ORIGINAL ARTICLE

The Edoxaban Hokusai VTE PEDIATRICS Study: An open-label, multicenter, randomized study of edoxaban for pediatric venous thromboembolic disease

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Abstract

Background: Little evidence is available for treatment of pediatric venous thromboembolism (VTE). Large randomized controlled trials are challenging in children. Current antithrombotic agents have many limitations, including nonoral administration and frequent monitoring. Edoxaban is an oral direct inhibitor of factor Xa without need of monitoring. In adults with VTE, edoxaban has shown to be effective and safe.

Objectives: The Edoxaban Hokusai VTE PEDIATRICS Study is an open-label, randomized clinical trial to evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of edoxaban and whether edoxaban is noninferior to standard of care in treatment of pediatric VTE.

Methods: A goal of 274 patients will be recruited in 5 age categories. A multidose PK/PD assessment on day 5 in the first 12 patients of each age group is incorporated into this study. The primary composite efficacy outcome comprises symptomatic recurrent VTE, death due to VTE, and no change or extension of thrombotic burden. The principal safety end point is a combination of major and clinically relevant nonmajor bleeding. PK end points include apparent systemic clearance and volume of distribution of edoxaban. PD end points include prothrombin time, activated partial thromboplastin time, and anti-factor Xa level for the edoxaban treatment arm.

Results: To increase feasibility, the multidose PK/PD study is integrated in the phase 3 trial. In addition, thrombotic burden, which is a prognostic factor for post thrombotic syndrome in children, is one of the components of the primary composite efficacy outcome.

Conclusion: This study will increase the level of evidence for treatment in pediatric VTE.

KEYWORDS
child, edoxaban, feasibility, standard of care, venous thromboembolism

Essentials

- All anticoagulant regimens currently used in pediatric patients have significant limitations.
- The study will evaluate efficacy and safety of edoxaban compared to standard of care in children.
- Multidose pharmacokinetics/pharmacodynamics study is integrated in phase 3 study to enhance feasibility.
- Feasibility is further increased by including thrombotic burden in composite efficacy outcome.

1 | INTRODUCTION

Venous thromboembolism (VTE) is increasingly diagnosed in pediatric patients.[1] The clinical presentation of pediatric VTE includes catheter-related thrombosis, pulmonary embolism, and deep vein thrombosis. In contrast to adults, most children have ≥1 clinical risk factors.[2]

Pediatric VTE is of clinical importance as it is associated with mortality and morbidity, including recurrent VTE, thrombotic burden and postthrombotic symptoms. Mortality as result of thrombosis is reported to be between 0% and 2.2%.[3,4] In the REVIVE trial, a randomized controlled trial comparing low molecular-weight heparin (LMWH) with unfractionated heparin (UFH) and vitamin K antagonists (VKAs), recurrent VTE occurred in 5 of 40 patients (12.5%) and 2 of 36 patients (5.6%) in the standard-of-care (SOC) group (UFH/VKA) and in the LMWH group, respectively.[4] Only few studies described thrombotic burden after antithrombotic treatment in children. In the study of Kuhle et al,[5] no change or extension of thrombotic burden occurred in 27 of 148 children (18.2%) after 3 months of treatment with tinzaparin. The incidence of postthrombotic symptoms after pediatric VTE varied between 10% and 70%. A meta-analysis showed a mean frequency of 26% (95% confidence interval [CI], 23%-28%).[6]

At present, the majority of children with VTE are initially treated with LMWH or UFH, usually followed by LMWH or VKAs for a total of 3 months or longer.[7] In some children, fondaparinux is used. All anticoagulant regimens currently used in pediatric patients have significant limitations. UFH is administered intravenously and needs to be frequently monitored by anti–factor Xa or activated partial thromboplastin time (APTT). Additional difficulties with UFH are the physiologically reduced levels of anthrombin in children as well as nonspecific binding to plasma proteins, both of which decrease the effectiveness of UFH.[8] LMWH and fondaparinux are administered by subcutaneous injections. VKAs have a narrow therapeutic index, unpredictable pharmacologic response, and multiple food and drug interactions, and therefore require frequent monitoring. In addition, administration of VKAs in young children is challenging due to lack of a commercially available liquid formulation.

