

## Original Article

**Cite this article:** Bhatt MD, Portman MA, Berger F, Jacobs JP, Newburger J, Duggal A, Grosso M, Pandya G, Dave J, and Goldenberg NA for the ENNOBLE-ATE Trial Investigators (2021) ENNOBLE-ATE trial: an open-label, randomised, multi-centre, observational study of edoxaban for children with cardiac diseases at risk of thromboembolism. *Cardiology in the Young* **31**: 1213–1219. doi: [10.1017/S1047951121002523](https://doi.org/10.1017/S1047951121002523)

Received: 19 April 2021

Revised: 7 June 2021

Accepted: 8 June 2021

First published online: 4 August 2021

### Keywords:


Paediatrics; anticoagulation; congenital heart disease; Kawasaki disease; edoxaban; direct oral anticoagulant

### Author for correspondence:

Neil A. Goldenberg, MD, PhD, Johns Hopkins All Children's Institute for Clinical and Translational Research, 601 5th Street South, St. Petersburg, FL 33701, USA.  
Tel: (727) 767-3674; Fax: (727) 767-6949.  
E-mail: [neil@jhmi.edu](mailto:neil@jhmi.edu)

\*Contributed equally as co-first authors

# ENNOBLE-ATE trial: an open-label, randomised, multi-centre, observational study of edoxaban for children with cardiac diseases at risk of thromboembolism

Mihir D. Bhatt<sup>1,\*</sup> , Michael A. Portman<sup>2,\*</sup>, Felix Berger<sup>3,4</sup>, Jeffrey P. Jacobs<sup>5,6</sup>, Jane Newburger<sup>7,8</sup>, Anil Duggal<sup>9</sup>, Michael Grosso<sup>9</sup>, Grishma Pandya<sup>9</sup>, Jay Dave<sup>9</sup> and Neil A. Goldenberg for the ENNOBLE-ATE Trial Investigators<sup>10,11</sup>

<sup>1</sup>Division of Pediatric Hematology/Oncology, Department of Pediatrics, McMaster Children's Hospital, McMaster University, Hamilton, Ontario, Canada; <sup>2</sup>Seattle Children's Research Institute, and Division of Cardiology, Department of Pediatrics, University of Washington, Seattle, Washington, USA; <sup>3</sup>Department of Congenital Heart Disease/Pediatric Cardiology, German Heart Institute Berlin, Augustenburger Platz 1, 13353, Berlin, Germany; <sup>4</sup>Department of Pediatric Cardiology, Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353, Berlin, Germany; <sup>5</sup>Division of Cardiac Surgery, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland; <sup>6</sup>Division of Cardiovascular Surgery, Department of Surgery, Johns Hopkins All Children's Heart Institute, St. Petersburg, Florida; <sup>7</sup>Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts; <sup>8</sup>Department of Pediatrics, Harvard Medical School, Boston, Massachusetts; <sup>9</sup>Daiichi Sankyo, Basking Ridge, NJ, USA; <sup>10</sup>Pediatric Thrombosis Program, All Children's Hospital Johns Hopkins Medicine, St. Petersburg, Florida and <sup>11</sup>Department of Pediatrics, Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

## Abstract

Children with cardiac diseases suffer from significant morbidity and mortality secondary to thromboembolic complications. Anticoagulant agents currently used for thromboprophylaxis have many limitations, including subcutaneous administration (low molecular weight heparins) and requirement for frequent monitoring via venipuncture (vitamin K antagonists). Edoxaban is an oral direct factor Xa inhibitor without need of monitoring. In the treatment of venous thromboembolism in adults, edoxaban has shown to be effective and safe.

This manuscript summarises the rationale and design of a phase 3, open-label, randomised controlled trial to evaluate and compare the safety and efficacy of edoxaban against standard of care (namely, vitamin K antagonist and low molecular weight heparin) in children with cardiac diseases.

A goal of 150 children with cardiac diseases at risk of thromboembolic complications who need primary or secondary anticoagulant prophylaxis will be recruited. Eligible children between 6 months and <18 years of age will be randomised in a ratio of 2 to 1 for edoxaban versus standard of care. Randomisation will be stratified based on underlying cardiac disease and concomitant use of aspirin for patients other than Kawasaki disease. The primary outcome will be safety, comprised of major and clinically relevant non-major bleeding in first 3 months of treatment. Bleeding beyond 3 months, symptomatic and asymptomatic thromboembolic events, and pharmacokinetic and pharmacodynamic parameters will be evaluated as secondary outcomes.

Randomised controlled anticoagulation trials are challenging in children. This study will evaluate a potentially valuable alternative of oral anticoagulant prophylactic use in children with cardiac diseases.

## Social media synopsis

Phase 3 randomised study evaluating safety of oral edoxaban as alternative anticoagulant for children with cardiac diseases who are at risk of thromboembolism.

