CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	206316 S-19
Priority or Standard	Priority
Submit Date(s)	12/19/2022
Received Date(s)	12/19/2022
PDUFA Goal Date	10/19/2023
Division/Office	DNH
Reviewer Name(s)	Julia Friend, MPH, PA-C Clinical Reviewer Virginia Kwitkowski, MS, ACNP-BC (Team Lead) Sarabdeep Singh, PhD Statistical Reviewer Lola Luo, PhD Statistical Team Leader Yeh-Fong Chen, PhD Statistical Supervisor
Review Completion Date	09/21/23
Established/Proper Name	Edoxaban
Trade Name	Savaysa
Applicant	Daiichi Sankyo, Inc.
Dosage Form(s)	Oral tablet
Applicant Proposed Dosing Regimen(s)	n/a
Applicant Proposed Indication(s)/Population(s)	n/a
Recommendation on Regulatory Action	Approval PREA PMR 2582-1 is fulfilled. PREA PMR 2852-2 is not fulfilled.
Recommended Indication(s)/Population(s)	n/a

Table of Contents

APPEARS THIS WAY ON ORIGINAL

Table of Tables

Table of Figures

Glossary

AE	Adverse event
aPTT	Activated partial thromboplastin time
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the concentration-versus-time curve
BID	Twice a day
BMI	Body Mass Index
BP	Blood Pressure
CDC	Centers for Disease Control and Prevention
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHD	Congenital heart disease
CHF	Congestive heart failure
CRO	contract research organization
CrCL	creatinine clearance
CRF	Case report form
CSVT	Cerebral Sinovenous Thrombosis
CT	Computed tomography
CVC	Central venous catheter
CYP	Cytochrome
CDER	Center for Drug Evaluation and Research
CRNM	Clinically relevant nonmajor
DCRP	Division of Cardio-Renal products
DMC	Data monitoring committee
DMIHP	Division of Medical Imaging and Hematology Products
DOAC	Direct oral anticoagulants
DSMB	Data and Safety Monitoring Board
DVT	Deep venous thrombosis
EDC	Electronic data capture
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FXa	Activated Factor X
GCP	Good clinical practice
HIT	Heparin-induced thrombocytopenia
HIIT	Heparin-induced thrombocytopenia thrombosis

IASAP	Interim statistical analysis plan
ICF	Informed consent form
ICH	International Council for Harmonization
INR	International Normalized Ratio
IPSP	Initial Pediatric Study Plan
IXRS	Interactive web voice response system
LMWH	Low molecular weight heparin
mITT	Modified intent-to-treat
NA	Not applicable
NDA	New Drug Application
NICU	Neonatal Intensive Care Unit
NSAID	nonsteroidal anti-inflammatory drugs
NVAF	nonvalvular atrial fibrillation
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PE	Pulmonary embolism
PK	Pharmacokinetics
PICU	Pediatric intensive care unit
PMR	Post-marketing requirements
PopPK	Population pharmacokinetics
PREA	Pediatric Research Equity Act
PROBE	Prospective, randomized, open-label, blinded endpoint evaluation
PP	Per protocol
(b) (4)	
PRO	patient reported outcome
PSP	Proposed pediatric study plan
PT	Prothrombin time
PTS	Post-thrombotic syndrome
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SE	Systemic embolism
SOC	Standard of Care
SP	Synthetic pentasaccharide
TE	Thromboembolism
UFH	Unfractionated heparin
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information

VAS	Visual analog scale
VKA	Vitamin K antagonist
V/Q	Nuclear ventilation/perfusion scan
VTE	Venous thromboembolism

1. Executive Summary

1.1. Product Introduction

Savaysa (edoxaban) is an anticoagulant agent; an orally active, selective, direct, and reversible inhibitor of activated factor X (FXa). Inhibition of FXa in the coagulation cascade prolongs clotting time and reduces the risk of thrombus formation. Edoxaban does not impair platelet aggregation.

Initially approved by the USFDA in 2015, Savaysa has been approved in the U.S. for adults for the following indications:

1. To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). Limitations of Use for NVAF: Savaysa should not be used in patients with creatinine clearance (CrCL) >95 mL/min because of increased risk of ischemic stroke compared to warfarin at the highest dose studied (60 mg)

2. For the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant.

This supplemental application was submitted to fulfill the existing post-marketing requirements (PMR) under the Pediatric Research Equity Act (PREA). PMR 2852-1 and PMR 2852-2 were established on 01/08/2015.

The applicant is not requesting a new indication.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This supplement provides for changes to the Savaysa USPI to reflect the findings from trial DU176B-D-U312. The primary efficacy endpoint was the composite endpoint (consisting of symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic

burden during the Main Treatment Period. The hazard ratio (HR) for the edoxaban group versus the SOC group was 1.01 (95% CI: 0.594 to 1.719). The upper bound of the 95% CI (1.719) was above the prespecified noninferiority margin of 1.5, and the noninferiority of edoxaban versus SOC was not confirmed. Therefore, as efficacy was not established, the benefit:risk assessment is negative. The application does not contain substantial evidence of effectiveness. No indication for pediatric patients was requested and none will be granted.

The Division has concluded that the Applicant:

- Has fulfilled the elements of PMR 3842-1.
- Has not fulfilled the elements of PMR 3842-2 (related to the Phase 3 pediatric trial) because they did not follow the statistical analysis plan with regards to resizing the trial based upon an interim analysis. The trial was not completed.

1.3. Benefit-Risk Assessment

Table 1 Benefit-Risk Integrated Assessment

Benefit-Risk Integrated Assessment
Pediatric venous thromboembolism (VTE) is an uncommon but serious and life-threatening condition with associated morbidity and mortality. Presence of a central venous catheter, admission to intensive care units, and conditions leading to a hypercoagulable state are risk factors for development of pediatric VTE. Dalteparin, Pradaxa, and Xarelto are the only anticoagulant products with a US-FDA-approved pediatric indication. Dalteparin, a low molecular weight heparin, is indicated for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older. Pradaxa (dabigatran oral pellets), a direct thrombin inhibitor, is indicated for the treatment of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated with a parenteral anticoagulant for at least 5 days and to reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated. Pradaxa (dabigatran capsules) are indicated for the treatment of VTE in pediatric patients 8 years to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days and to reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated. Xarelto (rivaroxaban tablets and for oral suspension), a factor Xa inhibitor, is indicated for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years and for thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure. Unfractionated heparin may be considered to have an implied indication, though the indication statement does not specify pediatric patients, the dosage and administration subsection of the USPI has specific pediatric dosage recommendations. The main advantages of DOACs over SOC therapies are the fixed dose administration without the need for monitoring, the oral formulation availability and the presence of a specific targeted antidote. It is important to note that DOACs have been less effective in the treatment of patients with prosthetic heart valves and in patients with antiphospholipid antibody syndrome. The main common adverse reaction among all anticoagulants is the risk of bleeding, which can result in life-threatening major bleeding in ~2-3% of patients. This application is supported by the results of a randomized, open-label, multicenter, actively-controlled trial to evaluate the pharmacokinetics

and pharmacodynamics of edoxaban and to compare the efficacy and safety of edoxaban with standard-of-care anticoagulant therapy in pediatric patients from birth to less than 18 years of age with confirmed venous thromboembolism. The primary study objective was to demonstrate the noninferiority of edoxaban to standard-of-care (including low-molecular weight heparin, vitamin K antagonist, or synthetic pentasaccharide Xa inhibitors) in the treatment and secondary prevention of VTE in pediatric subjects with regard to the composite efficacy endpoint (i.e., symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden) during the first 3-month treatment period (for cohort 5, the intended duration of treatment is 6 to 12 weeks).

The Applicant provided no evidence of non-inferiority for Savaysa (edoxaban) in pediatric patients. The primary efficacy endpoint was the composite endpoint consisting of symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden during the Main Treatment Period. The benefit:risk assessment is negative.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The annual incidence of VTE in children is reported as 0.07 - 0.14 per 10,000 children, with higher rates in neonates and adolescents. • The rate of VTE in hospitalized children has increased by 70% over the past 10-20 years. • The most significant VTE risk factors are the presence of a central venous catheter, admission to an intensive care unit and conditions that lead to a hypercoagulable state. • VTE is serious life-threatening medical condition with significant morbidity and mortality in pediatric patients, such as pulmonary embolism, postthrombotic syndrome and an untreated VTE-related mortality rate of ~3%.	VTE is an uncommon but serious disease in children. If untreated, VTE can lead to serious and life-threatening outcome, with significant morbidity and mortality.
Current Treatment Options	• Dalteparin, a low molecular weight heparin, is indicated for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older.	There is a need for new therapies for pediatric patients with VTE and for those at risk for VTE recurrence due to persistent VTE risk factors.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Pradaxa (dabigatran oral pellets), a direct thrombin inhibitor, is indicated for the treatment of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated with a parenteral anticoagulant for at least 5 days and to reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated. Pradaxa (dabigatran capsules) are indicated for the treatment of VTE in pediatric patients 8 years to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days and to reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated. • Xarelto (rivaroxaban tablets and for oral suspension), a factor Xa inhibitor, is indicated for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years and for thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure. • Other standard of care (SOC) treatment options, most of which are used in an off-label fashion, include heparin products, vitamin K antagonists, fondaparinux and parenteral thrombin inhibitors. • Unfractionated heparin may be considered to have an implied indication because the Dosage and Administration section of the USPI contains pediatric dosing recommendations. • The main advantages of DOACs over SOC therapies are the fixed dose administration without the need for monitoring, the oral formulation availability and the presence of a specific targeted antidote.	Specifically, there is a need for oral anticoagulant therapies in pediatric patients that require minimal to no monitoring and have a dependable reversal agent. DOACs offer a potentially significant new therapy for VTE in pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There are no FDA-approved antidotes/reversal agents for DOACs for • pediatric patients.	
Benefit	• The Edoxaban Hokusai VTE PEDIATRICS Study, a phase 3, randomized, open-label, actively controlled trial did not demonstrate non-inferiority to the standard-of—care arm with regards to the primary composite endpoint of "symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden". Therefore, efficacy was not demonstrated.	The trial did not demonstrate effectiveness for edoxaban in the treatment of VTE in pediatric patients.
Risk and Risk Management	• Safety results were comparable between the edoxaban and SOC arms with regards to the number of patients with an adjudicated confirmed major and clinically relevant nonmajor bleed during the Main Treatment Period and On-Treatment (HR 0.60 [95% CI; 0.139 to 2.597]). At least 1 adjudicated confirmed major and CRNM bleeding event occurred in 3 (2.1%) of patients in the edoxaban group and 5 (3.5%) of patients in the SOC group. • Treatment-emergent adverse events occurred in 71% of patients on the edoxaban arm and 67% of those on the SOC arm. The most common (≥4%) TEAEs on the edoxaban arm included headache, vomiting, nasopharyngitis, cough, dizziness, rash, and urinary tract infection.	Safety cannot be demonstrated without efficacy.

1.4. Patient Experience Data

Table 2 Patient Experience Data Relevant to this Application

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

"Venous thromboembolism (VTE) is a rare event in children (1 in 100,000) compared with adults (1 in 1000)" (Char Witmer, 2020). VTE is an increasing problem in children with underlying medical conditions. Adverse outcomes associated with VTE include death, pulmonary embolism, paradoxical emboli, stroke, organ dysfunction, infection, post-thrombotic syndrome, loss of venous access, and pain. "Hospital acquired VTE in pediatric patients is associated with an increased hospital stay and cost" (Goudie A, 2015). "The estimated mortality rate associated with pediatric VTE is 2.2%, although this is likely an underestimate" (Monagle P, 2000) .