Direct oral anticoagulants (DOACs) may overcome many of these limitations for pediatric patients. DOACs can be administered orally, are antithrombin independent, have a rapid onset and offset of action, few drug and food interactions, and predictable pharmacokinetics (PK) with no need of routine monitoring for anticoagulation activity. Drawbacks of DOACs might be heavy menstrual bleeding, which seemed to occur more often with DOACs as compared with other anticoagulants and lack of adherence in adolescents.[9] Recently, 2 phase 3 DOAC trials for pediatric VTE have been published. The rivaroxaban phase 3 study showed that rivaroxaban was as safe and effective as standard anticoagulants in children with VTE.[10] A prospective cohort study revealed that dabigatran showed a favorable safety profile for secondary VTE prevention in children between 3 months and 18 years old with persistent VTE risk factor(s).[11]

Edoxaban is, as rivaroxaban, an oral, direct, specific inhibitor of activated factor X (FX). The PK profile of edoxaban when compared to other DOACs offers several potential advantages.[12] Notably, the rapid peak plasma concentration, low cytochrome P450 metabolism, limited protein binding, and linear PK are especially relevant for use in pediatric VTE patients, which often take numerous other concomitant medications. After initial heparin, edoxaban therapy was noninferior to warfarin in adults with VTE, and adults treated with edoxaban have fewer major or clinically significant bleeding complications.[13] The pediatric investigational plan (PIP) of edoxaban starts with a phase 1, open-label study administering a single dose of either 30 or 60 mg of edoxaban to pediatric patients who require anticoagulant therapy for VTE and aims to identify pediatric doses that approximate drug exposure observed in adults in children ages 0 to <18 years (NCT02303431). The Edoxaban Hokusai VTE PEDIATRICS Study is a phase 3, prospective, randomized clinical trial that aims to evaluate the efficacy and safety of edoxaban compared to SOC and describes multiple-dose PK and pharmacodynamics (PD) in children with a confirmed VTE (NCT02798471). The aim of this article is to describe the rationale and design of the phase 3 Hokusai VTE Pediatrics Study.

2 | STUDY OBJECTIVE AND HYPOTHESIS

The primary objective is to evaluate whether edoxaban after at least 5 days of heparin (UFH, LMWH, or fondaparinux, with overlapping VKAs if given) is noninferior to SOC in the treatment of VTE in pediatric patients with regard to the composite efficacy end point, including symptomatic recurrent VTE, death as a result of VTE, and no change or extension in thrombotic burden, during the first 3-month treatment period. The secondary objectives are summarized in Table 1.

TABLE 1 Secondary objectives

To compare edoxaban versus standard of care with regard to
Combination of major and CRNM bleeding
Combination of major and CRNM bleeding and symptomatic
  recurrent VTE and death as result of VTE
All bleedings
All-cause mortality
Individual components of the composite efficacy outcome
Occurrence of DVT, catheter-related VTE, PE, sinovenous
  thrombosis
To characterize the multiple dose pharmacokinetics of edoxaban
  in pediatric patients on day 5 using population pharmacokinetic
  analysis
To evaluate the relationship between edoxaban exposure and
  safety and efficacy
To characterize the effect of edoxaban on biomarkers of
  coagulation, including PT, APTT, and anti-FXa

anti-FXa, anti–activated factor X; APTT, activated partial prothrombin time; CRNM, clinically relevant nonmajor; DVT, deep vein thrombosis; PE, pulmonary embolism; PT, prothrombin time; VTE, venous thromboembolic event.

3 | STUDY DESIGN

3.1 | Overview

This study is a phase 3, multinational, open-label, randomized, parallel-group study, which will be conducted in about 150 sites in about 38 countries. The trial is sponsored by Daichii Sankyo. The protocol was reviewed by institutional review boards at each participating center. Eligible participants or their parents/caretakers provide informed consent before randomization. The study is coordinated by a steering committee that provides clinical guidance on study implementation and study conduct. An independent data monitoring committee (IDMC) will monitor safety and outcomes of the participating patients and make recommendations to the steering committee at intervals during the study. A blinded independent clinical events committee (CEC) will review and adjudicate all safety and efficacy end points, such as all deaths, VTEs, thrombotic burden, bleeding events, and liver enzyme abnormalities.

3.2 | Patient population

The inclusion and exclusion criteria are listed in Table 2.

