Received: 29 June 2017 | Accepted: 26 January 2018

DOI: 10.1002/rth2.12086

ORIGINAL ARTICLE

rpth research & practice in thrombosis & haemostasis

Design and rationale for the DIVERSITY study: An open-label, randomized study of dabigatran etexilate for pediatric venous thromboembolism

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

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

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

[3]Department for Pediatrics, Baylor College of Medicine, Houston, TX, USA

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

[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, Scotland

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

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

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

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

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

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

Correspondence
Manuela Albisetti, Hematology Department, University Children's Hospital, Zürich, Switzerland.
Email: manuela.albisetti@kispi.uzh.ch

Funding information
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

Abstract

Background: The current standard of care (SOC) for pediatric venous thromboembolism (VTE) comprises unfractionated heparin (UFH), or low-molecular-weight heparin (LMWH) followed by LMWH or vitamin K antagonists, all of which have limitations. Dabigatran etexilate (DE) has demonstrated efficacy and safety for adult VTE and has the potential to overcome some of the limitations of the current SOC. Pediatric trials are needed to establish dosing in children and to confirm that results obtained in adults are applicable in the pediatric setting.

Objectives: To describe the design and rationale of a planned phase IIb/III trial that will evaluate a proposed dosing algorithm for DE and assess the safety and efficacy of DE versus SOC for pediatric VTE treatment.

Patients/Methods: An open-label, randomized, parallel-group noninferiority study will be conducted in approximately 180 patients aged 0 to <18 years with VTE, who have received initial UFH or LMWH treatment and who are expected to require ≥3 months of anticoagulation therapy. Patients will receive DE or SOC for 3 months. DE will be administered twice daily as capsules, pellets, or an oral liquid formulation according to patient age. Initial doses will be calculated using a proposed dosing algorithm.

Results: There will be two coprimary endpoints: a composite efficacy endpoint comprising the proportion of patients with complete thrombus resolution, freedom from recurrent VTE and VTE-related mortality, and a safety endpoint: freedom from major bleeding events.

Conclusion: Findings will provide valuable information regarding the efficacy and safety of DE for the treatment of pediatric VTE. ClinicalTrials.gov registration number: NCT01895777.

KEYWORDS

anticoagulants, dabigatran etexilate, direct thrombin inhibitors, pediatrics, venous thromboembolism

Essentials

- Current standard of care (SOC) for pediatric venous thromboembolism (VTE) has limitations.
- Dabigatran etexilate (DE) versus SOC will be studied in children with VTE in a phase IIb/III trial.
- A dosing algorithm for DE in children will be assessed guiding dosing.
- Valuable data on the safety and efficacy of DE for VTE in children will be obtained.

1 | INTRODUCTION

Venous thromboembolism (VTE) in children is associated with considerable morbidity and mortality.[1] The overall annual incidence of VTE in the pediatric population is approximately 0.07-0.14 events per 10 000 children, but this number is increasing,[2–4] which may be explained by improved detection of previously undiagnosed cases, increased awareness of VTE in children in pediatric hospitals, more frequent use of central venous lines (which is the most common risk factor for VTE in younger children), and improved survival from previously fatal conditions.[4,5]

The current standard of care (SOC) in pediatric VTE is initial treatment with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), then followed by LMWH or vitamin K antagonists (VKA).[6–8] However, all of these agents have limitations; LMWH, for example, is administered by subcutaneous injection, which may be a burden for both children and caregivers, whereas VKAs require coagulation monitoring, and are associated with drug–drug and drug–food interactions, which hamper the time within the therapeutic target range.[5,6,8]

Treatment recommendations for children are similar to those for adults and are based on extrapolation of data from adult clinical trials.[8] Nevertheless, there are important differences to consider with regard to VTE epidemiology and management in adults and children (especially in very young children). First, unlike in adults, VTEs in children usually occur secondarily to another identifiable risk factor, most commonly the presence of a central venous line, particularly in neonates and infants. Other risk factors include underlying conditions such as cancer or congenital heart disease.[2,8,9] Second, there are age-related differences in the hemostatic and coagulation systems that affect the pathophysiology of thrombosis and the effects of anticoagulant treatments.[7,8,10] Finally, distribution, binding, and clearance of drugs can all be affected by age; for example, when dosing renally excreted drugs in children, kidney maturation must be considered.[8,11] Given these differences, application of adult treatment recommendations to children may be inappropriate. Consequently, it is necessary to conduct pharmacologic evaluations of anticoagulants, specifically in pediatric patients.[7,10]

The direct thrombin inhibitor dabigatran, which is orally administered as the prodrug dabigatran etexilate (DE),[12] has demonstrated efficacy and safety in adults with VTE and may overcome some of the limitations associated with current SOC (UFH, LMWH, and VKA).[12–14] In addition, the mechanism of action of DE is independent of endogenous thrombin, levels of which are physiologically lower in children

than adults, thus offering a potential benefit over UFH/LMWH, which act by directly binding antithrombin.[6] To date, findings from studies conducted in children and adolescents are comparable to those seen in adults in terms of safety and pharmacokinetic (PK)/pharmacodynamic (PD) relationships (Table 1).[15–17] Moreover, because dabigatran is predominately excreted renally,[18] dosing according to renal function may lead to comparable exposure between adults and pediatric patients.[19]

2 | OBJECTIVE

The objective of the current manuscript is to describe the rationale and design of a study, the aim of which is to evaluate the appropriateness of a proposed DE dosing algorithm in pediatric patients aged between 0 and <18 years and to assess the safety and efficacy of DE versus SOC for the treatment of VTE in this patient group.