There are many known inherited and acquired clinical risk factors for the development of VTE in children, including venous stasis, endothelial injury, inflammation and thrombophilia [5-7]. More than 90% of pediatric patients who develop VTE have > 1 VTE risk factor, where the presence of a central venous catheter (CVC)[8] (Jaffray J, 2017) and admission to a pediatric intensive care unit (PICU) (Polikoff LA, 2014) [9] considered as two of the strongest risk factors for the development of VTE in children. Other risk factors for VTE in children include: chronic inflammatory conditions such as inflammatory bowel disease[10] (Irving PM, 2005) and cystic fibrosis[11](Takemoto, 2012), sickle cell disease[12] (Ko RH, 2017), acute inflammatory conditions such as systemic infections and sepsis, obesity, acute trauma[13] (Chima RS, 2017), major surgery especially orthopedic procedures or interventions leading to prolonged immobilization, malignancies[14] (Athale, 2013), nephrotic syndrome[15] (Kerlin BA, 2014), congenital heart disease (CHD) and other acquired cardiac diseases with and without congestive heart failure (CHF)[16,17] (Monagle, 2003), (Silvey M, 2017), inherited thrombophilias[18] (Goldberg, 2008), antiphospholipid antibody syndrome (APS)[19] (Rumsey DG, 2017) and contraceptive use [20,21] (Trenor CC, 2011), (Woods GM, 2016) and other drug-associated risk factors such as asparaginase, corticosteroids and heparin-containing products, with the latter resulting in heparin-induced thrombocytopenia thrombosis (HITT)[22] (Takemoto CM, 2011).

The signs and symptoms of VTE vary by location of the clot. DVTs can cause leg pain, leg swelling, warm skin, and erythema possibly with streaking on skin. PEs can cause cough (possibly with blood-streaked mucus), shortness of breath, pain on inspiration, rapid or irregular heart rate, lightheadedness or dizziness, diaphoresis, fever, or cyanosis (National, Heart, Lung, and Blood Institute, 2022).

VTE requires prompt evaluation and treatment, without which, serious complications (mentioned above) will likely occur.

The treatment of children with VTE is similar to the treatment of adults with VTE since the majority of cases will not resolve without treatment. Once a child has developed an image-proven [28,29] (Male C, 2003) (Lim W, 2018), symptomatic VTE, treatment with anticoagulant therapy is recommended to allow the gradual intrinsic thrombolysis of the thrombus while preventing its acute progression. Furthermore, since one of the strongest risk factors for VTE in children is the presence of past history of VTE, the persistence of significant VTE risk factors after completion of the acute treatment course may indicate the continuation of anticoagulant therapy to prevent the recurrence of VTE [30,31] (Radelescu, 2015) (Betensky M B. M., 2017). In certain situation, thrombolytic therapy maybe indicated in children with more severe VTE[32,33] (Goel R, 2013) (Tarango C, 2017). Overall, there is a need for effective and safe treatment of VTE in the pediatrics population. However, given the known VTE-related complications and the established treatment-associated risk of bleeding, there must be a comprehensive benefit and risk assessment of the treatment of VTE in children [Source: FDA Clinical Review NDA 214358 S41, Pradaxa pediatric efficacy supplement 2/23/2021].

There are recognized differences in the etiology and pathophysiology of VTE between the adult and pediatric population. In pediatrics, VTE are more likely to be related to the presence of multiple underlying transient or persistent risk factors (i.e. provoked VTE), while spontaneous VTE is more common in the adult population (i.e. unprovoked VTE). Similar to adults, VTE can result in significant morbidity and mortality in children, both related to the disease and to the treatment adverse events. Complications of VTE in children include: 1) VTE progression resulting in symptomatic pathology in the affected region such as post-CSVT chronic headache (Ichord, 2017) and superior vena cava syndrome (Nossair F, 2018), 2) PE (Ramiz S, 2018), 3) post-thrombotic syndrome (PTS) (Betensky M G. N., 2018), with a rate of moderate-severe PTS of 11-23% (Jones S, 2016), 4) persistent bacteremia and systemic infection, and 5) loss of catheter function in the case of catheter related VTE, 6) VTE recurrence, with a rate of 7-21% (Veldman A, 2008), 7) Death, with an untreated VTE-related mortality of ~3%. These short and long term VTE-related complications should be considered when weighing the benefits and risks of treatment, as pediatric VTE is a serious and life-threatening condition. [Source: FDA Clinical Review, NDA 214358, Pradaxa pediatric efficacy supplement 2/23/2021].

2.2. Analysis of Current Treatment Options

The treatment of pediatric thromboembolism has been historically based upon adult experience and indications (VC, 2017). Pediatric patients with symptomatic VTE are typically treated in tertiary care centers with pediatric hematology involvement and the majority of patients are treated with anticoagulants on an off-label basis (Young G, 2017). In general, randomized clinical trials or large single arm trials to inform dosing for anticoagulants in children are lacking, thus dosing guidelines are based on smaller, single arm studies and expert

opinion (Monagle P C. A., 2012), (Monagle P C. C., 2018). Unique considerations with regards to the treatment of children with VTE include the dynamics of the coagulation system in the developing child, pharmacokinetics (PK) and pharmacodynamic (PD) differences in younger pediatric patients requiring higher doses of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in younger patients, and potential distress caused by frequent therapeutic and/or diagnostic interventions involving needles.
At this time, Fragmin (dalteparin), Pradaxa (dabigatran etexilate), and Xarelto (rivaroxaban) are the only anticoagulants with pediatric indications.

Additionally, even though UFH is not formally indicated for pediatric patients, it may be considered to have an implied indication because the Dosage and Administration (2.4) section of labeling provides specific pediatric dosing for the indication of prophylaxis and treatment of venous thrombosis and PE.

The three main classic classes of anticoagulants used as the SOC off-label treatment in children are UFH, LMWH and vitamin K antagonists (VKA) (Hepponstall M, 2017), (Monagle P N. F., 2018). Of note, higher doses of LMWH are required in neonates and children compared to adults to achieve therapeutic anti-Xa levels, which is thought to be at least partially due to increased clearance and decrease antithrombin levels in infants and young children. Other, less commonly used but more novel classes of anticoagulants include factor Xa inhibitors and factor IIa (i.e. thrombin) inhibitors.

Despite the approval of a few anticoagulants for pediatric patients, there remains an unmet medical need in this setting; particularly in neonates as most drugs with a pediatric indication do not include neonates.

Table 3 provides a summary of the approved drugs as well as the drugs commonly used off-label for the treatment of pediatric VTE.

Table 3 Summary of treatments for pediatric VTE

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed)
FDA Approved Treatments						
Pradaxa (Dabigatran etexilate) Oral Pellets	Treatment of venous thromboembolic event (VTE) in pediatric patients aged 3 months to less < 12 years of age who have been treated with a parenteral anticoagulant for at	2021	Oral twice daily	The efficacy of Pradaxa was established based on a composite endpoint of patients with complete thrombus resolution, freedom from recurrent venous thromboembolic event, and	Most common adverse reactions (>15%) are gastrointestinal adverse reactions and bleeding	Safety and effectiveness of Pradaxa have not been established in pediatric patients with non-valvular atrial fibrillation

	least 5 days To reduce the risk of recurrence of VTE in pediatric patients aged 3 months to < 12 years of age who have been previously treated			freedom from mortality related to venous thromboembolic event (composite primary endpoint). Of the 267 randomized patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint. The corresponding rate difference and 95% CI was -0.038 (-0.161, 0.086) and thus demonstrated non-inferiority of Pradaxa to SOC, since the upper bound of the 95% CI was lower than the predefined non-inferiority margin of 20%		or those who have undergone hip replacement surgery
Unfractionated Heparin Heparin sodium injection NDA 17029	Anticoagulant	1939	Intravenous infusion, and subcutaneous injection, continuous IV infusion, bolus doses.	There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience.	Hemorrhage HIT, HIIT, Elevation of serum aminotransferases Serious and fatal adverse reactions in neonates and low-birth weight infants treated with benzyl alcohol-preserved formulation in infusion solutions	Pediatric dosing information is provided in Section 2 of the USPI
Fragmin (Dal-teparin) (LMWH)	Anticoagulant	2019	Subcutaneous injections Q12 hours	Treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older.	In pediatric patients with symptomatic VTE, the most common (greater than 10%) adverse reactions were injection site bruising (30%), contusion (12%), and epistaxis (10); thrombocytopenia	Use preservative-free Fragmin in neonates and infants. Serious adverse reactions including fatal reactions and the "gasping syndrome' occurred in premature neonates and low-birth weight infants in the neonatal intensive care unit who received benzyl alcohol preserved medications. In these cases, benzyl alcohol dos-

						ages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and Cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol
Xarelto (Rivaroxaban)	Treatment of VTE and reduction in risk of recurrent VTE in pediatric patients from birth to less than 18 yrs. For thrombo-prophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure.	2011 (original approval) 2021 Pediatric indication added.	tablets and for oral suspension, for oral use. Schedule varies from once, twice, to three times a day depending on formulation and weight of patient.	Confirmed VTE: 500 pediatric patients were randomly assigned to receive either Xarelto or standard-of-care medications for three months (or one month for children younger than two years with a central venous catheter related-VTE). At the end of the study, 1.2% of patients in the Xarelto treatment group had signs or symptoms of recurrent VTE, compared with 3.0% of patients in the standard-of-care group. Thromboprophylaxis after	Bleeding, cough, vomiting, gastroenteritis	Patients <6 months of age should meet the following criteria: at birth were at least 37 weeks of gestation, have had at least 10 days of oral feeding, and weigh ≥2.6 kg at the time of dosing

				Fontan procedure: effectiveness was studied in pediatric patients between ages 2 and 8 years with congenital heart disease who had a recent Fontan surgical procedure. In Part A of the study, patients received Xarelto for one year; in Part B, patients were randomly assigned to receive Xarelto or aspirin for one year. At the end of the study, 8.3% of patients in Part A (who all received Xarelto) had a blood clot. In Part B, 1.6% of patients who received Xarelto had a blood clot compared to 8.8% of patients who received aspirin.		
Products Commonly Used Off-Label in Pediatric Patients						
Enoxaparin/ LMWH	Anticoagulant	1993	Injection, for subcutaneous use; q12h	Safety and effectiveness of Lovenox in pediatric patients have not been established. Lovenox is not approved for use in neonates or infants.	Bleeding.	Contains benzyl alcohol. Serious adverse reactions including fatal reactions and the "gasping syndrome" occurred in premature neonates and low-birth-weight infants in the NICU who received drugs containing benzyl alcohol as a preservative.
Warfarin/ VKA	Anticoagulant	1954	Oral tablet once daily	Adequate and well-controlled studies with Coumadin have not been conducted in any pediatric population, and the optimum dosing, safety, and efficacy in pediatric patients is unknown. Pediatric use of Coumadin is based on adult data and recommendations and available limited pediatric data from	Bleeding, bruising	No pediatric dosing information is included in the USPI

				observational studies and patient registries.		
Fondaparinux/ Xa inhibitor	Anticoagulant	2001	Injection, for subcutaneous use once daily	Safety and effectiveness of ARIXTRA in pediatric patients have not been established. Because risk for bleeding during treatment with ARIXTRA is increased in adults who weigh <50 kg, bleeding may be a particular safety concern for use of ARIXTRA in the pediatric population	Bleeding.	No pediatric dosing information is included in the USPI
Bivalirudin/ Direct Thrombin Inhib-ibitor	Anticoagulant, for use during percutaneous coronary intervention	2000	For Injection, for intravenous use; continuous infusion	The safety and effectiveness of Angiomax in pediatric patients have not been established.	Bleeding	No pediatric dosing information is included in the USPI

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

01/08/2014 Submission of new NDA 206316, providing for the use of SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets. The application was divided by indication into Original 1, 2 (b) (4)

- NDA 206316/Original 1 - Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. This application was reviewed by the Division of Cardio-Renal products (DCRP)

- NDA 206316/Original 2 - Treatment of deep vein thrombosis and pulmonary embolism

(b) (4)

1/8/2015 Agency approval granted for use in adults to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF). Limitation of Use for NVAF: SAVAYSA should not be used in patients with creatinine clearance (CrCL) > 95 mL/min because of increased risk of ischemic stroke compared to warfarin at the highest dose studied (60 mg).