Thromboembolism is a major complication in children with cardiac diseases, congenital or acquired. Children with cardiac diseases constitute a major proportion of thrombosis patients admitted to tertiary hospitals.<sup>1–6</sup> Up to 50% of infants <6 months of age and 30% of older children with venous thromboembolism have underlying cardiac diseases.<sup>7</sup> The highest risk groups include children with shunt-dependent single ventricles, central lines, Fontan circuit, Kawasaki disease with coronary aneurysms, and cardiomyopathy.<sup>2</sup> The risk factors for thromboembolism include alteration in hemodynamics, prosthetic materials, surgically damaged blood vessels, intravenous catheters, and cardiopulmonary bypass.

Thromboembolism leads to significant morbidity and mortality in children with cardiac diseases.<sup>1,2,7</sup> In a large retrospective cohort study of children undergoing cardiovascular surgery,

© The Author(s), 2021. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike licence (<http://creativecommons.org/licenses/by-nc-sa/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the same Creative Commons licence is included and the original work is properly cited. The written permission of Cambridge University Press must be obtained for commercial re-use.

20.8% of the children diagnosed with thromboembolism died as its consequence.<sup>8</sup> In a more recent study among similar cohort of patients, thromboembolism was associated with

- longer intensive care unit stay (additional 10 days) and hospital stay (additional 15.2 days),
- higher odds of cardiac arrest (odds ratio: 4.9), catheter re-intervention (odds ratio: 3.3), and
- re-operation (odds ratio: 2.5) and increased mortality (odds ratio: 5.1).<sup>3</sup>

The use of anticoagulation prophylaxis in select subpopulations and settings has become the standard of care to prevent thromboembolism and associated complications.<sup>9</sup> Advances in medical and cardiac surgical techniques have led to improved survival in this group of children,<sup>10</sup> thus, the overall use of anticoagulation has increased in recent decades.

The commonly used agents for long-term anticoagulation in children are low molecular weight heparins and vitamin K antagonists.<sup>2,9</sup> The important disadvantage of low molecular weight heparin is subcutaneous administration.<sup>11</sup> Vitamin K antagonists have a delayed onset of action, narrow therapeutic index, unpredictable pharmacologic response, and multiple food and drug interactions, and therefore require frequent monitoring.<sup>12</sup> Monagle et al showed that 41% of all warfarin measurements were below the target range in a group of 54 patients over a period of 2 years.<sup>13</sup> The frequent blood monitoring and complexity of management pose a substantial burden on children and their families.<sup>9,14,15</sup> In one quality of life assessment study, 62% of parents reported warfarin therapy to be a burden “now and then” or “always”.<sup>16</sup> In addition, administration of vitamin K antagonists in young children is challenging due to a lack of commercially available liquid formulation. Therefore, there exists a need for safe, effective, and easily manageable oral antithrombotic agent for the treatment of paediatric cardiac patients at risk of thromboembolism.

Direct oral anticoagulants overcome many of the above limitations for children. Direct oral anticoagulants can be administered orally, are antithrombin independent, have a rapid onset and offset of action, few drug and food interactions, and predictable pharmacokinetics with no need of routine monitoring of anticoagulation activity.<sup>17</sup> Recently, two phase 3 direct oral anticoagulant trials for paediatric venous thromboembolism have been published.<sup>18,19</sup> The rivaroxaban phase 3 study showed that rivaroxaban was as safe and effective as standard anticoagulants in children with venous thromboembolism.<sup>18</sup> A prospective cohort study showed a favourable safety profile of dabigatran for secondary venous thromboembolism prevention in children 3 months to <18 years of age with persistent risk factor(s).<sup>19</sup> In addition, the phase 3 randomised controlled trial of dabigatran for a conventional course of venous thromboembolism treatment was recently published.<sup>20</sup>

Edoxaban is an oral, direct, specific inhibitor of activated factor X. Its pharmacokinetic properties include rapid peak plasma concentration, low cytochrome P450 metabolism, limited protein binding, and linear pharmacokinetics. These properties allow for once daily dosing, which is an important advantage in comparison with low molecular weight heparins and some direct oral anticoagulants.<sup>21</sup> After initial heparin, edoxaban therapy was non-inferior to warfarin in adults with venous thromboembolism, and adults treated with edoxaban had fewer major or clinically significant bleeding complications.<sup>22</sup> The paediatric investigational plan of edoxaban started with a phase 1, open-label study administering a single dose of edoxaban to children who required

anticoagulant therapy for venous thromboembolism and aimed to identify paediatric doses in children ages 0 to <18 years that approximate drug exposure observed in adults (NCT02303431). Following this, a phase 3, prospective, randomised clinical trial was started, which is evaluating the efficacy and safety of edoxaban compared with standard of care for the treatment of venous thromboembolism (NCT02798471).<sup>23</sup> This purpose of this manuscript is to describe the rationale and design of the DU176B-C-U313 study, which is a phase 3, prospective, randomised controlled trial comparing the safety of edoxaban with the standard of care treatment in children with cardiac diseases who require anticoagulation to prevent primary and secondary thromboembolic disease.