3 | MATERIALS AND METHODS

This is a phase IIb/III, noninferiority, open-label, randomized, parallel-group study that will be conducted in ~100 sites in ~30 countries. The trial is sponsored by Boehringer Ingelheim. An independent data monitoring committee (DMC) will assess the safety, tolerability, and efficacy, and will provide recommendations to the sponsor regarding continuation, modification, or termination of the study. A central independent adjudication committee, which will be blinded to treatment groups, will evaluate all elements of the coprimary endpoints and confirm or refute outcome events. Scientific leadership regarding study design and conduct will be provided by a steering committee. The administrative structure of the trial is shown in Figure 1.

The target population will comprise male and female patients aged 0-17 years with an objectively confirmed diagnosis of VTE (eg, deep vein thrombosis, pulmonary embolism, and/or cerebral venous sinus thrombosis). Individuals who have received initial parenteral treatment with UFH or LMWH for a minimum of 5 days (usually 5-7 days and no longer than 21 days) and who are expected to require anticoagulation therapy for at least 3 months (including an initial parenteral phase) will be eligible for study inclusion. A list of all inclusion and exclusion criteria is provided in Table 2.

Patients will be stratified into three age groups: stratum 1 (12 to <18 years), stratum 2 (2 to <12 years), and stratum 3 (birth to <2 years); recruitment will begin in stratum 1 then proceed to strata 2 and 3 based on recommendations from the DMC. The study will be conducted in accordance with the Declaration of Helsinki[20] and will be approved by an institutional review board/independent ethics committee and a competent authority according to national and international regulations. Written informed consent must be obtained from patients or their legal representatives according to the International Conference on Harmonisation Good Clinical Practice[21] and the regulatory and legal requirements of each participating country. The trial will be conducted according to the principles of Good Clinical Practice. Trial-related monitoring, audits, institutional

TABLE 1 Clinical studies of DE in pediatric subjects

Study	Objective	Age of subjects	Findings
NCT00844415[16]	Phase IIa trial to assess the safety, PK, and PD of DE capsules bid for 3 days after standard anticoagulant therapy for treatment of primary VTE. Patients initially received 1.71 (±10%) mg/kg (80% of a 150 mg/70 kg bid adult dose), followed by 2.14 (±10%) mg/kg (target adult dose adjusted for patient's weight).	12-<18 years (n = 9)	DE was generally well tolerated apart from two cases of mild dyspepsia. The PK/PD relationship was comparable to that seen in adults; the relationship between dabigatran plasma concentration was linear for dTT and ECT and nonlinear for aPTT.
NCT01083732[15]	Phase IIa study to assess PK, PD, safety, and tolerability of a single dose of an oral solution of DE, following standard anticoagulant therapy for treatment of VTE. DE was administered at a weight- and age-adjusted dose (calculated using a nomogram) equivalent to 150 mg bid in adults.	1-<12 years: Two groups: 1-<2 years (n = 6); 2-<12 years (n = 12)	The projected steady-state dabigatran trough concentrations were largely comparable to those seen in adult patients.[12] A linear PK/PD relationship was observed for ECT and dTT; nonlinear relationships were seen for aPTT; PK/PD relationships were comparable to those in adults and adolescents. The oral solution of DE was well tolerated.
NCT02223260[17]	Phase IIa study to assess PK, PD, safety, and tolerability of a single dose of DE oral solution (based on weight- and age-adjusted nomogram) given after standard anticoagulant therapy in neonates with VTE.	Birth to <1 year (n = 8)	The projected steady-state dabigatran trough concentrations were largely comparable to those observed in adult patients.[12] A linear PK/PD relationship was observed for ECT and dTT; nonlinear relationships were seen for aPTT; PK/PD relationships were comparable to those in adults and adolescents. The oral solution of DE was well tolerated.

aPTT, activated partial thromboplastin time; bid, twice daily; DE, dabigatran etexilate; dTT, diluted thrombin time; ECT, ecarin clotting time; PD, pharmacodynamics; PK, pharmacokinetics; VTE, venous thromboembolism.