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant. PREA PMRs were issued with the approval.

PMR 2852-1: Perform, complete and submit the full study report for a single-dose study of pharmacokinetics and pharmacodynamics (PK/PD) of edoxaban in pediatric patients at risk for venous thromboembolism (VTE), requiring anticoagulation or recently completing standard of care anticoagulation in accordance with your October 31, 2013 agreed upon Initial Pediatric Study Plan (iPSP).

- Final Protocol Submission: Completed 2/19/2014
- Study Completion: 6/30/2017
- Final Report Submission: 12/31/2017

PMR 2852-2: Perform, complete and submit the full study report for a phase 3 multicenter, randomized, active control study of edoxaban in pediatric patients with documented venous thromboembolism in accordance with your October 31, 2013 agreed upon Initial Pediatric Study Plan (iPSP)

- Final Protocol Submission: 12/14/2016
- Study/Trial Completion: 12/31/2021
- Final Report Submission: 6/30/2022

8/15/2016 Submission of pediatric study protocols (PMR2852-1 and PMR2852-2) under the iPSP as part of Post Marketing Requirements

2/19/2021 PMR/PMC milestones were revised for PMR 2852-1 due to difficulties with recruitment of study subjects.

2/19/2021 The Agency granted a pediatric deferral extension for the study completion to 09/2021 and the final report submission to 12/2021.

1/12/2023 The Agency granted a pediatric deferral extension for study completion of the Phase 3 trial to 12/2022 and final report submission date to 06/2023.

PMR 2852-1 a single-dose study of pharmacokinetics and pharmacodynamics (PK/PD) of edoxaban in pediatric patients at risk for venous thromboembolism (VTE), requiring anticoagulation or recently completing standard of care anticoagulation).
Final Report Submission: 03/2022 (submitted 01/28/2022)

PMR 2852-2, a phase 3 multicenter, randomized, active control study of edoxaban in pediatric patients with documented venous thromboembolism).
Study Completion: 12/2022 (revised date)
Final Report Submission: 6/2023 (submitted 12/19/2022)

3.2. Summary of Presubmission/Submission Regulatory Activity

DNH holds IND 63266 for edoxaban (Daiichi Sankyo, Inc.; Sponsor). This IND was submitted on 05/27/2004.

Two separate Type B (End of Phase 2) meetings with FDA were conducted. The first on August 13, 2008 (with the Division of Cardiovascular and Renal Products; DCRP) and the second on April 29, 2009 (with the former Division of Medical Imaging and Hematology Products; DMIHP), to discuss development plans for the AF and VTE indications, respectively. To address pediatric data requirements mandated by the Pediatric Research Equity Act (PREA), Daiichi Sankyo requested a waiver for pediatric studies in the AF indication and a deferral of pediatric studies for the VTE indication until after the safety and efficacy of edoxaban has been established in adults. In the FDA response, it was noted that a decision on the pediatric waiver (for AF) and pediatric deferral (for VTE) would not be made at the End of Phase 2 meetings. FDA indicated that the requests should be made upon submission of the NDA filing(s), at which time a decision would be made.

On 3/21/2012, the proposed pediatric study plan (PSP) (version 1) was submitted to the Agency. Two studies were proposed in the PSP:

A Phase 1 PK/PD Study in pediatric patients which was an open-label, sequential design study of edoxaban in five pediatric age groups (birth to <6 months, 6 months to <1 year, 1 to <2 years, 2 to <6 years, and 6 to <18 years). The objectives of the study were to evaluate the PK and PD of edoxaban in pediatric patients with initially treated deep vein thrombosis (DVT), and to identify recommended pediatric dose(s) for the Phase 3 VTE study (Study 4). Patients received three QD doses of edoxaban (following initial treatment of their deep vein thrombosis according to current treatment guidelines).

The second study was a Phase 3 VTE Study in pediatric patients. This was a randomized, open-label study to compare the efficacy and safety of low molecular weight heparin (LMWH)/unfractionated heparin (UFH) followed by edoxaban to active control (i.e., LMWH/UFH alone or LMWH/UFH followed by warfarin, as determined by the treating physician) In children from birth to less than 18 years of age with confirmed venous thromboembolic disease. The primary efficacy objective was to assess the incidence of recurrent VTE, VTE-related death, or thrombotic burden (defined as no regression of thrombus size or extension of thrombus) following 3 months of treatment (+3 days) in the two treatment groups. The primary safety objective of this study was to compare the safety of the two treatment groups with regards to major bleeding and clinically relevant non-major bleeding while on, or within 3 days of stopping treatment (major bleeds occurring up to 30 days after last treatment dose was also analyzed). Patients were treated for 3 months (with optional extension of treatment up to 12 months, per investigator discretion) with overall safety evaluation for up to 30 days following the last dose of treatment on study. This study was not started until after both the Phase 1 pediatric PK/PD study (Study 3) and the adult Phase 3 VTE study (Hokusai VTE) have been completed, and final results were available.

On 5/21/2012, in response to the submitted PSP, the Agency replied with the following recommendations:

- For the Phase 3 efficacy and safety study the trial should be blinded as to the 2 arms. It was recommended that a doubled dummy design with INR evaluation in both arms be employed.

- The various types of VTE (upper and lower extremity, catheter-related, abdominal and intracerebral) and distribution of VTE in the various age groups should be equally represented in both arms of the trial.

- The clinical significance of the endpoint of “Thrombotic burden” is not substantiated by the publications submitted. Convincing evidence of its clinical significance would need to be provided if it is to be used as an endpoint.

- The event rates for recurrent VTE and VTE-related deaths used to estimate a non-inferiority margin are based on publications reporting studies that contain small numbers of subjects, have variable follow-up periods, have not included comparison to placebo therapy, employ variable use of anticoagulants and have different disease conditions. Because of these factors, the proposed non-inferiority is not well-supported.

- The trial should be designed to establish superiority of edoxaban to warfarin therapy after initial treatment with heparin.

- The final draft of the phase 3 trial should be submitted to the Division for review and comments before embarking on the enrollment of subjects.

On 12/05/2012 the Agency (b) (4)

"

On 06/05/2013 a Pediatric Study Plan/Initial Pediatric Study Plan was resubmitted to the Agency.

A written response to the PSP was issued by the Agency on 8/16 2013 making recommendations regarding a wide range of doses to ensure adequate data is collected for comparing the PK/PD relationships in adult and pediatric populations. Other recommendations included use of a model-based approach in Study 2 to explore the PK/PD relationship in the pediatric population. This relationship should be compared to the relationship is adults and be used to guide dose selection for Study 3. Simulations using the PK and PK/PD models should be performed to justify dose selection in Study 3. Other comments noted that a single dose PK/PD study had been proposed. In order to do a study in pediatric patients, there must be "No greater than minimal level of risk" "Minor increase over minimal level of risk " (CFR 46.406). Any greater level of risk must provide the participating child with a "Prospect of direct benefit" In order for this study to be acceptable. Justification must be provided showing that participation involves no more than a "Minor increase over minimal level of risk" or justification that a single dose edoxaban will offer a "prospect of direct benefit" to the individual child enrolled on the study.

A detailed justification for the selection of non-inferiority margin of 5% should be included in the protocol. To develop a non-inferiority criterion, a reliable estimate of the active control effect should be computed from a meta-analysis of previous controlled randomized trials. The criteria should also consider the historical between trial variability in this patient population.

Subgroup analyses such as by gender, region and other important baseline characteristics should be also included in the protocol.

On 06/19/2014, Daiichi Sankyo submitted a meeting request to discuss the pediatric program (b) (4). The Division sent preliminary responses to their questions and Daiichi Sankyo canceled the meeting. The questions pertained to the U157 (PK/PD Study)

On 12/19/2022 the Applicant submitted the current Supplement under review; Supplement 19.

3.3. Foreign Regulatory Actions and Marketing History

Edoxaban was first approved in Japan on 22 Apr 2011 for use in prevention of VTE in subjects undergoing orthopedic surgeries. On 26 Sep 2014, indications for prevention of ischemic stroke and systemic embolism in patients with NVAF as well as for treatment and recurrence prevention of VTE (DVT and pulmonary thromboembolism [PE]) were approved.

Currently, edoxaban is approved in 69 countries and is marketed in 60 countries worldwide.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No site inspections were requested because no indication was requested.

4.2. Product Quality

No new CMC information was submitted.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted.

4.5. Clinical Pharmacology

The Clinical Pharmacology primary reviewer is Harisudhan Thanukrishnan, PharmD and his Team Leader is Sudharshan Hariharan, PharmD. The clinical pharmacology review was archived on 09/14/23. The executive summary from the primary review is as follows:

Edoxaban is an orally active, reversible Factor Xa (FXa) inhibitor, which was approved on January 8, 2015, under NDA 206316 for (a) the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant and to (b) reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). In this supplement, the Applicant has submitted the Clinical Study Report (CSR) for Study U312, a pivotal registrational study, conducted in pediatric patients (from birth to less than 18 years of age) with confirmed venous thromboembolism (VTE). The Applicant is not claiming an indication in pediatric patients, as the Study U312 failed to demonstrate efficacy of edoxaban in the treatment of pediatric patients with VTE.

The pediatric development for edoxaban included two Post-marketing Requirements (PMR). The Applicant had completed the first study (PMR 2852-1) titled, "A Phase 1, Open-label, Single-dose, Nonrandomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients" and submitted the CSR on 28 Jan 2022. This Phase 1 study (DU176b-A-U157) evaluated the PK and PD of edoxaban following a single-dose administration to allow dose selection for the subsequent Phase 3 study in pediatric patients. The study included five sequential pediatric age cohorts with evaluation of 2 different doses (low and high dose) that were selected to target exposures comparable to adult doses of 30 mg (low dose) or 60 mg (high dose) within each age cohort. The plasma concentration-time profiles for different age cohorts were comparable within the low and high dose groups, respectively. Across all cohorts, the median exposure was within 0.5- to 1.5-fold of the exposure in adult patients with VTE at the corresponding dose levels (30 mg once daily [QD] for low dose and 60 mg QD for high dose). The PD endpoints included observed absolute and percent change from baseline in prothrombin time (PT), activated partial thromboplastin time (aPTT), and anti-activated factor X (FXa). A trend for dose-dependent increase in the inhibitory effect of edoxaban on the PD markers PT, aPTT and anti-FXa was observed across all the age cohorts.

To support pediatric dosing, the Applicant developed edoxaban granules for oral suspension (60 mg). Patients younger than 12 years of age received edoxaban granules for oral suspension according to body weight, in the above Phase 1 study. The relative oral bioavailability of granules for oral suspension (10 mL of 6 mg/mL) versus tablets (2 x 30 mg) was assessed in healthy adult subjects (Study DU176b-AU154). The exposure (AUClast and AUCinf) was similar between both formulations but the Cmax of oral suspension was 13% lower than the tablets.