3.3 | Stratification and randomization

After patients are assessed for eligibility, they will be randomized in a 1:1 ratio into 1 of the 2 study arms: edoxaban treatment arm or SOC treatment arm. Randomization will be stratified by age cohorts and by region (United States/Canada, Europe, Asia/Pacific, and rest of the world). The patients will be recruited in

TABLE 2 Inclusion and exclusion criteria

Inclusion
1. All children between birth (38-wk gestational age) and <18 y with a radiologically confirmed VTE requiring anticoagulants for at least 90 d
2. At least 5 d of heparin (UFH, LMWH or fondaparinux, with overlapping VKAs if needed) prior to randomization

Exclusion
1. Active bleeding or high risk of bleeding contraindicating treatment with anticoagulants
2. Prior treatment with thrombolytic agents, thrombectomy, or insertion of a caval filter for the newly identified index VTE
3. >10 d of heparin therapy and/or VKA with therapeutic effect prior to randomization
4. Antiplatelet therapy except low-dose aspirin, defined as 1-5 mg/kg/d (with maximum of 100 mg/d)
5. Hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk (APTT > 50 s or INR > 0.2 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
6. Glomerular filtration rate < 30% of normal for age and size as determined by the Schwartz formula
7. Stage 2 hypertension defined as blood pressure systolic and/or diastolic confirmed > 99th percentile + 5 mmHg
8. Thrombocytopenia < 50×10^9/L at screening visit
9. Life expectancy less than the expected study duration (3 mo)
10. Pregnancy or breastfeeding
11. Any condition that, as judged by the investigator, would place the subject at increased risk of harm if he/she participated in the study
12. Participation in another trial or treated with an experimental therapy with <30-d washout period

ALT, alanine transaminase; APTT, activated partial thromboplastin time; INR, International Normalized Ratio; LMWH, low-molecular-weight heparin; UFH, infractionated heparin; VKA, vitamin K antagonists; VTE, venous thromboembolism.

5 age categories: 12 to <18 years, 6 to <12 years, 2 to <6 years, 6 months to <2 years and birth to <6 months. The patients will be enrolled from the oldest age cohort to the youngest age cohort.

3.4 | Edoxaban treatment arm

Edoxaban starting doses for each cohort will be selected based on edoxaban exposure for age-matched patients and safety data from the single-dose PK/PD study (NCT02303431), and on population-based PK. The first 12 patients of each age cohort (total of 60 patients) randomized to the edoxaban arm will participate in the multiple PK/PD assessment on day 5 (+3 days) (Figure 1). If this PK analysis confirms the exposure predictions and available safety data are satisfactory, further enrollment in the same age cohort will be allowed to start. Enrollment in the next younger age cohort is possible if PK and safety data analysis is performed on patients in the prior older age group in the phase 3 trial, and PK and safety data analysis is performed on patients in the next younger
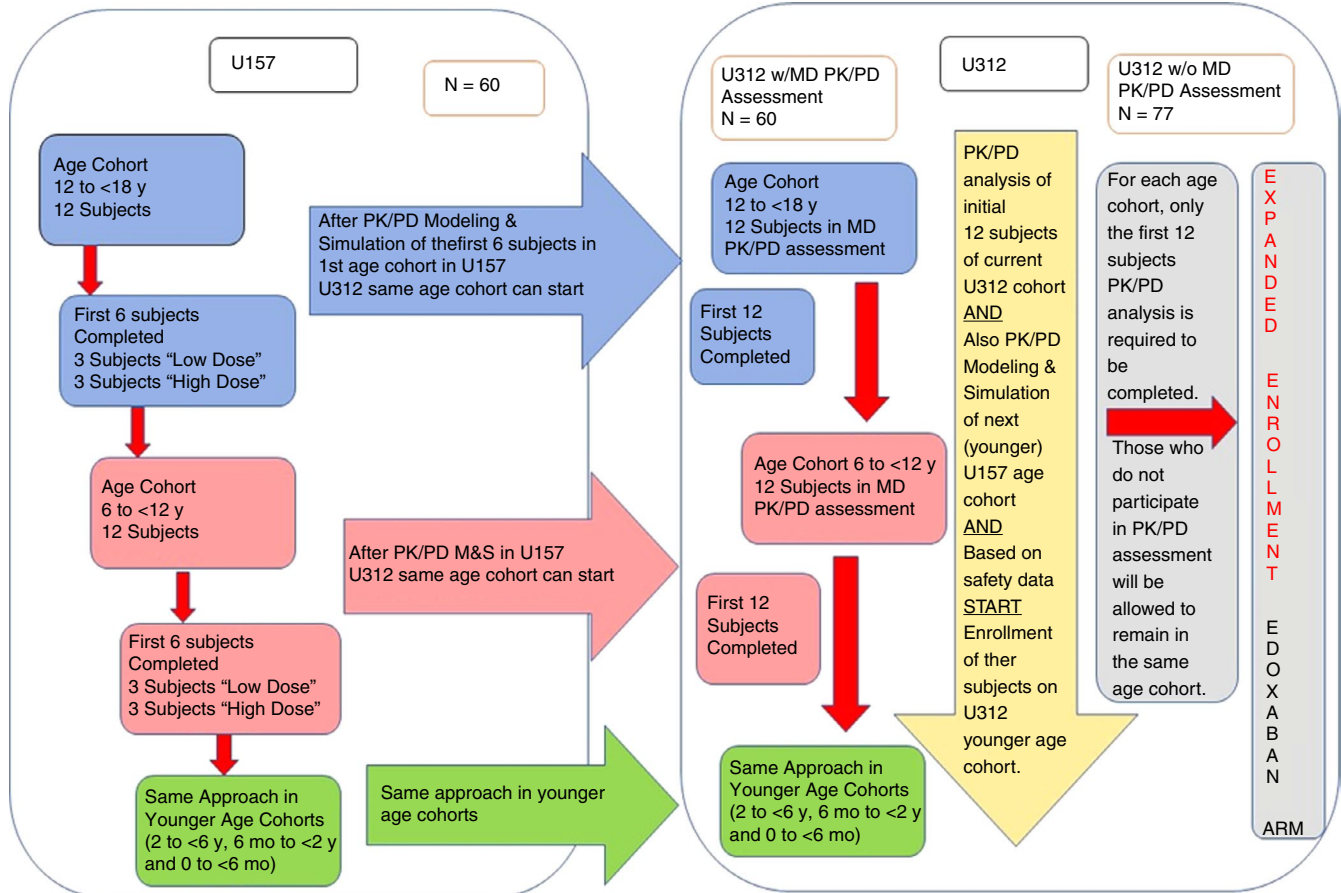
FIGURE 1 Multidose pharmacokinetic/pharmacodynamic assessment incorporated in the phase 3 trial