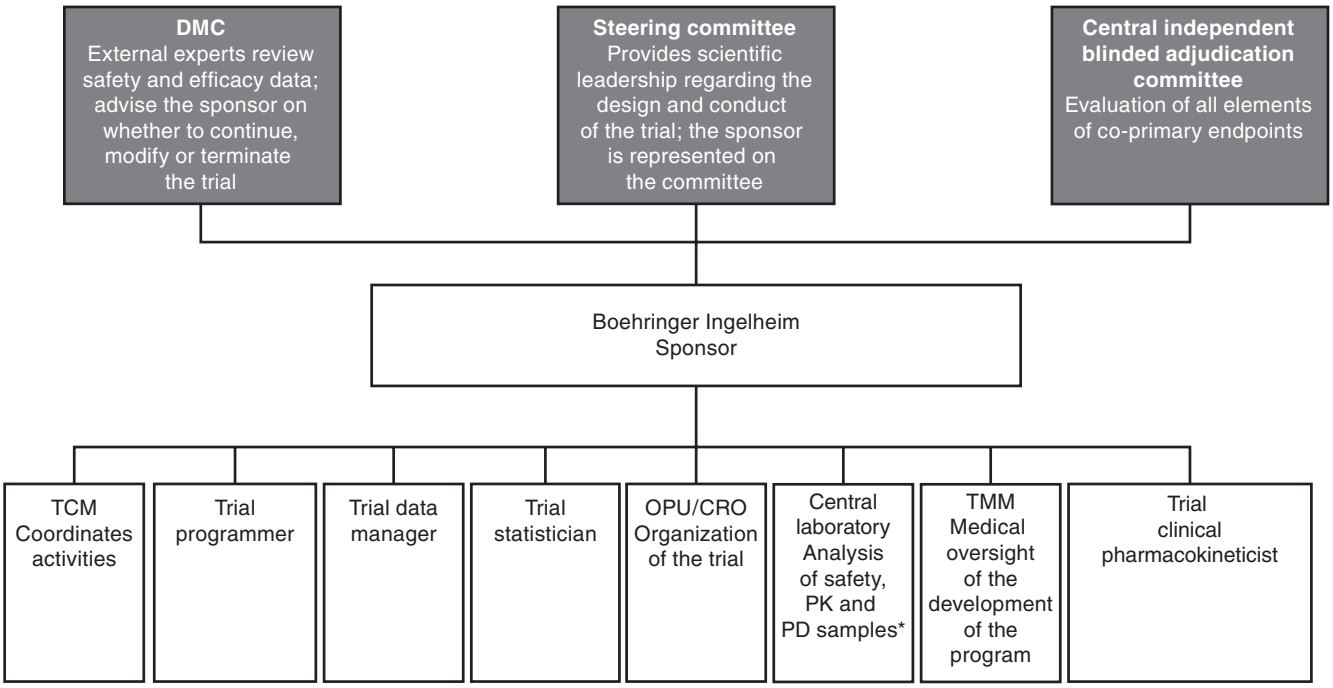

FIGURE 1 Administrative structure of the trial. CRO, contract research organization; DMC, data monitoring committee; OPU, local Boehringer Ingelheim operating unit; PK, pharmacokinetics; PD, pharmacodynamics; TCM, trial clinical monitor; TMM, team member medicine. *If approved by the sponsor, a local laboratory may be used in certain circumstances to analyze safety samples; PK and PD plasma samples may be analyzed at CROs.

review board/independent ethics committee review, and regulatory inspections will be performed to verify the accuracy of the data.

Patients will be randomized 2:1 to receive DE or SOC with LMWH or VKA. Randomization will be managed by Interactive Response Technology. DE will be administered twice daily (bid) as capsules, pellets, or an oral liquid formulation depending on the age of the patient and their ability to swallow capsules or pellets. Capsules will be given to patients aged 8-18 years who are able to swallow capsules; pellets will be given to patients aged 6 months to <8 years (and those aged ≥8 to <12 years who are unable to swallow capsules); an oral liquid formulation will be administered to patients aged 0 to <6 months (and those aged 6 to <12 months who are unable to take pellets).

According to guidance from the US Food and Drug Administration (FDA), findings on drug efficacy may be extrapolated from adults to children if the course of a disease and the effects of a particular drug treatment are similar between the two populations.[22] Although differences exist in the pathophysiology of pediatric and adult VTE[9] the principal pathological causes outlined in the Virchow triad (vessel wall abnormality, blood flow disturbances, and coagulability of the blood) largely apply to both. PD data obtained from previous studies indicate that the response to dabigatran in children is similar to that seen in adults.[15,17,23,24] Based on these similarities and in line with FDA guidelines, it was considered reasonable to assume that DE will be effective in pediatric patients.

It is generally accepted and recommended by regulatory agencies that pediatric dosing should lead to exposure comparable to that of adult levels, if a similar PK/PD relationship has been demonstrated.[25] Data from an in vitro study, previous phase II pediatric VTE studies of dabigatran, and a subsequent pooled analysis of pediatric PK/PD data, demonstrate that the PK/PD relationship observed in pediatric patients (from birth to <18 years old) was fairly consistent across ages, with the exception of those aged <1 month, and was similar to that seen in adults with VTE.[15,17,23,24] Therefore, for the current study it was deemed appropriate to target dabigatran exposure levels shown to be effective in the adult population.