The second study (PMR 2852-2) was the pivotal registrational study (Study U312, Hokusai VTE Pediatric Study) titled "A Phase 3, Open-label, Randomized, Multicenter, Controlled Trial to

Evaluate the Pharmacokinetics and Pharmacodynamics of Edoxaban and to Compare the Efficacy and Safety of Edoxaban with Standard-of-Care Anticoagulant Therapy in Pediatric Subjects from Birth to Less Than 18 Years of Age with Confirmed Venous Thromboembolism (VTE)" and the CSR was submitted in this supplement. The primary objective of the study was to demonstrate the non-inferiority of edoxaban to standard of care therapy in the treatment and secondary prevention of VTE in pediatric subjects during the first 3-month treatment period. The study also characterized multiple dose PK and PD in a subset of patients. Patients aged 12 to <18 years received fixed dose of 30 mg, 45 mg and 60 mg based on body weight of < 30 kg, ≥ 30 to <60 kg and ≥60 kg, respectively. Patients in age cohorts ≥6 to <12 years, ≥2 to <6 years, ≥6 months to <2 years, and ≥0 to <6 months, received body weight-based doses of 1.2 mg/kg, 1.4 mg/kg, 1.5 mg/kg and 0.8 mg/kg, respectively. The observed mean pre-dose plasma concentrations of edoxaban in pediatric subjects were comparable across 5 age cohorts from birth to <18 years and were comparable with those in adult patients with VTE administered with edoxaban at 60 mg QD estimated by adult population PK modeling. Overall, the median simulated steady state AUC0-24h, ss values in pediatric patients across five age groups were 18% to 27% lower than that in adult VTE patients receiving 60 mg QD dose. However, the exposure in pediatric patients were within the range of exposures observed in adult VTE patients. The nature of the PK/PD relationship (PT, aPTT, and anti-FXa) in pediatric subjects were consistent with those in adult VTE patients administered edoxaban at 60 mg QD. Study U312 did not demonstrate non-inferiority of edoxaban versus the standard-of-care (SOC) as the upper bound of the 95% CI (1.72) was above the prespecified non-inferiority margin of 1.5 (hazard ratio (edoxaban/SOC) is 1.01 with two-sided 95% CI (0.59 to 1.72). As per Applicant, the study was expected to observe 68 events, with an expected event rate of 24%, and the study was sized to have 274 patients.

However, during the interim analysis, the Applicant observed 23 events among the 138 enrolled patients, resulting in an event rate of 16.7%. Based on this analysis, the sample size was recalculated to be 422, which would have led to approximately 68 events by the end of the study, assuming the observed event rate remained constant. However, despite the recommendation from the interim analysis, the Applicant terminated the study at a sample size of 286. At that point, they had observed 57 events, with an event rate of 20%. Consequently, the resulting analysis yielded a wide 95% confidence interval of 1.01 (0.59, 1.72), with the upper bound exceeding the non-inferiority margin of 1.5. Based on these results, the statistical review team concludes that the study was underpowered, i.e., it did not have an adequate sample size to confirm non-inferiority. This is in contrast to the adult study, which was confirmed based on a hazard ratio of 0.89 (95% CI 0.70, 1.13), where the upper bound of the 95% confidence interval was below the threshold of 1.5.

Conclusion:

The Office of Clinical Pharmacology (OCP)/ Division of Cardiometabolic and Endocrine Pharmacology has reviewed the information contained in this supplement of NDA 206316. The Applicant has fulfilled PMR 2852-1 with completion of the single dose PK/PD study in pediatric

patients. Based on this PK/PD study, the Applicant identified doses for pediatric patients across different age cohorts for evaluation in the efficacy trial. While selection of pediatric doses resulted in exposures in the range of adult exposures equivalent to 60 mg in patients with VTE, the simulated median steady-state AUC0-24 was approximately 18 to 27% lower compared to adult exposures. The current pediatric efficacy trial failed due to inadequate sample size, however, if the Applicant were to conduct another trial, the pediatric dosing could be refined further to match adult exposures even closely.

No PMRs or PMCs were recommended by the Clinical Pharmacology review team.

4.6. Devices and Companion Diagnostic Issues

No device information was submitted.

4.7. Consumer Study Reviews

No human factor studies were submitted for review.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 4 Clinical Trials Conducted for NDA 206316 S19

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients en-rolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
DU176b-A-U157	NCT 02303431	A Phase 1, Open-label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics (PK) and Pharmacodynamics (PD) of Edoxaban in Pediatric Patients IND 62366	Single dose (randomized to high dose or low dose) Edoxaban (DU-176b) in any of the following formulations: Edoxaban 15 mg or 30 mg oral tablets Edoxaban granules for oral suspension 60mg reconstituted with water to provide a 6mg/mL suspension.	PK endpoints included Population PK (PopPK) model-estimated PK parameters such as apparent Systemic clearance (referred to as clearance from central compartment in the appended Pop PK Report), apparent volume of distribution (referred to as central compartment volume in the appended PopPK Report), and area under the concentration-time curve (AUC). PD endpoints included observed, change from Baseline, and percent change from Baseline prothrombin time (PT), activated partial thromboplastin time (aPTT), and anti-activated factor X (FXa).	1 day	66	Male and female pediatric patients (38 weeks gestation to <18 years of age on the day of dosing) who might have required or were currently on anticoagulant therapy.	32 Clinical sites in the United States, Canada, France, India, Italy, Jordan, Lebanon, Spain, Turkey, and the United Kingdom

DU176b-D-U312	NCT 02798471	A Phase 3, Open-Label, Randomized, Multicenter, Controlled Trial to Evaluate the Pharmacokinetics and Pharmacodynamics of Edoxaban and to Compare the Efficacy and Safety of Edoxaban with Standard-of-Care Anticoagulant Therapy in Pediatric Subjects from Birth to Less Than 18 Years of Age with Confirmed Venous Thromboembolism (VTE)	Edoxaban tablets (15- and/or 30-mg) or granules for oral suspension 60 mg (6 mg/mL). taken orally once daily 60-mg dose dispensed as two 30-mg tablets once daily taken orally 45-mg dose dispensed as one 30-mg tablet plus one 15-mg tablet 30-mg dose dispensed as one 30-mg tablet once daily taken orally	The primary efficacy endpoint was the composite endpoint of symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden (defined below) during the first 3-month period (for Cohort 5, the intended duration of treatment was 6 to 12 weeks). The secondary efficacy endpoints included: -A composite endpoint of symptomatic recurrent venous thromboembolic disease, death as a result of VTE, and no change or extension of thrombotic burden from randomization to the date of the last dose of study drug + 30 days. The individual components of the primary efficacy endpoint	The Main Treat-ment Period: time from randomization until the end of Month 3 of treat-ment. The Main Treatment Period for subjects <6 months old (Cohort 5) was the time from randomization	Edoxaban N=145 SOC N=141	Male or female pediatric subjects between birth (defined as 38 weeks gestational age) and less than 18 years of age at the time of consent. Pediatric subjects had documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 90 days.	US/Canada, Europe, Asia/Pacific, and Rest of the World (Belgium, Bulgaria, Czech Republic, Germany, Spain, France, Croatia, Hungary, Israel, Lebanon, Netherlands, Norway, Portugal, Russia, Turkey, Ukraine, Asia/Pacific, Korea, India, Malaysia, Taiwan, Thailand, Singapore, Chile, Guatemala, Brazil, Colombia, El Salvador, Panama).

				during the first 3-month period: -Symptomatic recurrent VTE -Death as a result of VTE -No change or extension of thrombotic burden. -All-cause mortality from randomization to the last dose + 30 days. -The DVT, catheter-related thrombosis, PE, and sinovenous thrombosis events within and after the first 3-month treatment period (for Cohort 5, the intended duration of treatment is 6 to 12 weeks).	until the end of anticoagulant therapy for at least 6 to 12 weeks. Subjects who completed the Main Treatment Period but did not continue into the Extension Period were followed for 30 days after the last dose of study drug. The Extension Period was discretionary for the			

					investigator and included treatment from the end of the Main Treatment Period (Month 3) up through the end of Month 12. Subjects who discontinued the treatment at any time after Month 3 had a Month 12 Discontinuation Visit performed with the subsequent 30-Day			

					Follow-Up. Subjects who completed the Extension Period treatment at Month 12 were followed for 30 days after the last dose of study drug.			

5.2. Review Strategy

The main focus of this review is to:

1. Evaluate whether Daiichi Sankyo has successfully fulfilled the PMR requirements (PMR 2852-1 and PMR 2852-2) under the Pediatric Research Equity Act (PREA) for NDA 206316.
2. Update the Pediatric Use section of labeling with a high-level summary of the trial.

For PMR 2852-1, the requirement was to conduct a single-dose study of pharmacokinetics and pharmacodynamics (PK/PD) of edoxaban in pediatric patients from birth to less than 18 years of age at risk for venous thromboembolism (VTE), requiring anticoagulation or recently completing standard of care anticoagulation.

For PMR-2852-2, the requirement was to perform, complete and submit the full study report for a phase 3 multicenter, randomized, active control study of edoxaban in pediatric patients with documented venous thromboembolism: "A Phase 3, open-label, randomized, multi-center, controlled trial to evaluate the pharmacokinetics and pharmacodynamics of edoxaban and to compare the efficacy and safety of edoxaban with standard of care anticoagulant therapy in pediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE),"

To that end, the study reports for the clinical studies DU176b-A-U157 and DU176b-D-U312 were summarized in Section 5.1 and study results in Section 6.1.2
The PMR request is included in Section 12 Postmarketing Requirements and Commitments.

Additionally, the results of the pivotal pediatric clinical trial were interrogated to attempt to identify a root cause for the failure of the trial.

This supplement provides for changes to the Savaysa USPI to reflect the findings from trial DU176B-D-U312. The primary efficacy endpoint was the composite endpoint (consisting of symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden during the Main Treatment Period. The hazard ratio (HR) for the edoxaban group versus the SOC group was 1.01 (95% CI: 0.594 to 1.719). The upper bound of the 95% CI (1.719) was above the prespecified noninferiority margin of 1.5, and the noninferiority of edoxaban versus SOC was not confirmed. Therefore, as efficacy was not established, the benefit:risk assessment is negative. The application does not contain substantial evidence of effectiveness. No indication for pediatric patients was requested and none will be granted.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Clinical Study/Trial Intended to Demonstrate Efficacy [DU176B-D-312]

6.1.1. Study DU176b-D-U312 Edoxaban Hokusai VTE PEDIATRICS Study (pivotal study)

Overview and Objectives

The purpose of this study was to evaluate the PK and pharmacodynamics (PD) of edoxaban and to compare the efficacy and safety of edoxaban after at least 5 days of heparin (LMWH or SP Xa inhibitors or unfractionated heparin (UFH); with overlapping VKAs if needed) against SOC (LMWH, VKA, or SP Xa inhibitors) in pediatric subjects with confirmed VTE.

Primary Objective:
The primary objective was to demonstrate the non-inferiority of edoxaban to standard of care (SOC; including low molecular weight heparin (LMWH), vitamin K antagonist (VKA), or synthetic pentasaccharide (SP) Xa inhibitors) in the treatment and secondary prevention of VTE in pediatric subjects with regard to the composite efficacy endpoint (i.e., symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden) during the first 3-month treatment period (for Cohort 5, the intended duration of treatment is 6-12 weeks).