TABLE 3 Secondary end points

Efficacy end points	Safety end points	PK/PD end points
The individual components of the primary efficacy end point during the first 3-mo period	A combination of major and CRNM bleedings occurring during treatment + 3 d during the first 3-mo period	PK: apparent systemic clearance and apparent volume of distribution
All-cause mortality from randomization to the last dose of study drug + 30 d	All bleeding episodes from the first to the last study drug dose + 30 d	PD: PT, APTT, anti–factor Xa for the edoxaban treatment arm
DVT, catheter-related thrombosis, PE, and cerebral sinus venous thrombosis events within and after the first 3-mo treatment period	A combination of major and CRNM bleedings from the first to the last study drug dose + 30 d	

Note: The clinical outcome end point is a composite combination of major and CRNM bleedings and symptomatic recurrent VTE and death as result of VTE during the whole study period.

APTT, activated partial thromboplastin time; CRNM, clinically relevant nonmajor; DVT, deep vein thrombosis; PD, pharmacodynamics; PE, pulmonary embolism; PK, pharmacokinetics; PT, prothrombin time; VTE, venous thromboembolism.

age cohort in the single-dose PK/PD study. IDMC will review PK and safety data and approve the start of the next younger age cohort. Edoxaban dosages will be reduced for patients with moderate renal impairments ≥30% to ≤50% of normal for the patient's age and size at randomization as determined by the Schwartz formula, and for patients requiring concomitant administration of certain P-glycoprotein inhibitors. Children from 12 to <18 years will receive tablets, which may be crushed and served with applesauce or water; all younger children will receive granules for oral suspension.

3.5 | Standard of care treatment arm

The SOC arm consists of LMWH, VKA, or fondaparinux according to the site SOC treatment regimen.

3.6 | Duration of study

The main treatment period is defined as the time from randomization, until the end of month 3 of treatment. On discretion of the

investigator, all patients may continue into the extension period for a maximum period of an additional 9 months using edoxaban.

3.7 | Study end points

The primary efficacy end point is a composite end point consisting of the incidence of symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden during the first 3-month period. To assess the thrombotic burden, the same radiologic technique that is used at the enrollment of the patient will be used at the end of the observational period ± 3 days. All secondary end points are listed in Table 3. Bleeding complications are defined as recommended by the ISTH pediatric subcommittee.[14] Menstrual bleeding resulting in a medical consultation and/or intervention will be classified as a minor bleeding event.