Age determines the renal function of a child, which is essential for the dosing of DE, and therefore the dosing in children differs from adult dosing. Whereas changes in renal function are physiological across the years of childhood, maturation of renal function is completed after adolescence allowing for simplified fixed dosing in healthy adults. Dosing based on Hayton's formula[19] accounts for the maturation of renal function across childhood, resulting in a more individualized dosing algorithm in children. As renal function in children and adolescents is relatively higher than in adults, dose estimations were based on a young adult patient (reference patient: 20 years old; 70 kg) whose renal function more closely resembled that of the target pediatric population. Hayton predicted a glomerular filtration rate of 136 mL/min for a 20-year-old patient of 70 kg body weight.[19] To achieve the median trough exposure as observed in a typical adult patient given dabigatran 150 mg bid, the 20-year-old reference patient would need to receive a dose of 300 mg bid. This dose and reference patient was used as the denominator to derive fractional dosages for pediatric patients according to a child's estimated renal function.

TABLE 2 Inclusion and exclusion criteria

Inclusion criteria
Male or female subjects aged 0-<18 years
Documented diagnosis of VTE (eg, DVT, PE, central line thrombosis, sinus vein thrombosis), initially treated with parenteral anticoagulation, eg, UFH, LMWH, in general for 5-7 days; no more than 21 days
Anticipated treatment with anticoagulants for VTE for at least 3 months (including initial parenteral treatment period)
Written informed consent from parent/legal guardian and agreement of patient (if applicable)
Exclusion criteria
Conditions associated with an increased risk of bleeding
Any prior intracranial hemorrhage
Intracranial or intraspinal surgeries within 6 months of visit 2; any other major surgery within 4 weeks of visit 2
Any major planned procedure with increased risk of bleeding within 5 days prior to study treatment
History of intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding unless cause permanently resolved
Gastrointestinal hemorrhage within the year prior to screening unless cause permanently resolved
History of gastroduodenal ulcer disease
History of hemorrhagic disorder or bleeding diathesis
Fibrinolytic agents within 48 h of DE administration
Uncontrolled hypertension on antihypertensive treatment
Any other disease, condition or intervention with increased bleeding risk
Renal dysfunction (eGFR <60 mL/min/1.73 m^2 for patients aged 12-<18 years or eGFR <80 mL/min/1.73 m^2 for patients aged 0-<12 years or requirement for dialysis
Active infective endocarditis
Prosthetic heart valve requiring anticoagulation
Hepatic disease
Active liver disease including active hepatitis A, B, and C
Persistent ALT or AST or AP > 3 × ULN within prior 3 months
Pregnant or breastfeeding. Female patients who have reached menarche but not using contraceptive
Patients in stratum 3 (0-<2 years) with gestational age at birth <37 weeks or with body weight lower than the third percentile
Anemia (hemoglobin <80 g/L) thrombocytopenia (platelet count <80 × 10^9/L) at screening
Taken prohibited or restricted medication within 1 week of the first dose of study medication other than medication for prior VTE treatment and P-glycoprotein inhibitors
Taken an investigational drug in the past 30 days
Allergic/sensitive to any component of study medication
Patients or parents/legal guardians considered unreliable to participate or any condition that would be a safety hazard to the patients
Patients or parents/legal guardians unwilling or unable to undergo or permit repeat of baseline imaging tests to confirm thrombus resolution at study day 84 (or at early end of treatment) or patients in whom such repeat tests would not be in their best interest medically

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, alanine aminotransferase; DE, dabigatran etexilate; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; ULN, upper limit of normal; VTE, venous thromboembolism.

The chosen dosing nomogram based on Hayton's formula[19] has been applied in previous pediatric phase IIa studies of DE.[15,17] In these studies, dabigatran exposure achieved with the dosing nomogram in VTE patients from birth to 12 years of age[15,17] was comparable to that seen in adult patients,[12] indicating that it is appropriate to use in the pediatric population.

Initial doses are expected to achieve steady-state trough concentrations of dabigatran of between 50 and <250 ng/mL. Thereafter, DE may be titrated up or down (if needed) throughout the study period, to maintain steady-state trough plasma concentrations within this range. The chosen lower and upper limits of 50 and <250 ng/mL, respectively, are based on findings in adult patients[12,14,26–28] and represent a range in which a beneficial benefit-risk balance is expected. PK simulations show that a bid dosing regimen with calculated doses (with a maximum 330 mg bid starting dose) reduces the probability of trough levels falling below 50 ng/mL and 25 ng/mL to approximately 18% and 3%, respectively, ie, exposure will be sufficient for the vast majority of patients.

Levels will be measured within the first week of dosing to potentially adjust the dose. A 3-month treatment period (which includes the initial parenteral treatment phase) will precede a 1-month follow-up phase. At the follow-up visit, patients will be assessed for VTE. Eligible patients with an unresolved clinical risk factor at the end of the 3-month treatment period may continue into study NCT02197416, a phase III, single-arm study of DE for secondary VTE prevention in patients aged 0 to <18 years, who will be evaluated for up to 12 months.

