younger age groups. In addition, previous dabigatran studies have confirmed that the PK-PD relationship in children is comparable with that seen in adults.[32,33] The design of the phase 3 study we describe in this paper takes into consideration the efficacy and safety data of dabigatran in adults with VTE (due to the difficulties of conducting a fully powered study in children) and will also continue to assess PK and PD parameters, as per the ISTH recommendations for pediatric VTE clinical studies.[41] In addition, the study will evaluate age-appropriate formulations of dabigatran (pellets and an oral liquid formulation), the importance of which is highlighted in the ISTH recommendations.[41]

5 | STUDY LIMITATIONS

This study has some design limitations that affect extrapolation of its findings beyond the predetermined safety objectives. As the overriding objective of this study is to evaluate the safety of dabigatran etexilate, the design does not include a comparator arm or efficacy endpoints. However, this study will provide safety data that will be complementary to those obtained from study NCT01895777, which does contain a standard-of-care comparator arm. Additionally, regulatory guidance notes that findings on efficacy can be extrapolated from adults to children if the effects of a drug and the course of a disease are similar in both populations.[31] Finally, the duration of treatment in this study will be 12 months, which may not be long enough to identify certain long-term complications (eg, osteoporosis) that have been reported with long-term oral VKA use in pediatric patients,[1,42] or to provide more information on PTS, which can also be a longer-term complication of VTE.[1] With regard to PTS, it is also important to note that some patients recruited into this study will have been treated for the previous 3 months with dabigatran for their first episode of VTE and some with standard care.

6 | CONCLUSIONS

This study is designed to provide data on the safety of dabigatran etexilate for the secondary prevention of VTE in children aged 0 to 18 years during up to 12 months of treatment. It will provide information to further guide dabigatran dosing for pediatric patients and about treatment compliance and choice of formulations for this population. Further data on the natural history of VTE recurrence in children and the risk of consequences such as PTS will also become available as a result of this study.

ACKNOWLEDGMENTS

The study was funded by Boehringer Ingelheim Pharma GmbH & Co. KG. Medical writing assistance was provided by Debbie Sherwood of PAREXEL, with funding from Boehringer Ingelheim.

RELATIONSHIP DISCLOSURES

M. Luciani, M. Albisetti, L. Bomgaars, E. Chalmers, and J.M.L. Halton are members of a Paediatric Expert Working Group for Boehringer Ingelheim. B. Biss, M. Brueckmann, S. Gropper, R. Harper, F. Huang, I. Manastirski, I. Tartakovsky, and B. Wang are employees of Boehringer Ingelheim. L.G. Mitchell is a consultant for Boehringer Ingelheim, Pfizer, and Bristol-Myers Squibb. L. R. Brandão has served as a consultant for Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS

B. Biss is the Associate Trial Clinical Monitor and is responsible for coordinating and managing the trial in accordance with applicable regulations, as well as directing the clinical trial team in the preparation, conduct, and reporting of the trial. M. Brueckmann, S. Gropper, R. Harper, and I. Tartakovsky were involved in the development of the study design, its conduct, and the development and review of this publication. F. Huang is the Trial Clinical Pharmacokineticist and is responsible for the applied dosing nomogram in this study and was involved in the development and review of this publication. I. Manastirski is the Trial Clinical Monitor and is responsible for coordinating and managing the trial in accordance with applicable regulations, as well as directing the clinical trial team in the preparation, conduct, and reporting of the trial. B. Wang is the Trial Statistician and is involved in the development of the study design, its conduct, and the development and review of this publication. M. Luciani, M. Albisetti, L. Bomgaars, E. Chalmers, J.M.L. Halton, L.G. Mitchell,

and L. R. Brandão are members of the pediatric expert board with oversight over the study; they were involved in the development of the study design, its conduct, and the development and review of the paper.

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How to cite this article: Luciani M, Albisetti M, Biss B, et al. Phase 3, single-arm, multicenter study of dabigatran etexilate for secondary prevention of venous thromboembolism in children: Rationale and design. *Res Pract Thromb Haemost*. 2018;2:580–590. https://doi.org/10.1002/rth2.12093