Secondary Objectives:

- To compare edoxaban against SOC with regard to the combination of major and clinically relevant nonmajor (CRNM) bleedings occurring during treatment or within 3 days of completing or interrupting or stopping study treatment during the first 3-month treatment period (for Cohort 5, the intended duration of treatment is 6-12 weeks).
- To compare edoxaban against SOC with regard to a combination of major and CRNM bleedings and symptomatic recurrent VTE, and death as result of VTE which occur from first to the last dose + 30 days.
- To compare edoxaban against SOC with regard to all bleedings which occur from first to the last dose + 30 days.
- To compare edoxaban against SOC with regard to the composite efficacy endpoint as described in the primary objective from randomization to the last dose + 30 days.
- To compare edoxaban against SOC with regard to all-cause mortality from randomization to the last dose + 30 days.
- To compare edoxaban against SOC with regard to the individual components of the composite efficacy endpoints as described in the primary objective during the first 3-month treatment period (for Cohort 5, the intended duration of treatment is at least 6 to 12 weeks).
- To compare edoxaban against SOC with regard to occurrence of DVT, catheter-related

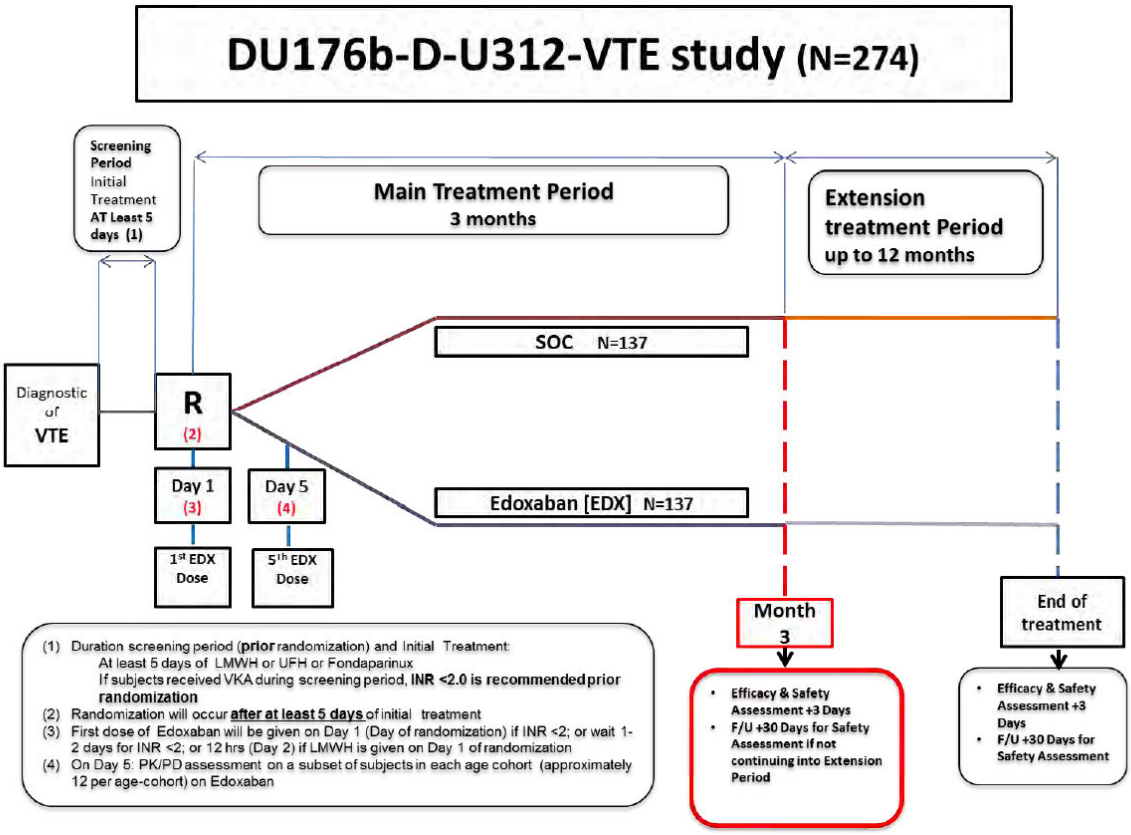
thrombosis, PE, sinovenous thrombosis within and after the first 3-month treatment period (for Cohort 5, the intended duration of treatment is at least 6-12 weeks).

- To compare edoxaban against SOC with regard to a composite combination of major and CRNM bleedings from first to the last dose + 30 days.
- To characterize the multiple dose pharmacokinetics of edoxaban in pediatric subjects at Day 5 using population pharmacokinetic (PK) analysis (apparent systemic clearance [CL/F] and apparent volume of distribution [V/F]) and to assess the effect of covariates such as age, body weight, and renal function on the PK of edoxaban.
- To evaluate the relationship between edoxaban exposure and safety (such as bleeding) and efficacy (thromboembolic events).
- To characterize the effect of edoxaban on biomarkers of coagulation (ie, prothrombin time [PT], activated partial thromboplastin time [aPTT], and activated factor X [anti-FXa]).

6.1.1.1 Study Design

Study Design: Study DU176b-D-U312 was a Phase 3, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group study in pediatric subjects (from birth to < 18 years of age3) with confirmed venous thromboembolism (VTE) conducted to satisfy the PREA PMR requirement. Efficacy was not established in this study, and noninferiority of edoxaban versus SOC was not confirmed. In trying to assess the reason for failure to show efficacy, issues of subject withdrawal, drug compliance and drug interaction were assessed to see if these issues contributed to patients not meeting the study endpoint.

Figure 1 Study Schema DU176b-D-U312-VTE Study



Source: Applicant CSR

This was an event driven Phase 3, prospective, randomized, open label, blinded endpoint evaluation (PROBE) parallel group study in subjects with confirmed VTE. This study was designed to evaluate the PK and pharmacodynamics (PD) of edoxaban and to compare the efficacy and safety of edoxaban after at least 5 days of heparin (LMWH or SP Xa inhibitors or unfractionated heparin (UFH); with overlapping VKAs if needed) against SOC (LMWH, VKA, or SP Xa inhibitors) in pediatric subjects with confirmed VTE. The adjudication of the efficacy and safety endpoints was conducted by a blinded adjudication committee.

The study included two periods:

- The Main Treatment Period is defined as the time from randomization, until the end of Month 3 of treatment. The Main Treatment Period for subjects less than 6 months (Cohort 5) old is defined as the time from randomization until the end of anticoagulant therapy for at least 6 to 12 weeks.

  - Subjects who discontinued early in the Main Treatment Period were followed monthly

according to the Schedule of Events (Table 17.1) through Month 3 visit (Visit 5) and 30 day Follow-Up Visit (Visit 9).

- Subjects who completed the Main Treatment Period but did not continue into the Extension Period were followed for 30 days after last dose of study drug (Visit 9).
- If a subject discontinued study medication before Month 2, the follow up visit was combined with the Month 3 Visit.
- The Extension Period was discretionary for the Investigator and included treatment from the end of the Main Treatment Period (Month 3, Visit 5) up through the end of Month 12 (Visit 8).
- Subjects who discontinued the treatment at any time after Month 3 had a Month 12/Discontinuation Visit (Visit 8) performed with the subsequent 30-day follow-up (Visit 9).
- Subjects who completed Extension Period treatment at Month 12 (Visit 8) were followed for 30 days after last dose of study drug (Visit 9).
- Subjects who required anticoagulant treatment after discontinuation of the study treatment at any time were transitioned to a therapy as determined by the Investigator.

The study was conducted in locations in US/Canada, Europe, Asia/Pacific, and Rest of the World (Belgium, Bulgaria, Czech Republic, Germany, Spain, France, Croatia, Hungary, Israel, Lebanon, Netherlands, Norway, Portugal, Russia, Turkey, Ukraine, Asia/Pacific, Korea, India, Malaysia, Taiwan, Thailand, Singapore, Chile, Guatemala, Brazil, Colombia, El Salvador, Panama).

Table 5 Schedule of events DU176b-D-U312-VTE Study

Study Period	Screening/ Qualification Visit	Randomization[a]	On-Treatment Study Visits							Required 30 Day Follow-up Visit[b]
			Main Treatment Period				Extension Period (Optional)			
Visit Number	1	2	2a	3	4	5	6	7	8	9
Study Day	At least Day -5 to -1 Index VTE Event Identified Pre-randomization treatment selected by PI (LMWH or SP Xa inhibitor or UFH)	Day 1 1st EDX Dose	Day 5 EDX arm Only N=53 to 60	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12/ Discontinuation Visit	
Visit Window (Days)[c]			+3	±5	±5	±5	±5	±5	±5	±5
IXRS transaction	X									
IXRS Randomization		X								
Study Informed Consent	X									
Confirm Diagnosis of Index VTE	X									
Inclusion/Exclusion Criteria	X									
Demographic Information	X									
Medical /Surgical History	X									
Physical Examination and Body Height/Weight Assessments[d]	X			X	X	X	X	X	X	
Vital Signs[e]	X			X	X	X	X	X	X	
Liver function assessment (ALT, AST, TBL, ALP)	X**			X		X		X	X	

Study Period	Screening/ Qualification Visit	Randomization[a]	On-Treatment Study Visits							Required 30 Day Follow-up Visit[b]
			Main Treatment Period				Extension Period (Optional)			
Visit Number	1	2	2a	3	4	5	6	7	8	9
Study Day	At least Day -5 to -1 Index VTE Event Identified Pre-randomization treatment selected by PI (LMWH or SP Xa inhibitor or UFH)	Day 1 1st EDX Dose	Day 5 EDX arm Only N=53 to 60	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12/ Discontinuation Visit	
Visit Window (Days)[c]			+3	±5	±5	±5	±5	±5	±5	±5
Serum Creatinine	X**		X°	X		X	X	X	X	
Serum Chemistry Panel excluding creatinine	X**		X°							
Screening only: INR Measurement on VKA and or aPTT	X									
Post-randomization: INR, Anti-FXa, aPTT, assessment on SOC[f,g]		X								

Study Period	Screening/ Qualification Visit	Randomization[a]	On-Treatment Study Visits							Required 30 Day Follow-up Visit[b]
			Main Treatment Period				Extension Period (Optional)			
Visit Number	1	2	2a	3	4	5	6	7	8	9
Study Day	At least Day -5 to -1 Index VTE Event Identified Pre-randomization treatment selected by PI (LMWH or SP Xa inhibitor or UFH)	Day 1 1st EDX Dose	Day 5 EDX arm Only N=53 to 60	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12/ Discontinuation Visit	
Visit Window (Days)[c]			+3	±5	±5	±5	±5	±5	±5	±5
Hematology	X**					X			X	
PK/PD assessment for first 12 subjects in each age cohort in EDX arm (See Protocol Section 8)			X							
VTE Radiologic Imaging[h]	X					X[n]			X	
Urinalysis	X									
Urine Pregnancy Test[i]	X	X				X			X	
AE/SAE Reporting[j]	..... X									

Study Period	Screening/ Qualification Visit	Randomization[a]	On-Treatment Study Visits							Required 30 Day Follow-up Visit[b]
			Main Treatment Period				Extension Period (Optional)			
Visit Number	1	2	2a	3	4	5	6	7	8	9
Study Day	At least Day -5 to -1 Index VTE Event Identified Pre-randomization treatment selected by PI (LMWH or SP Xa inhibitor or UFH)	Day 1 1st EDX Dose	Day 5 EDX arm Only N=53 to 60	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12/ Discontinuation Visit	
Visit Window (Days)[c]			+3	±5	±5	±5	±5	±5	±5	±5
Endpoints Reporting (VTE, Bleeding)[k]	..... X									
Prior and Concomitant Medications[l]	X	X		X	X	X	X	X	X	X
Study Drug Dispensing via IXRS will occur on a monthly basis unless locally sourced then no IXRS updates[m]		..... X								
Study Drug Compliance will occur on a monthly basis or every 3 months (in extension phase) basis from returned study drug[m]			..... X							

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; EDX = edoxaban; FXa=activated factor X; INR = International Normalized Ratio; IXRS = interactive web/ voice response system; LMWH = Low molecular weight heparin; PD = pharmacodynamics; PK = pharmacokinetics; PI Principal Investigator; SOC = standard of care; SP = Synthetic Pentasacchairde; TBL = total bilirubin level; UFH = unfractionated heparin; VKA: vitamin K antagonist; VTE = venous thromboembolism.

**Samples taken as part of routine care outside study requirements may be analyzed by local laboratories and the results used to qualify the subject provided the tests were performed for the newly diagnosed index VTE before randomization. If central laboratory is also used at the same visit with a resulting discrepancy for exclusion criteria, the local laboratory result will still be used to qualify the subject.

[a] Randomization may occur in IXRS the day prior to dosing for clinical logistics.

Source: Applicant's Clinical Study Report

Diagnostic Criteria

VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 90 days.

Study Population Inclusion and Exclusion Criteria

Subjects satisfied all of the following criteria to be included in the study:

1. Male or female pediatric subjects between birth (defined as 38 weeks gestational age) and less than 18 years of age at the time of consent.
2. Pediatric subjects with the presence of documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 90 days (list of VTE provided in Section 7.1).
3. Subjects must have received at least 5 days of heparin (LMWH or SP Xa inhibitors or UFH according to the edoxaban label for VTE treatment) therapy prior to randomization to treat the newly identified index VTE. In addition, prior to being randomized to edoxaban or SOC, subjects initially treated with VKA are recommended to have an INR< 2.0.
4. Subject and/or parent(s)/legal guardian(s) or legally acceptable representative is informed and provides signed consent for the child to participate in the study with edoxaban treatment. Pediatric subjects with appropriate intellectual maturity will be required to sign an assent form in addition to the signed informed consent from the parent(s)/legal guardian(s) or any legally acceptable representative.
5. Female subjects who have menarche must test negative for pregnancy at Screening and must consent to avoid becoming pregnant by using an approved contraception method throughout the study.