## Materials and methods

### Study objectives and hypothesis

The primary objective of this study is to compare the safety of edoxaban with standard of care in regard to the combination of major and clinically relevant non-major bleeding in the main treatment period. Major and clinically relevant non-major bleeding is defined per published International Society on Thrombosis and Haemostasis criteria.<sup>24</sup> The main treatment period will consist of the duration from randomisation to month 3 visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier.

The secondary and exploratory objectives are summarised in Table 1.

The study hypothesis is that edoxaban is at least as safe as the current standard of care (low molecular weight heparins and/or vitamin K antagonists) with regard to the incidence of major and clinically relevant non-major bleeding in children with cardiac diseases at risk of thromboembolism.

### Study design

This is a phase 3, multi-national, open-label, randomised, parallel-group, observational trial to evaluate and compare the safety and efficacy of edoxaban against standard of care. The trial is sponsored by Daichii Sankyo. The protocol was reviewed by institutional review boards at each participating centre. Eligible patients or their parents/caretakers provide informed consent before randomisation. The study is coordinated by a steering committee that provides clinical guidance on study implementation and study conduct. An independent data monitoring committee will monitor safety and other outcomes of the participating patients and make recommendations to the steering committee at intervals during the study. The adjudication of the safety and efficacy endpoints will be conducted by a blinded adjudication committee. The overall study design is shown in Figure 1.

The inclusion and exclusion criteria are listed in Table 2. After assessment and confirmation of eligibility, patients will be randomised in a 2 to 1 ratio for edoxaban arm to standard of care arm, respectively. Randomisation will be stratified based on:

Underlying cardiac disease:

- Kawasaki disease,
- Previous Fontan operation,
- Heart failure, and
- Other (including post-surgical procedures other than the Fontan operation).

**Table 1.** Secondary and exploratory objectives of the study and corresponding time points

Secondary/exploratory objectives	Corresponding time points
To compare the efficacy of edoxaban against standard of care with regard to the development of symptomatic TE and asymptomatic intracardiac thrombus identified by cardiac imaging	Main treatment period: First dose to month 3 visit Extension period: month 3 visit to last dose + 30 days
To compare the safety of edoxaban against standard of care with regard to all bleeding in the main treatment period and in the extension period	As above
To assess the safety of edoxaban with regard to the combination of major and clinically relevant non-major bleeding occurring during the extension period	As above
To compare the efficacy of edoxaban against standard of care with regard to death as a result of a TE	Main treatment and extension periods as above
To compare edoxaban against standard of care with regard to all-cause mortality	Main treatment and extension periods as above
To evaluate the population PK and PD of edoxaban in relation to the efficacy and safety endpoints in children with cardiac conditions at risk of TE. These measurements are for study evaluation only and not for dosing adjustments.	PK: pre-dose and 1–3 hours post-dose at Month 1 visit; diagnosis of TE or major or CRNM bleeding PD: pre-first dose (randomisation) and 1–3 hours post-dose at Month 1 visit; diagnosis of TE or major or CRNM bleeding
To assess the quality of life using validated questionnaires	Randomisation and at the end of Main treatment period
To compare the intra-patient safety (investigator reported bleeding) and efficacy (investigator reported TE) during the main treatment period compared with the prior treatment occurring within 3 months of randomisation	Main treatment period as above
To compare edoxaban regimen with available existing historical data based on literature review and search for registered clinical trials with similar endpoints	N/A
To analyse the primary prevention and secondary prevention of TE	Main treatment and extension periods as above

CRNM = clinically relevant non-major; PD = pharmacodynamics; PK = pharmacokinetics; TE = thromboembolism

Patients with conditions other than Kawasaki disease will be further stratified based on the concomitant use of low-dose aspirin (1–5 mg/kg/day).

The patients will be recruited in four age cohorts: 12 to <18 years, 6 to <12 years, 2 to <6 years, and 6 months to <2 years. Patients from 1 to <18 years of age will be enrolled in the study as soon as the dosing regimen is established for each age cohort in the phase 1 single-dose edoxaban study. Patients <1 year of age will be admitted to the study after review by the independent data monitoring committee of safety data from 50% of patients in the 1 to <18 year age group who have completed the main treatment period of 3 months.

### Treatment groups

The recommended dosing of edoxaban for the 12- to <18-, 6- to <12-, and 2- to <6-year-old patients is shown in Table 3. Dosing recommendations for patients <1 year of age will be provided as the phase 1 single-dose edoxaban study completes the pharmacokinetic exposure analysis for similar age cohorts (NCT02303431). Cohort 1 (12 to <18 years old) and Cohort 2 (6 to <12 years old) will receive tablets (15 and/or 30 mg strength), which may be crushed and served with applesauce or water. Children <6 years of age or those with a swallowing issue will receive edoxaban granules for oral suspension. Edoxaban doses will be reduced for patients with moderate renal impairment (defined as glomerular filtration rate of  $\geq 30$ – $\leq 50\%$  of normal as determined by the Schwartz formula) and for patients requiring concomitant administration of certain P-glycoprotein inhibitors.