The coprimary endpoints are as follows: (i) composite efficacy endpoint: the proportion of patients with complete thrombus resolution, freedom from recurrent VTE (including symptomatic and asymptomatic, contiguous progression or noncontiguous new thrombus, deep vein thrombosis, pulmonary and paradoxical embolism and thrombus progression) and freedom from VTE-related mortality[29]; and (ii) safety endpoint: freedom from major bleeding events defined as fatal bleeding, clinically overt bleeding associated with a decrease in hemoglobin of at least 20 g/L in 24 h, bleeding that is retroperitoneal, pulmonary, intracranial or otherwise involving the central nervous system, or bleeding that requires an operation.[29]

All components of the coprimary safety and efficacy endpoints will be centrally adjudicated by an independent blinded committee. All secondary endpoints and other assessments are listed in Table 3. Time periods, visits, and key assessments are shown in Table 4. The trial aims to include a minimum of 180 patients who will be evaluable for the coprimary endpoints. Recruitment will be driven by opening new sites in additional countries, to ensure that the minimum number of patients are included. Study teams will also be encouraged to increase awareness of asymptomatic pediatric VTE.

3.1 | SAMPLE SIZE RATIONALE AND ANALYSIS PLAN

The efficacy and safety coprimary endpoints will be tested for noninferiority using a noninferiority margin of 20% and 9%, respectively,

TABLE 3 Secondary and other endpoints

Secondary endpoints
PK and PD assessments 3 days after start of treatment (after at least six consecutive DE doses) and after 3 days following any DE dose adjustment
Frequency of dose adjustments, temporary and permanent discontinuation from therapy and number of laboratory monitoring requirements for dose adjustment during the treatment phase
Frequency of switch of type of anticoagulation therapy (including dabigatran to SOC) and a switch from an intended SOC to another SOC
Freedom from thrombus progression at the end of treatment (day 84 after randomization or the early end of treatment)
Acceptability of an age-appropriate formulation at end of treatment
All bleeding events
All-cause mortality
All components of the coprimary efficacy endpoints
Other endpoints
Proportion of patients with thrombus progression, unchanged thrombus, thrombus with partial regression, and complete resolution per treatment group at day 84 after randomization or at the early end of treatment (whichever comes first)
Proportion of patients with freedom from recurrent VTE and freedom from mortality related to VTE
Proportion of patients with either complete or partial thrombus resolution, freedom from recurrent VTE and freedom from mortality related to VTE
Acceptability of capsules, pellets, and OLF reconstituted with flavored or unflavored solvent at 3, 21, and 84 days after randomization

DE, dabigatran etexilate; OLF, oral liquid formulation; PD, pharmacodynamic; PK, pharmacokinetic; SOC, standard of care; VTE, venous thromboembolism.

with a one-sided level of 0.05. Sample size was justified for the efficacy coprimary endpoint. It is assumed that the proportion of patients with complete thrombus resolution and no recurrent VTE or VTE-related death on SOC at 3 months is 72%.[30–40] Given that complete thrombus resolution is expected to be very low (eg, 5% up to at most 20%) without treatment, a noninferiority margin of 20% for the efficacy coprimary endpoint is considered acceptable to preserve at least 62% and up to 70% of the effect size under SOC treatment.

For the coprimary efficacy endpoint, 180 patients will be evaluable in the intent-to-treat population, giving 89% power to demonstrate noninferiority with a margin of 20% at a one-sided significance level of 5%, assuming dabigatran and SOC have equivalent effect. If noninferiority is demonstrated, the coprimary endpoints will subsequently be tested for superiority at a one-sided level of 0.05, without multiplicity correction.

For the efficacy coprimary endpoint, an intent-to-treat analysis will be performed on the randomized set; data will be stratified by age group using a Mantel-Haenszel–type weighted average of differences. The safety coprimary endpoint will be analyzed as a time-to-event endpoint using the Kaplan-Meier method on the treated set; age group stratification will not be used.

A secondary analysis will be performed to assess the proportion of patients with complete thrombus resolution with no recurrent VTE and no VTE-related death using age group as a covariate. All bleeding events and all-cause mortality will be analyzed as a time-to-event endpoint using a stratified Cox proportional hazard model. Components of the coprimary efficacy endpoint will be analyzed as proportions using the same model as the primary analysis. PK and PD assessments will include all treated patients with a baseline and at least one post-baseline PK/PD measurement set; concentrations will be compared descriptively and descriptive statistics will be calculated for the activated partial thromboplastin time, ecarin clotting time, and additional PD assays. In addition, the PK/PD relationship will be examined. Other endpoints will be summarized descriptively.