3.8 | Follow-up

In the main treatment period, all patients will return to the clinic monthly. All randomized patients including those who have discontinued treatment will have an end-of-treatment assessment after 3 months, which includes radiologic evaluation of the thrombotic burden. In the extension period, patients will be followed every 3 months. After discontinuation of the study or after completing 12 months of study treatment, a discontinuation study or month 12 visit will be performed. Furthermore, all patients will have an end-of-study safety follow-up visit 1 month after the last dose of study treatment.

3.9 | Sample size and statistical analysis

The sample size calculation is based on the statistical approach and results of the adult Hokusai-VTE study.[13] In that study, a noninferior margin for the hazard ratio of 1.5 was used because of the high effectivity of the SOC therapy.[15] The sample size of the pediatric study is event driven to collect approximately 68 overall primary efficacy events during the main treatment period. Assuming the edoxaban treatment group will observe a 24% reduction of the event rate compared to SOC and a noninferiority margin of 1.5, the study will have about 80% of power to demonstrate noninferiority with α = .05 (2-sided). Based on literature, we expect an incidence of composite primary efficacy endpoint of 28% in the SOC treatment arm during the main study period.[4,16,17] As a consequence, 274 patients (137 in each treatment arm) need to be randomized to study drug treatment. An interim assessment of incidence rate of the composite efficacy end point in both treatment arms will take place after completion of the main treatment period by the first 140 patients. This will allow for adjustment of number of patients in the study if necessary.

The primary efficacy analysis will be based on a modified intention-to-treat (mITT) analysis set, and will include the primary composite outcome occurring from randomization up to 3 months + 3 days from randomization. The mITT analysis set is defined as all randomized patients receiving at least 1 dose of the study drug. Analyses will be based on the randomized treatment arm even if a patient accidentally received the inappropriate study drug. The time to the first event of the composite primary efficacy outcome will be analyzed using Cox's proportional hazard regression model including treatment arm and age groups as covariates. Region is not included in this model as a covariate because some age groups by region may be very small due to the small sample size. The edoxaban-to-SOC hazard ratio will be calculated with 95% CI based on this model. Edoxaban will be considered noninferior to SOC if the upper limit of the 95% CI is <1.5. If noninferiority of edoxaban is established, edoxaban will be tested for superiority to SOC. Edoxaban will be considered superior if the upper limit of the 95% CI from above analysis is <1.0. The secondary efficacy outcomes will be analyzed using Cox's proportional hazard model similar to the primary efficacy analysis.

All patients who received 1 dose of study drug will be included in the safety analyses. These safety analyses will be based on the randomized treatment, unless a patient received the incorrect drug. Such a patient will be redirected to the appropriate treatment group. Safety end points will be compared between the 2 treatment groups, using a similar Cox's proportional hazard model as described in the primary efficacy analysis.

4 | DISCUSSION

In the past few decades, it has become clear that performing randomized clinical trials in children with VTE is a challenging mission. Until recently, only a few clinical trials have been done and most of them closed early due to slow recruitment or were not powered for efficacy.[4,18-20] The Kids-Dott study, investigating the duration of anticoagulant therapy, started in March 2008 and stopped inclusion only a few months ago.[21] Multiple industry-sponsored phase 3 studies of DOACs are currently being performed or have just been completed, comprising treatment of pediatric VTE, prophylaxis of cardiac thrombosis, and prophylaxis of VTE.[22] These trials provide important data, but most of them are not powered to demonstrate safety and efficacy. Several reasons are responsible for the difficulty of performing large clinical trials in pediatric VTE patients. The most important reason is the rarity of the disease.[23,24] Although the incidence is increasing, VTE remains infrequent in children, with incidence peaks in neonates and teenagers.[1] Furthermore, in contrast to adults, VTE mainly occurs in sick children with multiple underlying diseases with various bleeding risks, and many concurrent medications. As a consequence, a large proportion of eligible patients with VTE are excluded from studies. Moreover, it remains difficult for parents to give permission for study participation, especially when their children are young and very sick. Thus, pediatric VTE clinical trials need to be executed in many centers all over the world.

This is reflected in all phase 3 studies of DOACs, which need to be performed at multiple centers around the world to include sufficient pediatric patients (rivaroxaban, NCT02234843; apixaban, NCT02464969; dabigatran, NCT01895777).