The standard of care arm consists of low molecular weight heparins or vitamin K antagonists according to the treating physician's preferred regimen. It is the investigator's discretion based on local practice and on the patient's underlying cardiac disease to consider if heparin bridging is necessary when initiating vitamin K

antagonists post randomisation until an International Normalised Ratio between 2.0 and 3.0 is reached.

All patients randomised to standard of care arm will be treated with standard of care regimen during the main treatment period (randomisation to month 3) and then offered edoxaban for the extension period (month 3 to month 12).

### Study endpoints

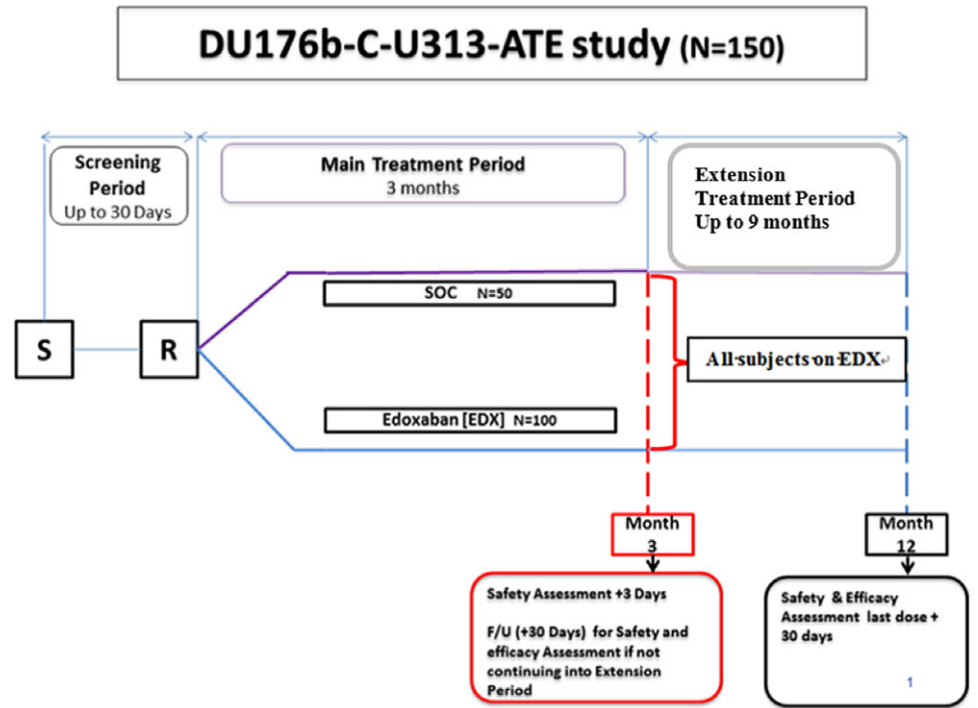
All safety and efficacy endpoints described will be adjudicated in a blinded manner by the clinical events committee. An independent data monitoring committee will monitor safety throughout the duration of the study. The primary safety endpoint is a combination of major bleeding, as per International Society on Thrombosis and Haemostasis definition, and clinically relevant non-major bleeding occurring during the main treatment period.

Secondary endpoints are listed in Table 1.

### Duration of study and follow-up

The study is divided into main treatment and extension periods. In the main treatment period, patients will be treated with edoxaban or standard of care as per their randomisation. During the extension period, all patients will be offered treatment with edoxaban.

All patients will undergo safety and efficacy evaluations at the end of main treatment period at month 3 with a 30-day follow-up. Along with review of symptomatic endpoints such as bleeding and symptomatic thromboembolism, safety evaluations will include complete blood count, liver function tests, creatinine, and estimated glomerular filtration rate measurements. Patients who discontinue treatment prior to month 3 will continue with the scheduled visits up to month 3 with the 30-day follow-up. Patients who participate in the extension period will undergo safety and efficacy endpoint evaluations (described above) at months 6, 9,



**Figure 1.** Overall study design: the figure outlines screening period of up to 30 days, main treatment period of 3 months from randomisation, followed by extension treatment period of up to 9 months from month 3 to month 12. Note: S – screening; R – randomisation; SOC – standard of care; F/U – follow-up.

and 12, and 30 days after cessation of treatment if treatment up to 12 months is required.

A follow-up echocardiogram will be taken at month 3 to ascertain asymptomatic intracardiac or coronary artery thrombosis. A month 3 echocardiogram will be optional if the patient experiences symptomatic thrombosis documented by an image, such as standard or CT angiogram, prior to this time. In the extension period after month 3, any symptomatic event will be documented, and a recommended image captured to support the event. A month 12 echocardiogram will be optional.