4 | DISCUSSION

Effective treatment of thromboembolic events is important to prevent significant morbidity and mortality in children. VTE, for instance, can lead to death from pulmonary embolism, nonlethal pulmonary embolism, recurrent VTE, and post-thrombotic syndrome.[2,7] DE may provide an alternative treatment for pediatric VTE, overcoming the limitations of the current SOC, which include the requirement for coagulation monitoring (for VKA), variable PK, the risk of heparin-induced thrombocytopenia (for UFH), and parenteral administration and dependency on antithrombin levels (for UFH and LMWH).[5,6,8] Although data on DE for the treatment of VTE are available from adult patients, studies are still required in pediatric patients due to differences in organ maturation, coagulation system, and dosing.[7,10]

Ease of administration is particularly important for children, who are likely to object to injections and may not be willing or able to swallow capsules, leading to compliance issues. Currently, no licensed pediatric formulations of antithrombotic drugs are available. Therefore, the pellet and oral liquid formulations of DE used in the current study would provide much-needed child-friendly alternatives.

An objective of the current study is to evaluate the appropriateness of the proposed dosing algorithm. Should results confirm that it is appropriate, dabigatran levels may not need to be monitored in children in routine clinical practice. Preliminary findings from earlier phase IIa studies that assessed the PK and PD of single doses of DE administered as an oral liquid formulation in children aged 0 to <12 years indicated that the proposed dosing algorithm is appropriate and leads to comparable exposure between pediatric and adult patients, with moderate variability of plasma concentrations.[15,17] In addition, the PK/PD relationships are similar between pediatric and adult VTE patients.[15,17] The dosing nomogram is also being used in a phase III trial for the secondary prevention of VTE in pediatric patients aged 0 to <18 years (NCT02197416).

The current study is the result of an academic–industry partnership. Collaborations of this nature can provide mutual benefits to both parties, the pharmaceutical company gaining the knowledge of

TABLE 4 Key assessments at each study visit

Trial period	Screening	Treatment period (open-label) with DE or SOC											Follow-up
Study week	−1	1	1[a]	2	3[b]	6	9	12	DE titration visit if needed	INR/anti- Xa visit if needed	Unscheduled visit if needed	eEOT (only for early discontinued patients [before week 12])	12 or eEOT + 28 days[c]
Baseline assessment of VTE	X												
Evaluate thrombosis or symptoms[d]		X	X	X	X	X	X	X	X	X	X	X	X
Assessment of thrombus extension[d]	X							X				X	
aPTT, ECT and dTT (only for DE)		X[e]	X	X	X	X	X	X	X		X[e]	X	
PK sample (only for DE)[f]			X	X	X	X	X	X	X		X	X	
Possible titration of DE			X	X	X	X	X				X		
Possible titration of SOC		X	X	X	X	X	X			X			
Termination of trial medication								X				X	

aPTT, activated partial thromboplastin time; DE, dabigatran etexilate; dTT, diluted thrombin time; ECT, ecarin clotting time; eEOT, early end of treatment; INR, international normalized ratio; PK, pharmacokinetic; SOC, standard of care; VTE, venous thromboembolism.

[a]This visit is only needed for patients taking DE; trough dabigatran concentration is taken to ensure within 50-<250 ng/mL.

[b]This visit should be conducted at least 3 days after visit 4 (study week 2).

[c]End of the trial occurs after approximately 4 months after start of trial drug.

[d]VTE should be evaluated using appropriate imaging.

[e]aPTT and ECT only.

[f]Pre-dose trough PK samples should be taken 10-16 h after the last dose.

leading experts in a given field and benefitting from their first-hand experience of routine clinical practice, and the academic parties receiving funding and essential resources to conduct clinical trials. Collaborative efforts between industry and academia are needed for the implementation of high-quality, well-designed, adequately powered trials, which have previously been lacking in children with VTE, who have historically received treatment based on low-quality evidence extrapolated from adult practice.[41] Having a clear administrative structure (eg, with a steering committee and a data monitoring committee), like the one outlined for the current study, ensures the appropriateness of clinical research conduct for such collaborations.

There are several issues in designing and conducting trials of antithrombotic therapy in children. First, dosing must be adapted to the pediatric population, taking into account developmental changes in the hemostatic system and an individual child's weight (or weight and age).[41] As previously discussed, the dosing strategy in the current study has been carefully considered and is expected to result in safe and effective DE doses. Another major challenge in conducting large anticoagulant trials in children is the low frequency of pediatric VTE.[41] For example, slow recruitment was the reason for early termination of two previous pediatric antithrombotic trials, PROphylaxis of ThromboEmbolism in Kids Trial (PROTEKT) and REVIparin in Venous ThromboEmbolism (REVIVE).[42] In both studies, the final sample size was not sufficient to achieve the anticipated power.[42] The target enrollment count of 180 patients in the current study is considered to be achievable and will allow adequate power to demonstrate the noninferiority of DE versus SOC. To ensure that the minimum number of patients are enrolled, new sites may be opened in additional countries. This strategy of increasing the number of participating sites was used to successfully increase the patient accrual rate in the feasibility phase of Kids-DOTT, a multicenter, randomized controlled trial of shortened (6-week) versus conventional (3-month) duration of anticoagulation for the treatment of venous thrombosis in neonates, children, and young adults.[41,43]