Exclusion Criteria:

Subjects who meet any of the following criteria will be disqualified from entering the study:
1. Subjects with active bleeding or high risk of bleeding contraindicating treatment with LMWH, SP Xa inhibitors, VKAs, or direct oral anticoagulants (DOACs; identified high risk of bleeding during prior experimental administration of DOACs).
2. Subjects who have been or are being treated with thrombolytic agents, thrombectomy or insertion of a caval filter for the newly identified index VTE.
3. Administration of antiplatelet therapy is contraindicated in both arms except for low dose aspirin defined as 1-5 mg/Kg/day with maximum of 100 mg/day (see Appendix 17.3.1).
4. Subjects with hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk (aPTT > 50 seconds or international normalized ratio [INR] > 2.0 not related to anticoagulation therapy) or ALT > 5 × the upper limit of normal (ULN) or total bilirubin > 2 × ULN with direct bilirubin > 20% of the total at Screening Visit.
5. Subjects with glomerular filtration rate (GFR) < 30% of normal for age and size (see Appendix 17.6) as determined by the Schwartz formula.

6. Subjects with stage 2 hypertension defined as blood pressure (BP) systolic and/or diastolic confirmed > 99th percentile + 5 mmHg (see Appendix 17.7).
7. Subject with thrombocytopenia < 50 × 10^{9}/L at Screening Visit. Subjects with a history of heparin- induced thrombocytopenia may be enrolled in the study at the Investigator's discretion.
8. Life expectancy less than the expected study treatment duration (3 months).
9. Subjects who are known to be pregnant or breastfeeding.
10. Subjects with any condition that, as judged by the Investigator, would place the subject at increased risk of harm if he/she participated in the study.

Randomization:
Subjects randomized to SOC treatment arm will receive SOC anticoagulant according to the study site's SOC treatment as follows (alone or combination):
- LMWH (alone or followed with VKA)
- SP Xa inhibitors (alone or followed with VKA)
- Vitamin K antagonist (VKA)

If Investigators choose to use centrally sourced SOC treatment from Sponsor, the subject will be treated as follows:
- For subjects randomized to enoxaparin: for neonates or children receiving either once- or twice-daily therapeutic enoxaparin the drug should be monitored to a target anti-FXa level of 0.5 to 1.0 units/mL in a sample taken at 4 hours post-dose for therapeutic levels. Monthly monitoring of anti-FXa levels is recommended. More frequent anti-FXa levels can be recommended as per Investigator's decision.

Conditions for dose reduction and stopping rules were thoroughly described and are acceptable.

The edoxaban starting dose for each cohort was selected on the basis of edoxaban exposure for age matched subjects and safety data from the single-dose PK/PD study (DU176b-U157) and on population-based PK data. The dose was selected as an age/weight/renal function-appropriate dose for the treatment period.

Edoxaban was given as a tablet or granule formulation depending on the age cohort. For age cohorts <12 years, edoxaban was provided in granule form and the dose was calculated on the basis of body weight. If appropriate, subjects <12 years old were provided with tablets. Subjects were instructed to take edoxaban (orally) once a day at the same time every day with or without food. Tablets were to be swallowed with a glass of water. However, if a subject in the 12- to <18-year old group did not have the capacity to swallow tablets, the tablets were allowed to be crushed and served with applesauce or mixed with 2 to 3 ounces of water and immediately administered by mouth or through a gastric tube

The SOC anticoagulants (LMWH, SP Xa inhibitor, or VKA) were provided either as central or local source and dosage calculations were provided as per standard clinical practice or based on INR maintenance in the therapeutic range.

Assignment to Treatment:
Method of Assigning Subjects to Treatment Groups
All subjects were assessed for eligibility in the study in accordance with the inclusion/exclusion criteria after VTE diagnosis. Eligible subjects were stratified by age and region (ie, US/Canada, Europe, Asia/Pacific, and Rest of the World), and then randomized in a 1:1 ratio to the edoxaban treatment arm or the SOC treatment arm, respectively.

An independent biostatistician generated the randomization schedule in accordance with the operating procedure for allocating study drug. At randomization, the investigator provided the IXRS with the study center number and the subject's presenting diagnosis (symptomatic VTE) and date of birth. Dose reduction stratification was taken into account for:

- eGFR (30%-50% of normal for age)
- concomitant treatment with P-glycoprotein (P-gp) inhibitors
- body weight <fifth percentile of subject's age.

Blinding: Open-label trial

Dose modification:
Conditions for dose reduction:
If a subject required concomitant administration of P-gp inhibitor, edoxaban dose was reduced during P-gp administration and reestablished to the original dose once P-gp inhibitor administration had concluded.

Edoxaban dosage regimen was reduced permanently for subjects with moderate renal impairment for the subject's age and size at randomization as determined by the age-appropriate formula.

If a subject experienced a change in renal function from normal to eGFR ≥30% to ≤50% after randomization, the measurement will be repeated within 1 week to 10 days after correction of the underlying factors causing pre-azotemia. If the repeat measurement confirmed the reduced eGFR, the edoxaban dose reduction would have been permanent even if the subject experienced an improvement in the eGFR during the course of the study.

Dose reduction due to body weight applied only for fixed doses in subjects 12 to <18 years of age:

If body weight increased or decreased from the categories of weight defined at consent, the subject was dose adjusted. Subjects who were ≥60 kg of body weight at consent and dropped below that body weight received a 45-mg dose at any subsequent visit. Subjects who were ≥30 and <60 kg at consent and increased their weight to ≥60 kg increased their dose to 60 mg.

Edoxaban dosage regimen was reduced permanently for subject with body weight <fifth percentile for age.

If body weight increased or decreased from the categories of weight defined at consent, the subject was dose adjusted. Subjects who were ≥60 kg of body weight at consent and dropped below that body weight received a 45-mg dose at any subsequent visit. Subjects ≥30 and <60 kg at consent increasing their weight to ≥60 kg increased their dose to 60 mg.

Clinical Reviewer comment: The pre-specified dose modifications seem reasonable and are acceptable.

Administrative Structure:

- Daiichi Sankyo, Inc., was the Sponsor for this study. The study was conducted by IQVIA™, a contract research organization (CRO).
- An independent DMC was created to further protect the rights, safety, and well-being of subjects who were participating in this study by monitoring the study's progress and ongoing review of the safety, laboratory, and adjudication data unblinded to the study treatment. The independent DMC comprised qualified scientists who were not investigators in the study and not otherwise directly associated with the Sponsor.
- An independent CEC was created to evaluate all investigator-reported endpoints. The CEC was blinded to the study treatments received by individual subjects. The CEC adjudicated all investigator -reported bleeding events, hepatic events or hepatic laboratory abnormalities leading to study drug discontinuation in the absence of alternative etiology, all stroke/transient ischemic attack, suspected venous thromboembolism (VTE), all systemic embolic events, myocardial infarction and all deaths, regardless of etiology. The independent CEC comprised qualified scientists who were not investigators in the study and not otherwise directly associated with the Sponsor.
- A Study Steering Committee was created to provide clinical guidance on study implementation and conduct of the study and interpretation of results as specified in the Committee Charter. It consisted of principal investigator(s) (PI) and key opinion leaders who participated in the study (as requested), as well as the designated Sponsor and CRO members.

Prior and Concomitant Therapy

- Medications taken within 30 days prior to randomization were to be recorded.
- There were no concomitant medications required as part of the study design. The following drugs and devices were not to be used during the entire study treatment period and their unavoidable use required study drug therapy interruption unless specifically indicated for study drug discontinuation:
- Anticoagulants, other than the assigned study drugs, by any route require study drug discontinuation.
- Fibrinolytic agents, if required to treat thromboembolism (TE) events, require study drug discontinuation and consideration of a transfusion of fresh frozen plasma
- Single or dual antiplatelet therapy with any antiplatelet agent was prohibited except for low--dose aspirin defined as 1 to 5 mg/kg/day with maximum of 100 mg/day. If a clinical indication for antiplatelet therapy (other than low-dose aspirin) arose after randomization, study drug was discontinued.
- Chronic use of oral or parenteral nonsteroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 and cyclooxygenase-2 inhibitors other than aspirin for ≥4 days/week. Use of NSAIDs via other routes (eg, topical, inhaled, intranasal, intraocular, etc.) was not restricted.
- All P-gp inhibitors (Protocol Appendix 17.4.6 [Appendix 16.1.1]) excluding amiodarone required dose reduction of edoxaban.
- Information regarding concomitant medications was collected with start date, stop date, drug name, dose, and dosing regimen for population PK analyses.

Treatment Compliance:

Dosing compliance for subjects in the edoxaban treatment arm was assessed by means of tablet/bottle counts remaining or bottles returned. All drug packaging was to be returned at each subject visit including bottles with dilutions made for dosing. Administration of the IMP was recorded in the CRF/eCRF/Drug Accountability Record. The method of compliance calculation based on the returned number of tablets/bottles was recorded. If zero tablets/bottles were returned, subjects were asked whether any were disposed/thrown away, rather than taken orally.

Subjects in the SOC (VKA) treatment arm were monitored for compliance by measuring INR levels. Subjects in the SOC (enoxaparin) treatment arm were monitored for compliance by measuring anti-FXa levels. Subjects in the SOC (fondaparinux) treatment arm were monitored for compliance by measuring fondaparinux levels. These results were entered into the EDC system.

Dietary restrictions: None specified

Study Endpoints

- Efficacy:

Primary Endpoint: A composite endpoint consisting of incidence of symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden (defined below) during the first 3-month period (for Cohort 5, the intended duration of treatment is 6 to 12 weeks) for the modified intent to treat (mITT) Analysis Set.

Efficacy endpoints (adjudicated in a blinded manner by the clinical events committee).
Radiologic examination

- Utilizing the same diagnostic technique at baseline and follow-up to determine the thrombotic burden.

Diagnosis of new/recurrent PE requires meeting 1 or more of the following criteria:

- A (new) intraluminal filling defect in segmental or more proximal branches of the pulmonary artery on spiral CT scan
- A mismatched defect on a nuclear ventilation/perfusion (V/Q) scan compared to the prior imaging
- A non-diagnostic lung scan accompanied by documentation of new deep vein thrombosis by (Doppler) ultrasonography or venography.

Diagnosis of symptomatic recurrent VTE requires the confirmation by appropriate diagnostic imaging using imaging criteria of recurrent VTE and at least one of the symptoms of VTE in the table Symptoms of VTE.

Secondary Efficacy Endpoints

- A composite endpoint consisting of the incidence of symptomatic recurrent venous thromboembolic disease, death as a result of VTE, and no change or extension of thrombotic burden from randomization to the date of the last dose of study drug + 30 days.
- The individual components of the primary efficacy endpoint during the first 3-month period:
  o Symptomatic recurrent VTE
  o Death as a result of VTE
  o No change or extension of thrombotic burden during the first 3-month period
- All-cause mortality from randomization to the last dose + 30 days.
- The DVT, catheter-related thrombosis, PE, and sinovenous thrombosis events within and after the first 3-month treatment period (for Cohort 5, the intended duration of treatment is 6 to 12 weeks).

Clinical Outcome Endpoint

- A composite combination of major and CRNM bleedings, symptomatic recurrent VTE, and death as result of VTE that occurred from the first to the last dose + 30 days

6.1.1.2 Statistical Analysis Plan

Sample Size Determination

This was an event driven trial and the total number of subjects randomized to treatment was to be adjusted to ensure accumulation of 68 events in the modified intent-to-treat (mITT) Analysis Set during the Main Treatment Period.