### Sample size and statistical analysis

This study is not powered to demonstrate statistically significant differences in the rate of endpoint occurrences between edoxaban and standard of care. An adequately powered study would be unachievable due to the very large sample size required and the enormous challenge inherent in enrolling these children. To estimate a reasonable sample size, data were extrapolated from the adult Hokusai-VTE study (i.e., 8.5 and 10.3% in edoxaban and standard of care arms, respectively) as there is no pre-existing data for edoxaban in children.<sup>22</sup> Assuming that the major and clinically relevant non-major bleeding event rates in the paediatric cohort will be similar, the 95% confidence interval around the point estimate of the risk difference between edoxaban and standard of care is –11.8 to 8.2% with 100 patients in edoxaban arm and 50 patients in standard of care arm. There is no intent to compare this paediatric study results with the adult Hokusai-VTE trial data.

The primary safety analysis will be performed according to the actual treatment received and will include composite of major and clinically relevant non-major bleeding occurring during the main treatment period. The time to major or clinically relevant non-major bleeding will be compared between treatment groups using the Cox proportional hazards regression model including treatment group, concomitant usage of aspirin, and underlying disease

(Kawasaki disease, previous Fontan operation, heart failure, or other) as covariates. Hazard ratio between edoxaban and standard of care treatment groups will be calculated with corresponding 95% confidence intervals. The incidence, annualised event rate, and rate difference between edoxaban and standard of care treatment groups will also be calculated and compared with event rates in similar paediatric populations/indications from prior literature. All secondary safety analyses will also be performed based on the actual treatment received. All efficacy analyses will be based on the treatment group assigned at randomisation (modified intention to treat).

There is no formal interim analysis planned. However, an interim assessment by the independent data monitoring committee of safety endpoints of the study will take place after the first 50 patients in the edoxaban treatment group and 25 patients in the standard of care arm from 1 to <18 years of age complete the first 3 months of treatment. This assessment is pre-requisite to opening enrolment of patients <1 year of age on the trial.

Plasma concentration and biomarker data will be summarised by age, dose, and time point using descriptive statistics. The plasma concentration data will be pooled with data from other studies for a population pharmacokinetic analysis using non-linear mixed effects modelling. Exposure–response relationships will be evaluated for the safety and efficacy endpoints through a model-based approach, if data allow.

### Discussion

Large randomised controlled trials are very difficult to perform in children with thrombosis or at risk of thrombosis secondary to multiple challenges. First, despite increasing incidence, thromboembolism remains an infrequent condition in children overall.<sup>25–27</sup> Second, children who experience thromboembolism or are at risk of thromboembolism are sick with multiple underlying diseases and many concomitant medications. As a result, a large proportion



**Table 2.** Inclusion and exclusion criteria

Inclusion criteria:
1. Children (>38 weeks to <18 years of age) with cardiac diseases who are at risk for thromboembolic complications and require at least 3 months anticoagulant prophylaxis.
2. Informed consent from patient and/or parent(s)/legal guardian(s) or legally acceptable representative.
3. If a patient has a history of thromboembolism, it must be old, organised and/or resolved per the discretion of the principal investigator (previously known thromboembolism that is >3 months old and does not require active treatment).
Exclusion criteria:
1. Symptomatic venous or arterial thromboembolism.
2. Asymptomatic venous or arterial thromboembolism newly found by routine imaging.
3. Asymptomatic intracardiac thrombosis newly discovered by an echocardiogram during study screening period.
4. Active bleeding or high risk of bleeding contraindicating treatment with anticoagulant.
5. Contraindication to the use of low molecular weight heparin and/or vitamin K antagonist.
6. Requires co-administration of antithrombotic therapy except for low-dose aspirin defined as 1–5 mg/kg/day with maximum of 100 mg/day. Requires rifampin during study period.
8. Hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk (APTT >50 seconds or INR > 2.0 not related to anticoagulation therapy) or ALT >5 × the upper level of normal or total bilirubin >2 × upper level of normal with direct bilirubin >20% of the total at screening visit.
9. Glomerular filtration rate <30% of normal for age and size as determined by the Schwartz formula.
10. Stage 2 hypertension defined as blood pressure systolic and/or diastolic confirmed >99th percentile + 5 mmHg.
11. Thrombocytopenia <50 × 10 <sup>9</sup> /L at screening visit.
12. Fontan procedure with a history of or signs/symptoms suggestive of protein-losing enteropathy.
13. Life expectancy less than the expected study duration (3 months).
14. Pregnancy, breastfeeding, or not using approved method of contraception.
15. Any condition that, as judged by the investigator, would place the patient at increased risk of harm if he/she participated in the study.
16. Participation in another trial or treated with an experimental therapy with <30-day washout period.
17. Hypersensitivity to the active ingredient or to any of the excipients of any components of the trial treatment.
18. Patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome.