The current study does have limitations. Clinical trials are ideally randomized with a double-blind design. Blinding of the current study is not possible for ethical reasons relating to the vulnerable patient population and due to the difficulties associated with comparing pediatric formulations of DE with SOC that require subcutaneous administration (in the case of LWMH) or monitoring and dose adjustments (in the case of VKA). For example, in order to blind the trial, dummy subcutaneous injections or dummy INR testing would need to be performed for the LWMH and VKA comparisons, respectively, which cannot be justified in pediatric subjects. In addition, a specific comparator is not being used, making comparisons more difficult; however, the choice of an SOC treatment according to local practice is considered to reflect the real-world situation well. Another consideration is the relatively small sample size, although it is considered to be sufficient to provide conclusive information regarding efficacy (VTE resolution and recurrent VTE events), based on the complete resolution rate determined from historical pediatric data. Lastly, the 4-month study period is not sufficient to evaluate the study drugs' effects on prevention of long-term complications of DVT, such as post-thrombotic syndrome, which usually takes at least 1 year to develop following the DVT event.

In conclusion, findings from the current study, which is one of the largest for VTE in pediatric patients, will provide valuable information regarding the efficacy and safety of DE for this indication in this patient population.

ACKNOWLEDGMENTS

All authors have had full access to data and contributed to drafting of paper.

RELATIONSHIP DISCLOSURE

M. Albisetti is a member of a Pediatric 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. Bomgaars is a member of a Pediatric Expert Working Group for Boehringer Ingelheim. L.R. Brandão has acted as a consultant for Boehringer Ingelheim. E. Chalmers is a member of a Pediatric Expert Working Group for Boehringer Ingelheim. M. Luciani is a member of a Pediatric Expert Working Group for Boehringer Ingelheim. L.G. Mitchell is a consultant for Boehringer Ingelheim, Pfizer, and Bristol-Myers Squibb. J.M.L. Halton is a member of a Pediatric Expert Working Group for Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS

I. Manastirski: Trial Clinical Monitor, was responsible for coordinating and managing the trial in accordance with applicable regulations, as well as for 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. B. Wang, Trial Statistician, was involved in the development of the study design, its conduct, and the development and review of this publication. B. Biss, Associate Trial Clinical Monitor, was responsible for coordinating and managing the trial in accordance with applicable regulations, as well as for directing the clinical trial team in the preparation, conduct, and reporting of the trial. F Huang, Trial Clinical Pharmacokinetist, was responsible for the applied dosing nomogram in this study and involved in the development and review of this publication. M. Albisetti, L. Bomgaars, L.R. Brandão, E. Chalmers, M. Luciani, L.G. Mitchell, and J.M.L. Halton are members of the pediatric expert board with oversight over the study; they were involved the development of the study design, its conduct, and the development and review of the paper.