The sample size calculation was based on statistical approach and results of Hokusai-VTE study (DU176b-D-U305), a study of LMWH/edoxaban versus (vs.) LMWH/warfarin in the treatment of acute VTE in adults. A non-inferiority margin of 1.5 (in hazard ratio) was used in the Hokusai-VTE study and was aimed at preserving 70% of warfarin effect in the adult population. A hazard ratio of 0.76 of recurrent VTE between edoxaban and warfarin for the first 3 months was also observed in Hokusai-VTE study.

This pediatric study was designed to accumulate, approximately 68 overall primary efficacy events in the mITT Analysis Set during the main treatment period. Assuming that the edoxaban group will observe a 24% relative reduction to SOC arm, a total of 68 events will give approximately 80% power to demonstrate that LMWH/edoxaban is non-inferior to the comparator, considering a relative non-inferiority margin for the hazard ratio of 1.5 (two-sided α=0.05).

Based on the completed clinical trials and literature review, we expect an incidence of composite primary efficacy endpoint of 28% in the control arm during the main study period. Based on these estimates, 274 subjects (137 each arm) were expected to be randomized to study drug in order to accrue 68 primary efficacy events in the mITT Analysis Set during the Main Treatment Period.

Statistical Reviewer Comment: On August 22, 2014, the Applicant submitted a Type C meeting request to discuss the study design for pediatric study DU176b-D-U312. In the study design, the Applicant proposed sample size was "Assuming a 28% event rate in the SOC-treatment group, a total of 500 subjects, approximately 250 subjects per treatment group, will be the randomization target for the study. Approximately 130 primary efficacy events are expected to be accumulated."

On August 26, 2016, the Applicant submitted an updated protocol where they proposed to change the sample size to the following:
"Assuming that the edoxaban group will observe a 24% reduction of the event rate relative to standard of care and a non-inferiority margin of 1.5, then the study with 68 total primary endpoint events will have approximately 80% of power to demonstrate non-inferiority with alpha=0.05 (two sided). Assuming that 28% of event rate in the SOC treatment group, 274 subjects, 137 subjects per treatment group, will be the randomization target for the study."

In response to the above change in the sample size, the Agency stated the following:
"As we communicated to you before, we have the concern for your proposal of decreasing the study sample size to 274 patients. The reduction in sample size will decrease the robustness of the study for evaluation of efficacy."

The Applicant did not follow Agency's recommendation and decided to continue this study with sample size of 274.

Analysis Population:

All Enrolled Subjects: All Enrolled Subject who signed the ICF (Informed Consent Form).

Randomized Analysis Set: The Randomized Analysis Set included all enrolled subjects who were randomized.

Safety Analysis Set: The Safety Analysis Set included all subjects in the Randomized Analysis Set who received at least one dose of study drug actually taken.

Modified Intent-to-Treat (mITT) Analysis Set: The mITT Analysis Set included all subjects in the Randomized Analysis Set who received at least one dose of randomized study drug. This set was used for the primary efficacy analysis.

Per-Protocol (PP) Analysis Set: The Per-protocol (PP) Analysis Set included all subjects in the mITT Analysis Set who were sufficiently comply with the protocol.

Statistical Reviewer Comment: Regarding including mITT population for the primary efficacy and secondary efficacy analysis, the Applicant on August 22, 2014, under IND63266 asked the following question to the Agency:
"DS previously received FDA comments on December 5, 2012 recommending the use of the Intent-to-Treat (ITT) population for the primary analysis in the Phase 3 VTE study (U312); however the sponsor believes that the modified Intent-to-Treat (mITT) population would be the most appropriate analysis set to use for this NI study. Does the Agency agree with using the mITT population for the primary efficacy analysis?"

In response, the Agency stated the following:
"Yes, for non-inferiority study, it is acceptable to use mITT population, which includes all randomized subjects who receive at least one dose of study treatment, for the primary efficacy analysis. However, you should perform supporting analyses on ITT and PP population. Also, sensitivity analyses will need to be conducted to evaluate impact of missing data."

Interim Analysis

An interim assessment of incidence rate of the composite efficacy endpoint in both treatment arms of the study took place after first 140 subjects (about 50% of subjects) complete the first 3 months treatment. This would allow for adjustment of number of subjects in the study if necessary. Because the sample size re-estimation was based on overall event rate across two treatment arms, no type I error adjustment was needed for this interim analysis.
In addition, a DMC was considered to monitor the safety data throughout the study and inform the Study Steering Committee on fixed intervals.

Censoring for Efficacy Endpoint

Subjects who did not have a primary efficacy outcome during the 3 months + 3 days period were censored at 3 months + 3 days or the last day the subject had a complete assessment for study outcomes, whichever came first. Subjects who did not have a primary efficacy outcome during the First 3-Month Period and did not have image taken in the First 3-Month Period was censored at the date of randomization. The incidence of the primary composite endpoint was summarized by treatment group for the First 3-Month Period.

Analysis for Primary Efficacy Endpoint

The primary efficacy analysis was based on the mITT Analysis Set using the randomized treatment group even if a subject inadvertently receives the incorrect study drug. The primary efficacy endpoint was the composite endpoint including symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden for the First 3-Month Period. In this analysis, the time to the first event of the composite primary efficacy outcome was analyzed using a Cox proportional hazard regression model.

The edoxaban-to-comparator hazard ratio was computed with 1-sided p-values for noninferiority and 95% confidence interval (CI) (2-sided) based on this model. Edoxaban was considered non-inferior to comparator if the upper limit of the 95% CI is < 1.5.
If non-inferiority of edoxaban is established, edoxaban was to be tested for superiority to comparator. Edoxaban was considered superior to comparator if the upper limit of the 95% CI from above analysis is < 1.0. Two-sided p-values for superiority was also to be reported from the same model.

Statistical Reviewer Comment: To provide justification for the NI margin of 1.5, on August 22, 2014, under the IND63266, the Applicant asked the Agency the following question:

"Due to the lack of historical placebo-controlled data in pediatric VTE patients to establish a formal non-inferiority (NI) analysis, the Applicant proposes to set the NI margin in the Phase 3 pediatric study (U312) based on the edoxaban Phase 3 VTE study in adults (Hokusai-VTE). Does the Agency agree with the justification provided to support the proposed NI analysis of the composite primary endpoint with an NI margin 1.5 in hazard ratio and a 2-sided significance of 0.05?"

In response, the Agency agreed with the proposed NI margin.

Analysis for Secondary Efficacy Endpoints

For the secondary composite endpoint, including symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden for the Overall Treatment Period, the same proportional hazard model that was used for the primary efficacy analysis will be used.

The time to first event is defined as the time (days) from the date of randomization to the date of first event experienced by a subject during the Overall Treatment Period. Subjects who did not have this outcome during the Overall Treatment Period will be censored at the last day the subject had a complete assessment for study outcomes or the date of last study drug + 30 days, whichever came first. Subjects who did not have this outcome during the Overall Treatment Period and do not have image taken in the Overall Treatment Period will be censored at the date of Randomization.

For the secondary endpoints of all-cause mortality and each single component as per CEC definition of death (VTE related death, cardiovascular death, and other known causes death) for the Overall Treatment Period, incidences were provided by treatment group for the mITT Analysis Set.

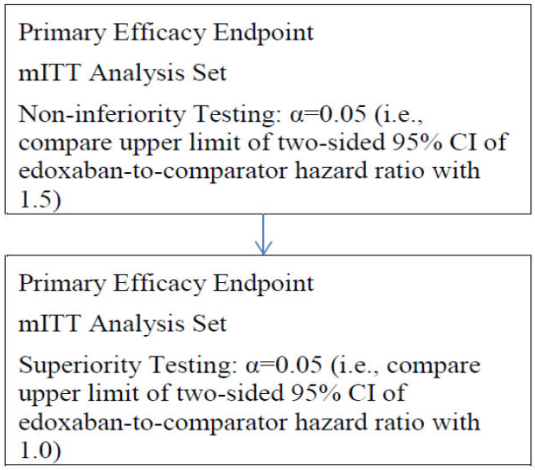
For the secondary endpoint of each component of the composite primary endpoint (symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden) during the First 3-Month Period, the incidences were provided by treatment group for the mITT Analysis Set and PP Analysis Set.

For the secondary endpoints of DVT, catheter-related thrombosis, sino-venous thrombosis, and PE during the First 3-Month Period, after 3-month treatment period (Extension Treatment Period), as well as for the Overall Treatment period, the incidences were provided by treatment group for the mITT Analysis Set.

Multiple Comparison

To control the family-wise type I error rate (FWER), fixed sequence testing procedure was used for testing non-inferiority and superiority for the primary efficacy analysis (see Figure 2).

Figure 2 Fixed testing procedure for study DU176B-D-U312



Source: Applicant CSR

Subgroup Analysis

The incidence of the primary efficacy endpoint was summarized by treatment groups using mITT Analysis Set and PP Analysis Set for the subgroups defined on the basis of the following categorized variables:

- Age cohort,
- Region,
- Sex,
- Race,
- Index VTE type (PE vs. DVT),
- Index DVT characteristic (catheter vs. not),
- Recurrent VTE supported by a new identified thrombus by imaging (yes vs. no).

6.1.1.3 Results and Analysis

Patient Disposition

Of the 286 subjects in the mITT Analysis Set, a total of 141 (49.3%) subjects completed the 3-month Main Study Period, 30-day Follow-Up, and the Extension Period: 77/145 (53.1%) subjects

in the edoxaban group and 64/141 (45.4%) subjects in the SOC group. A total of 107 (37.4%) subjects completed the 3-month Main Study Period and 30-day Follow-Up but did not participate in the Extension Period: 53 (36.6%) subjects in the edoxaban group and 54 (38.3%) subjects in the SOC group (see Table 6).

A total of 16 subjects prematurely discontinued the study prior to Month 3, and 23 subjects discontinued prematurely prior during the Extension Period due to withdrawal of consent, AEs, death, physician decision or "other" reasons. The most frequent reason for discontinuing from the study prior to Month 3 was "withdrawal by subject" (1.4%). Three (1%) subjects discontinued prior to Month 3 due to death (1 in the edoxaban group and 2 in the SOC group) and 2 subjects discontinued during the Extension Period due to death (see Table 6).

Table 6 Subject Disposition (mITT Analysis Set)

	Edoxaban (N = 145) n (%)	**SOC (N = 141) n (%)**	**Total (N = 286) n (%)**
Completed study[a]	131 (90.3)	119 (84.4)	250 (87.4)
Completed 3-month Main Study Period and 30-day Follow-up and did not participate in the Extension Period[b]	53 (36.6)	54 (38.3)	107 (37.4)
Completed 3-month Main Study Period, 30-day Follow-up, and the Extension Period[b]	77 (53.1)	64 (45.4)	141 (49.3)
Prematurely discontinued from the study prior to Month 3	6 (4.1)	10 (7.1)	16 (5.6)
Withdrawal by subject	0	4 (2.8)	4 (1.4)
Physician decision	2 (1.4)	1 (0.7)	3 (1.0)
Death	1 (0.7)	2 (1.4)	3 (1.0)
Other	2 (1.4)	1 (0.7)	3 (1.0)
Adverse event	1 (0.7)	1 (0.7)	2 (0.7)
Lost to follow-up	0	1 (0.7)	1 (0.3)
Prematurely discontinued from the study in Extension Period	11 (7.6)	12 (8.5)	23 (8.0)
Adverse event	6 (4.1)	1 (0.7)	7 (2.4)
Withdrawal by subject	0	2 (1.4)	2 (0.7)
Physician decision	1 (0.7)	6 (4.3)	7 (2.4)

Death	1 (0.7)	1 (0.7)	2 (0.7)
Other	3 (2.1)	2 (1.4)	5 (1.7)

CRF = case report form; ICF = informed consent form; mITT = Modified Intent-to-Treat; SOC = standard of care
[a] Defined as collected in the CRF page "Subjects Status – Study Completion/Study Discontinuation." 30-day Follow-up is part of the completion of study.
[b] Participation in the Extension Period is defined as per CRF page "Subject Status – Continuation." For subjects who did not participate in the Extension Period, completion is defined as having Month 3 Visit with 30-day Follow-up. For subjects who participated in the Extension Period, having post-Month 3 Visit is considered as completion.
Note: Percentages are based on the number of subjects in the mITT Analysis Set.
Note: Enrolled is defined as signed ICF.
Note: Subjects enrolled but not randomized are not counted in the Total header.