ALT = alanine transferase; APTT = activated partial thromboplastin time; INR = International Normalised Ratio

of eligible patients are excluded from studies due to increased bleeding risk. Third, it is difficult for parents to give permission for study participation, especially when their children are young and very sick. These challenges were reflected in the early closure of some trials due to slow recruitment.<sup>13,28–30</sup> In the paediatric anticoagulant field, few phase 3 trials have successfully completed planned enrolment; recent exceptions include the investigator-led NIH-sponsored Kids-DOTT trial,<sup>31</sup> EINSTEIN-Junior,<sup>18</sup> and DIVERSITY.<sup>20</sup> A few additional industry-sponsored phase 3 studies of direct oral anticoagulants are ongoing, but few have been powered to demonstrate non-inferior or superior safety and efficacy relative to the standard of care.<sup>32</sup>

The paediatric direct oral anticoagulant trials, including this study, are the outcome of collaboration between pharmaceutical companies and academic experts in the fields of paediatric thrombosis and paediatric cardiac care. To develop high-quality trials to increase the evidence of antithrombotic treatment in children with

thromboembolism or at risk of thromboembolism, collaboration between industry and a multi-disciplinary group of thought leaders is needed, from program development and specific trial design to trial oversight, analysis, and reporting.<sup>33</sup> Pharmaceutical companies benefit from the knowledge of the academic experts in the domains of paediatric thrombosis and paediatric cardiac care for the development of their paediatric investigational plan, and in return, the pharmaceutical companies provide logistics and funding for the large, international trials. Recently, the International Society on Thrombosis and Haemostasis paediatric subcommittee has established a task force for drug development in paediatric thrombosis to provide expert input into the development of industry-initiated studies.<sup>34</sup>

The strengths of the ENNOBLE-ATE trial design include a more inclusive bleeding outcome, two-level stratification for randomisation, observational data with edoxaban for all patients, and objective quality of life assessments. As edoxaban is being evaluated for prophylaxis, it is appropriate to employ an inclusive definition for the outcomes of clinically important bleeding events. In a given target population, thromboembolism prevention (in comparison to treatment) involves a lower a priori risk of new thromboembolism events. Hence, from a net clinical benefit perspective, a higher rate (and/or greater severity) of bleeds is generally found to be acceptable for treatment of thromboembolism in comparison with prevention of thromboembolism. Hence, it is important to measure safety broadly by including all clinically relevant bleeding events, in addition to major bleeding, when evaluating net clinical benefit of the employed strategy of prevention of thromboembolism.

Two-level stratification is employed in this study to address the a priori differential risk of thromboembolism and bleeding based on underlying cardiac disease and the use of concomitant aspirin. Stratified randomisation assures that within each stratum of interest, a balance in randomised arms of treatment will be achieved. In children with Kawasaki disease, the incidence of coronary artery aneurysms is 5% with upfront treatment with immunoglobulin and high dose aspirin (previously 20–25%).<sup>35</sup> Coronary artery aneurysms pre-dispose children to significant risk of coronary arterial thromboembolism, myocardial infarction, or sudden death. The risk of thromboembolism following the Fontan operation is reported to be 17–33%,<sup>36</sup> while the prevalence of thromboembolism is 14% among children with heart failure secondary to cardiomyopathy.<sup>37,38</sup> The second level of stratification, based on the use of concomitant aspirin, is employed to address the suspected a priori differential risk of bleeding associated with anticoagulant monotherapy versus a combination of anticoagulation plus antiplatelet therapy. A similar study assessing another direct oral anticoagulant for patients with cardiac diseases has employed stratification based on age and type of cardiac disease, but not concomitant use of aspirin.<sup>39</sup> Another recent large randomised controlled trial in the field of paediatric anticoagulation, the Kids-DOTT trial on duration of anticoagulation for thromboembolism treatment, has also used stratified randomisation—specifically, based on age and thrombus location.<sup>40</sup>

This study will generate observational data with edoxaban on all enrolled patients. While in the main treatment period, patients will be treated with edoxaban or standard of care as per their randomisation, all patients will be offered treatment with edoxaban in the extension period. This design feature distinguishes the ENNOBLE-ATE study from another paediatric direct oral anticoagulant trial in this population,<sup>39</sup> as it will provide comparative short-term data,

**Table 3.** Edoxaban doses for 6- to <18-year-old children

Age	Body weight	Dose (tablet)	Dose (suspension) (6 mg/ml concentration)	Dose reduction*
12 to <18 years	≥60 kg	60 mg QD	10 ml	45 mg QD
	≥30 and <60 kg	45 mg QD	7.5 ml	30 mg QD
	<5th percentile for age	30 mg QD	5 ml	NA
6 to <12 years	≥60 kg	60 mg QD	10 ml	45 mg QD
	<60 kg Dose based on mg/kg	NA	1.2 mg/kg (max 45 mg)	0.8 mg/kg (max 45 mg)
2 to <6 years	Dose based on mg/kg	NA	1.4 mg/kg (max 45 mg)	0.7 mg/kg (max 24 mg)

NA = not applicable; QD = once a day

\*Conditions for dose reduction: concomitant administration of P-glycoprotein inhibitor and moderate renal impairment (defined as glomerular filtration rate of ≥30–≤50% of normal as determined by the Schwartz formula)

as well as longer-term prophylaxis data in those electing to continue in the extension study.