REFERENCES

1. Goldenberg NA. Long-term outcomes of venous thrombosis in children. Curr Opin Hematol. 2005;12:370–6.

2. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood. 1994;83:1251–7.
3. van Ommen CH, Heijboer H, Buller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in the Netherlands. J Pediatr. 2001;139:676–81.
4. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics. 2009;124:1001–8.
5. Chan AK, Monagle P. Updates in thrombosis in pediatrics: where are we after 20 years? Hematology Am Soc Hematol Educ Program. 2012;2012:439–43.
6. Parasuraman S, Goldhaber SZ. Venous thromboembolism in children. Circulation. 2006;113:e12–6.
7. Bonduel MM. Oral anticoagulation therapy in children. Thromb Res. 2006;118:85–94.
8. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e737S–801S.
9. Spentzouris G, Scriven RJ, Lee TK, Labropoulos N. Pediatric venous thromboembolism in relation to adults. J Vasc Surg. 2012;55:1785–93.
10. Kuhle S, Male C, Mitchell L. Developmental hemostasis: pro- and anticoagulant systems during childhood. Semin Thromb Hemost. 2003;29:329–38.
11. Crom WR. Pharmacokinetics in the child. Environ Health Perspect. 1994;102(Suppl. 11):111–7.
12. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361:2342–52.
13. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368:709–18.
14. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129:764–72.
15. Halton JML, Albisetti M, Luciani M, et al. Clinical pharmacology, safety and tolerability of a single-dose oral solution of dabigatran given after standard anticoagulant therapy in children (two age groups: 1-<2 and 2-<12 years old), with venous thromboembolism. Blood. 2016;128:87.
16. Halton JML, Lehr T, Cronin L, et al. Safety, tolerability and clinical pharmacology of dabigatran etexilate in adolescents: an open-label phase IIa study. Thromb Haemost. 2016;116:461–71.
17. Halton JML, Picard A, Harper R, et al. Pharmacokinetics (PK) and pharmacodynamics (PD), safety and tolerability of a single-dose oral solution of dabigatran etexilate given after standard anticoagulant therapy in children from birth to less than one year old, with venous thromboembolism. Blood. 2016;128:1441.
18. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet. 2008;47:285–95.
19. Hayton WL. Maturation and growth of renal function: dosing renally cleared drugs in children. AAPS PharmSci. 2000;2:E3.
20. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310:2191–21-4.
21. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6. International Conference on Harmonisation of Technical Requirements for Registrations of Pharmaceuticals for Human use [updated 2017 May 16]. Available from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
22. US Department of Health and Human Services Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry and review staff: pediatric information incorporated into human prescription drug and biological products labeling [updated 2017 September 20]. Available from https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf
23. Maas H, Gropper S, Huang F, et al. Anticoagulant effects of dabigatran in paediatric patients compared with adults: combined data from three paediatric clinical trials. Res Pract Thromb Haemost. 2017;1:1178.
24. Dietrich K, Stang L, Van Ryn J, Mitchell LG. Assessing the anticoagulant effect of dabigatran in children: an in vitro study. Thromb Res 2015;135:630–5.
25. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). General clinical pharmacology considerations for pediatric studies for drugs and biological products. Guidance for industry. [updated 2014 December 30]. Available from https://www.fda.gov/downloads/drugs/guidances/ucm425885.pdf.
26. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
27. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. N Engl J Med. 2010;363:1875–6.
28. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol. 2014;63:321–8.
29. Mitchell LG, Goldenberg NA, Male C, Kenet G, Monagle P, Nowak-Gottl U. Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary embolism in children. J Thromb Haemost. 2011;9:1856–8.
30. Revel-Vilk S, Sharathkumar A, Massicotte P, et al. Natural history of arterial and venous thrombosis in children treated with low molecular weight heparin: a longitudinal study by ultrasound. J Thromb Haemost. 2004;2:42–6.
31. Michaels LA, Gurian M, Hegyi T, Drachtman RA. Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. Pediatrics. 2004;114:703–7.
32. Biss TT, Brandao LR, Kahr WH, Chan AK, Williams S. Clinical features and outcome of pulmonary embolism in children. Br J Haematol. 2008;142:808–18.
33. Wright JM, Watts RG. Venous thromboembolism in pediatric patients: epidemiologic data from a pediatric tertiary care center in Alabama. J Pediatr Hematol Oncol. 2011;33:261–426.
34. Gasior AC, Marty KE, St Peter SD. Management of peripherally inserted central catheter associated deep vein thrombosis in children. Pediatr Surg Int. 2013;29:445–59.
35. Zitomersky NL, Levine AE, Atkinson BJ, et al. Risk factors, morbidity, and treatment of thrombosis in children and young adults with active inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2013;57:343–7.
36. Andrade-Campos MM, Montes-Limon AE, Fernandez-Mosteirin N, et al. Dosing and monitoring of enoxaparin therapy in children: experience in a tertiary care hospital. Blood Coagul Fibrinolysis. 2013;24:194–8.
37. O'Brien SH, Kulkarni R, Wallace A, Hamblin F, Burr S, Goldenberg NA. Multicenter dose-finding and efficacy and safety outcomes in neonates and children treated with dalteparin for acute venous thromboembolism. J Thromb Haemost. 2014;12:1822–5.
38. Ko RH, Michieli C, Lira JL, Young G. FondaKIDS II: long-term follow-up data of children receiving fondaparinux for treatment of venous thromboembolic events. Thromb Res. 2014;134:643–7.

39. Warad D, Rao AN, Mullikin T, et al. A retrospective analysis of outcomes of dalteparin use in pediatric patients: a single institution experience. Thromb Res. 2015;136:229–33.
40. Manlhiot C, Brandao LR, Schwartz SM, et al. Management and outcomes of patients with occlusive thrombosis after pediatric cardiac surgery. J Pediatr. 2016;169:146–53.
41. Goldenberg NA, Takemoto CM, Yee DL, Kittelson JM, Massicotte MP. Improving evidence on anticoagulant therapies for venous thromboembolism in children: key challenges and opportunities. Blood. 2015;126:2541–7.
42. Massicotte MP, Sofronas M, deVeber G. Difficulties in performing clinical trials of antithrombotic therapy in neonates and children. Thromb Res. 2006;118:153–63.
43. Goldenberg NA, Abshire T, Blatchford PJ, et al. Multicenter randomized controlled trial on Duration of Therapy for Thrombosis in Children and Young Adults (the Kids-DOTT trial): pilot/feasibility phase findings. J Thromb Haemost. 2015;13:1597–605.

How to cite this article: Albisetti M, Biss B, Bomgaars L, et al. Design and rationale for the DIVERSITY study: An open-label, randomized study of dabigatran etexilate for pediatric venous thromboembolism. *Res Pract Thromb Haemost*. 2018;2:347–356. https://doi.org/10.1002/rth2.12086