The pediatric DOAC trials, including the Edoxaban Hokusai VTE PEDIATRICS Study, are the outcome of collaboration between pharmaceutical companies and academic experts in the field of pediatric thrombosis. To develop high-quality trials to increase the evidence of antithrombotic treatment in children with VTE, collaboration between both parties is needed. Pharmaceutical companies benefit from the knowledge of the academic pediatric thrombosis experts for the development of their PIPs, and in return they provide logistics and funding for the large, international trials.[14] Very recently, the ISTH pediatric subcommittee has established a task force for drug development in pediatric thrombosis to provide expert input into the development of industry-initiated studies and to create a trial network to perform both industry and academic studies under the umbrella of the International Pediatric Thrombosis Network.[25]

Two study design features increase the feasibility of the edoxaban PIP, including the phase 3 Edoxaban Hokusai VTE PEDIATRICS Study. First, multiple-dose PK/PD assessment was incorporated in the phase 3 trial to ease participation of patients in that part of the PIP. The first 12 patients of each age cohort of the randomized trial are included in the multidose PK/PD assessment on the day of the fifth dose of edoxaban. Second, a composite efficacy outcome has been used. No change or progression of thrombotic burden after 3 months of treatment is one of the components of this composite efficacy outcome. In adult studies, clot-burden change has often been used as a surrogate end point for clinical anticoagulation trials. A systematic review of adult studies showed a predictive correlation between change in clot-burden and long-term clinical outcome.[26] In the pediatric literature, the frequency of no change or progression of thrombotic burden has been described to be about 18%.[5,27,28] Lack of thrombus resolution is one of the prognostic factors for the development of postthrombotic syndrome in children, which is a long-term complication that occurs in about 26% of the children after leg or arm DVT.[6] Therefore, it seems reasonable to use thrombotic burden as a surrogate outcome measure in this trial. It increases feasibility by decreasing the sample size.

One of the limitations of this trial is the open design. However, reported potential study end points will be reviewed by a panel of independent CEC adjudicators for confirmation while being blinded to the treatment arm. In children, it is unethical to use placebo subcutaneous injections as a comparator of LMWH or to perform false International Normalized Ratio tests when patients are randomly assigned to edoxaban. Furthermore, the study patient group will be heterogeneous, including, among others, neonates and oncology patients with catheter-related thrombosis, children with cerebral sinus venous thrombosis or pulmonary embolism, and adolescents with estrogen-associated DVT. These neonates and children have diverse short-term and long-term complications and different risk-benefit ratios of anticoagulant treatment. Moreover, thrombotic burden is part of the composite outcome and may cause information bias. Comparing ultrasound images over time will be especially challenging. Ultrasonography will be done frequently by different radiologists. To ensure adequate adjudication of this end point, detailed instructions in obtaining images are provided to the study sites, and both initial and follow-up imaging are independently and blindly assessed by the CEC.

In summary, randomized controlled anticoagulation trials are challenging in children. The Edoxaban Hokusai VTE PEDIATRICS Study incorporates multiple-dose PK/PD assessment in the phase 3 trial and uses a composite efficacy outcome, including thrombotic burden, to increase feasibility of the trial. This study will provide useful information, not only about the efficacy and safety of edoxaban in children with VTE, but also about these two study design features.

RELATIONSHIP DISCLOSURE

AUTHOR CONTRIBUTIONS

CO, MA, AKC, JE, JJ, GK, and GY are members of the steering committee of the Edoxaban Hokusai VTE PEDIATRICS Study; they were involved in the development of the study design. All authors contributed to the writing of the manuscript and approved the final version.

BRIEF SUMMARY FOR GENERAL PUBLIC

All current anticoagulants have important limitations in children for treatment of venous thrombosis. Edoxaban is one of the new direct oral anticoagulants without need of monitoring. In adults with venous thrombosis, edoxaban has shown to be effective and safe. The Edoxaban Hokusai VTE PEDIATRICS Study will evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of edoxaban and whether edoxaban is similar to standard of care in treatment of pediatric venous thrombosis. Performing randomized clinical trials in children with thrombosis is a challenging mission, mainly due to the rarity of the disease. To increase feasibility, the multiple-dose PK/PD study is integrated in the phase 3 trial. In addition, thrombotic burden which is a prognostic factor for postthrombotic syndrome in children, is one of the components of the primary composite efficacy outcome.

SOCIAL MEDIA POST

Feasibility phase 3 pediatric HOKUSAI study increased by integration of multidose PK/PD study and thrombotic burden in composite efficacy outcome.

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