An important exploratory objective of this study is quality of life assessment. Once-daily oral anticoagulant prophylaxis without need for frequent blood monitoring is an ideal solution against issues with current standard of care that pose significant burden for children and families. Quality of life is a key design element for current and future trials of antithrombotic therapy in children, particularly those trials that address non-hospitalised settings and/or chronic use. This issue has received too little attention in historical trials designs, but is particularly important in trials of oral agents that offer potential pragmatic benefits relative to parental agents used in the standard of care, even when safety and/or efficacy of the newer oral agents may be only non-inferior to parental agents used in the standard of care.

This study is not powered with intention to draw conclusions based on statistically significant differences between edoxaban and standard of care. An adequately powered study would not be feasible due to the significantly large sample size required in such a specialised paediatric population, as discussed above. However, the sample size does allow for appropriate 95% confidence interval around the point estimate of the risk difference between edoxaban and standard of care, based on observed bleeding rates in the adult Hokusai-VTE study.<sup>22</sup>

One of the limitations of this trial is the open design. However, investigator-reported outcome events (potential safety and efficacy endpoints) will be reviewed by an independent panel of clinical endpoint committee adjudicators who are blinded to treatment arm. In children, it is unethical to use placebo subcutaneous injections (for masking in regard to the use of low molecular weight heparins) or to perform false international normalised ratio tests (for masking in regard to the use of warfarin) in patients randomised to edoxaban.

In summary, randomised controlled anticoagulation trials are challenging in children. The edoxaban phase 3 study in children with cardiac diseases will adequately assess safety of edoxaban in comparison with current standard of care as a primary objective, as well as efficacy as a secondary objective. If the primary hypothesis regarding safety is supported by the findings of the trial, this study will provide key evidence towards a valuable alternative for anticoagulant thromboprophylaxis in children with cardiac diseases who are at risk of thromboembolism.

**Acknowledgements.** We would like to acknowledge and thank all the participating investigators, coordinators, patients, and parents.

**Financial support.** This trial is funded by Daiichi Sankyo Inc. The drafting and revision of this manuscript, however, was completed by the listed authors only.

**Conflicts of interest.** Any conflicts of interest by the authors have been disclosed to the journal.

**Ethical standards.** The authors state that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

## References

- Checchia PA, Karamlou T, Maruszewski B, Ohye RG, Bronicki R, Dodge-Khatami A. Haematological and infectious complications associated with the treatment of patients with congenital cardiac disease: consensus definitions from the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease. *Cardiol Young* 2008; 180 (Suppl 2): 226–233. doi: [10.1017/S1047951108002965](https://doi.org/10.1017/S1047951108002965). PMID: 19063796.
- Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. *Circulation* 2013; 128: 2622–2703.
- Manlihot C, Menjak I, Brandao L, et al. Risk, clinical features, and outcomes of thrombosis associated with pediatric cardiac surgery. *Circulation* 2011; 124: 1511–1519.
- Tzanetos D, Yu C, Hernanz-Schulman M, Barr F, Brown N. Prospective study of the incidence and predictors of thrombus in children undergoing palliative surgery for single ventricle physiology. *Intensive Care Med* 2012; 38: 105–112.
- Chollete J, Rubenstein J, Alfieri G, et al. Elevated risk of thrombosis in neonates undergoing initial palliative cardiac surgery. *Ann Thorac Surg* 2007; 84: 1320–1325.
- Emani S, Zurakowski D, Baird C, Pigula F, Trenor C, Emani S. Hypercoagulability markers predict thrombosis in single ventricle neonates undergoing cardiac surgery. *Ann Thorac Surg* 2013; 96: 651–656.
- Monagle P. Thrombosis in pediatric cardiac patients. *Semin Thromb Hemost* 2003; 29: 547–555.
- Giglia TM, Bulas DI, Sell JE, et al. Thrombotic complications in a pediatric cardiovascular surgery population: a nine-year experience [abstract]. *J Am Coll Cardiol* 2001; 37: 465A.
- Monagle P, Chan AKC, 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–e801S.
- Jacobs JP, He X, Mayer JE Jr, et al. Mortality trends in pediatric and congenital heart surgery: an analysis of The Society of Thoracic Surgeons Congenital Heart Surgery database. *Ann Thorac Surg* 2016; 102: 1345–1352. doi: [10.1016/j.athoracsur.2016.01.071](https://doi.org/10.1016/j.athoracsur.2016.01.071). Epub 31 August, 2016. PMID: 27590683.

11. Bidlingmaier C, Kenet G, Kurnik K, et al. Safety and efficacy of low molecular weight heparins in children: a systematic review of the literature and meta-analysis of single-arm studies. *Semin Thromb Hemost* 2011; 37: 814–825.
12. Monagle P, Newall F. Management of thrombosis in children and neonates: practical use of anticoagulants in children. *Hematology Am Soc Hematol Educ Program* 2018; 2018: 399–404.
13. Monagle P, Cochrane A, Roberts R, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. *J Am Coll Cardiol* 2011; 58: 645–651.
14. Andrew M, Marzinotto V, Brooker LA, et al. Oral anticoagulation therapy in pediatric patients: a prospective study. *Thromb Haemost* 1994; 71: 265–269.
15. Newall F, Monagle P, Johnston L. Home INR monitoring of oral anticoagulant therapy in children using CoaguChek S point-of-care monitor and a robust education program. *Thromb Res* 2006; 118: 587–593.
16. Jones S, Monagle P, Manias E, Bruce AAK, Newall F. Quality of life in children commencing home INR self-testing. *Thromb Res* 2013; 132: 37–43.
17. Albisetti M. Use of direct oral anticoagulants in children and adolescents. *Hamostaseologie* 2020; 40: 64–73.
18. Male C, Lensing AWA, Palumbo JS, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol* 2020; 7: e18–e27.
19. Brandao LR, Albisetti M, Halton J, et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. *Blood* 2020; 135: 491–504.
20. Halton J, Brandao LR, Luciani M, et al. Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial. *Lancet Haematol* 2021; 8: e22–e33.
21. Parasrampur DA, Truitt KE. Pharmacokinetics and pharmacodynamics of edoxaban, a non-vitamin K antagonist oral anticoagulant that inhibits clotting factor Xa. *Clin Pharmacokinet* 2016; 55: 641–655.
22. Buller HR, Decousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; 369: 1406–1415.
23. Van Ommen CH, Albisetti M, Chan AK, et al. The Edoxaban Hokusai VTE PEDIATRICS Study: an open-label, multicenter, randomized study of edoxaban for pediatric venous thromboembolic disease. *Res Pract Thromb Haemost* 2020; 4: 886–892.
24. Schulman S, Kearon C. Subcommittee on control of anticoagulation of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692–694.
25. 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: 1001–1008.
26. 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: 1251–1257.
27. 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: 676–681.
28. Massicotte P, Julian JA, Gent M, et al. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. *Thromb Res* 2003; 109: 85–92.
29. Massicotte P, Julian JA, Gent M, et al. An open-label randomized controlled trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children: the PROTEKT trial. *Thromb Res* 2003; 109: 101–108.
30. Mitchell L, Andrew M, Hanna K, et al. Trend to efficacy and safety using antithrombin concentrate in prevention of thrombosis in children receiving l-asparaginase for acute lymphoblastic leukemia. Results of the PAARKA study. *Thromb Haemost* 2003; 90: 235–244.
31. 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: 1597–1605.
32. Male C, Thom K, O'Brien SH. Direct oral anticoagulants: what will be their role in children? *Thromb Res* 2019; 173: 178–185.
33. Goldenberg NA, Spyropoulos AC, Halperin JL, et al. Improving academic leadership and oversight in large industry-sponsored clinical trials: the ARO-CRO model. *Blood* 2011; 117: 2089–2092.
34. Male C, Monagle P, Chan AK, Young G. Pediatric/Neonatal haemostasis and thrombosis standardization subcommittee of the International Society on Thrombosis and Haemostasis. Recommendations for the development of new anticoagulant drugs for pediatric use: communication from the SSC of the ISTH. *J Thromb Haemost* 2015; 13: 481–484.
35. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017; 135: e927–e999.
36. Balling G, Vogt M, Kaemmerer H, Eicken A, Meisner H, Hess J. Intracardiac thrombus formation after the Fontan operation. *J Thorac Cardiovasc Surg* 2000; 119: 745–752.
37. McCrindle BW, Karamlou T, Wong H, et al. Presentation, management and outcomes of thrombosis for children with cardiomyopathy. *Can J Cardiol* 2006; 22: 685–690.
38. Gunthard J, Stocker F, Bolz D, et al. Dilated cardiomyopathy and thromboembolism. *Eur J Pediatr* 1997; 156: 3–6.
39. Payne RM, Burns KM, Glatz AG, et al. A multi-national trial of direct oral anticoagulant in children with cardiac disease: design and rationale of the Safety of ApiXaban On Pediatric Heart disease On the prevention of Embolism (SAXOPHONE) study. *Am Heart J* 2019; 217: 52–63.
40. Goldenberg NA, Triputti M, Crowther M, et al. The “parallel-cohort RCT”: novel design aspects and application in the Kids-DOTT trial of pediatric venous thromboembolism. *Contemp Clin Trials* 2010; 31: 131–133.