Source: Applicant CSR

Demographic Characteristics and Baseline Characteristics

Demographics and baseline characteristics were generally similar between the 2 groups in the mITT Analysis Set. Approximately half of the overall subjects were male (52.4%), and the majority were White (61.9%). The mean weight was 45.4 kg (range: 2.6 to 183.0 kg), and the mean body mass index was 20.4 (range: 11 to 56). The majority of subjects (58.4%) were in the 12 to <18-year-old age cohort (see Table 7).

The most common type of index event among all subjects was DVT (86.0%), and it was confirmed in 71.0% of subjects (see Table 7).

Table 7 Demographic and Baseline Characteristics (mITT Analysis Set)

	Edoxaban (N = 145)	**SOC (N = 141)**	**Total (N = 286)**
Age (years)			
Mean (± SD)	10.935 (± 5.9701)	11.072 (± 6.0752)	11.002 (± 6.0119)
Median	12.850	13.490	13.240
Minimum, maximum	0.07, 17.93	0.05, 17.95	0.05, 17.95
Age cohort (n, %)			
12 to <18 years	85 (58.6)	82 (58.2)	167 (58.4)
6 to <12 years	23 (15.9)	21 (14.9)	44 (15.4)
2 to <6 years	15 (10.3)	16 (11.3)	31 (10.8)
6 months to <2 years	13 (9.0)	15 (10.6)	28 (9.8)
0 to <6 months	9 (6.2)	7 (5.0)	16 (5.6)
Sex (n, %)			
Male	77 (53.1)	73 (51.8)	150 (52.4)

12 to <18 years	41 (28.3)	32 (22.7)	73 (25.5)
6 to <12 years	16 (11.0)	16 (11.3)	32 (11.2)
2 to <6 years	9 (6.2)	10 (7.1)	19 (6.6)
6 months to <2 years	5 (3.4)	10 (7.1)	15 (5.2)
0 to <6 months	6 (4.1)	5 (3.5)	11 (3.8)
Female	68 (46.9)	68 (48.2)	136 (47.6)
12 to <18 years	44 (30.3)	50 (35.5)	94 (32.9)
6 to <12 years	7 (4.8)	5 (3.5)	12 (4.2)
2 to <6 years	6 (4.1)	6 (4.3)	12 (4.2)
6 months to <2 years	8 (5.5)	5 (3.5)	13 (4.5)
0 to <6 months	3 (2.1)	2 (1.4)	5 (1.7)
Race (n, %)			
Asian	24 (16.6)	26 (18.4)	50 (17.5)
Black or African American	8 (5.5)	10 (7.1)	18 (6.3)
American Indian or Alaska Native	1 (0.7)	0	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.7)	1 (0.3)
White	92 (63.4)	85 (60.3)	177 (61.9)
Other	15 (10.3)	8 (5.7)	23 (8.0)
Not applicable	1 (0.7)	1 (0.7)	2 (0.7)
Baseline weight (kg)			
Mean (± SD)	44.99 (± 28.099)	45.72 (± 31.369)	45.35 (± 29.688)
Median	45.90	48.50	47.00
Minimum, maximum	2.6, 138.0	2.6, 183.0	2.6, 183.0
Baseline BMI (kg/m^2)			
Mean (± SD)	20.3 (± 6.04)	20.6 (± 7.31)	20.4 (± 6.68)
Median	19.0	19.0	19.0
Minimum, maximum	11, 44	11, 56	11, 56
Type of index event (n, %)			
Index DVT	125 (86.2)	121 (85.8)	246 (86.0)
Index PE	26 (17.9)	25 (17.7)	51 (17.8)

PE only	20 (13.8)	20 (14.2)	40 (14.0)
PE with DVT	6 (4.1)	5 (3.5)	11 (3.8)
Classification of index VTE (n, %)			
Confirmed	129 (89.0)	111 (78.7)	240 (83.9)
PE with DVT	4 (2.8)	4 (2.8)	8 (2.8)
PE without DVT	13 (9.0)	16 (11.3)	29 (10.1)
DVT	112 (77.2)	91 (64.5)	203 (71.0)
Not confirmed	16 (11.0)	30 (21.3)	46 (16.1)
Dose reduction status at randomization			
No	145 (100)	141 (100)	286 (100)

BMI = body mass index; DVT = deep vein thrombosis; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SD = standard deviation; SOC = standard of care; VTE = venous thromboembolism

Source: Applicant CSR

Efficacy Results

Primary Efficacy Endpoint:

The primary efficacy analysis of the composite endpoint (consisting of symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden during the Main Treatment Period is presented in Table 8 for the mITT Analysis Set.

A total of 26 (17.9%) subjects in the edoxaban group and 31 (22.0%) subjects in the SOC group had primary efficacy events during the Main Treatment Period. Symptomatic recurrent VTE occurred in a total of 5 (3.4%) subjects in the edoxaban group compared to 2 (1.4%) subjects in the SOC group (see Table 8).

The HR for the edoxaban group versus the SOC group was 1.01 (95% CI: 0.594 to 1.719). The upper bound of the 95% CI (1.719) was above the prespecified noninferiority margin of 1.5, and the noninferiority of edoxaban versus SOC was not confirmed (see Table 8).

Table 8 Adjudicated Composite Primary Efficacy Endpoint – Main Treatment Period (mITT Analysis Set)

	Edoxaban (N = 145)	**SOC (N = 141)**
Subjects with events (n, %)	26 (17.9)	31 (22.0)
Symptomatic recurrent VTE (n, %)	5 (3.4)	2 (1.4)
PE with or without DVT (n, %)	0	1 (0.7)
Fatal PE (n, %)	0	0
Nonfatal PE (n, %)	0	1 (0.7)
DVT only (n, %)	5 (3.4)	1 (0.7)
Fatal DVT (n, %)	0	0
Nonfatal DVT (n, %)	4 (2.8)	0
Unexplained death which VTE cannot be ruled out (n, %)	1 (0.7)	1 (0.7)
No change or extension of thrombotic burden based on imaging (n, %)	21 (14.5)	29 (20.6)
Time to first event (days)	26 (17.9)	31 (22.0)
Hazard ratio[a]	1.01	-
2-sided 95% CI for hazard ratio	(0.594, 1.719)	-
2-sided p-value	0.9694	-

CI = confidence interval; DVT = deep vein thrombosis; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

[a] Edoxaban-to-SOC hazard ratio

Note: Adjudicated composite primary efficacy endpoint includes symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden based on imaging.

Note: Main Treatment Period is defined as from randomization to Month 3 Visit + 3 days.

Source: Applicant CSR

Statistical Reviewer Comment: Although region was a stratification factor, it was not included in the model as a covariate. According to the Applicant, this is because some of the age by region subgroups may be very small due to the small sample size.

Statistical Reviewer Comment: This pediatric study aimed to observe a total of 68 events, with an expected event rate of 24%, and it initially had a sample size of 274. However, during the interim analysis, the Applicant observed 23 events among the 138 enrolled patients, resulting in

an event rate of 16.7%. Based on this analysis, the sample size was recalculated to be 422, which would have led to approximately 68 events by the end of the study, assuming the observed event rate remained constant.

Despite the recommendation from the interim analysis, the Applicant chose to disregard it and terminated the study at a sample size of 286. At that point, they had observed 57 events, with an event rate of 20%. Consequently, the resulting analysis yielded a wide 95% confidence interval of 1.01 (0.59, 1.72), with the upper bound exceeding the non-inferiority margin of 1.5.

Based on these findings, the study seemed to be underpowered, meaning it did not have a sufficient sample size to assess the non-inferiority of edoxaban to SOC arm. This is in contrast to the adult study (DU176b-D-U305 (Hokusai VTE)), which was confirmed based on a hazard ratio of .89 (95% CI 0.70, 1.13), where the upper bound of the 95% confidence interval was below the threshold of 1.5.

We submitted the following information request to the Applicant on 02/14/23:

- *We are interested in exploring whether the non-inferiority margin of 1.5, which aims to preserve 70% of warfarin effect in adult population, can be too small. To do this, we recommend you calculate the non-inferiority margin using different levels of preservation (e.g., 60%, 50%, 40%, 30% etc.).*
- *We recommend conducting Bayesian analysis with dynamic borrowing (Bayesian mixture prior) in this study, using efficacy data from pediatric and adult studies. If this type of analysis is not feasible, indicate the reasons why.*
- *Provide your conclusion from your NI margin exploration and potential Bayesian analysis.*

In reply, the Applicant responded:

- *Based on the adult information from study DU176b-D-U305 (Hokusai VTE) to keep 60% of warfarin effect a non-inferiority margin of HR is 1.74 and a margin of HR of 2 should keep 50% of warfarin effect. The upper bound of the 95% CI (1.719) is below both 1.74 and 2.0.*

- *Regarding the Bayesian analyses, the Applicant indicated that they are not able to perform this Bayesian analysis as they do not have the relevant pediatric data from other studies and the endpoints in the adult study (Hokusai VTE) are different.*

It appears that the Applicant had a different understanding about the FDA's request on conducting Bayesian analysis, so the Agency sent the follow-up IR on April 25, 2023.

Follow-up IR:

"Please perform the Bayesian analyses the Agency recommended in the previous information request on February 14 of 2023. According to your response that we received on March 24 of 2023, there appears some misunderstanding. Our request is for a Bayesian dynamic borrowing (Bayesian mixture prior) analysis using efficacy data associated with the primary endpoint (i.e., time to the first occurrence of recurrent VTE or VTE-related death during the 12-month study period) from pediatric (DU176B-D-U312) and adult (DU176b-D-U305) studies. Your response of not being able to conduct the Bayesian analysis because you do not have the relevant pediatric data from other studies and the endpoints in the adult study (Hokusai VTE) are different do not seem reasonable. Please refer to the following paper: Travis J, Rothmann M, Thomson A. Perspectives on informative Bayesian methods in pediatrics. J Biopharm Stat. 2023 Jan 29:1-14. doi: 10.1080/10543406.2023.2170405. Epub ahead of print. PMID: 36710384 for more details."

In response to the follow-up IR, the Applicant submitted results from their Bayesian Borrowing analysis on May 24, 2023. In the results, the Applicant did not provide any information regarding the informative and non-informative priors used for the analysis and therefore the Agency could not replicate the analysis.

The above recommended analyses, including Bayesian analyses, were mainly to further understand why the trial failed. No conclusion can be made.

Sensitivity Analysis of Primary Efficacy Endpoint (Per-Protocol Analysis Set)

A summary of the composite primary efficacy endpoints during the Main Treatment Period in the PP Analysis Set is presented in Table 10.

In the PP Analysis Set, a total of 5 (3.9%) subjects in the edoxaban group and 2 (1.8%) subjects in the SOC group had a recurrent VTE during the Main Treatment Period. The HR for noninferiority was 0.94 (95% CI: 0.50 to 1.80). The results were similar to mITT population.

Table 9 Adjudicated Composite Primary Efficacy Endpoint – Main Treatment Period (Per-protocol Analysis Set)

	Edoxaban (N = 129)	**SOC (N = 110)**
Subjects with events (n, %)	19 (14.7)	19 (17.3)
Symptomatic recurrent VTE (n, %)	5 (3.9)	2 (1.8)
PE with or without DVT (n, %)	0	1 (0.9)
Fatal PE (n, %)	0	0
Nonfatal PE (n, %)	0	1 (0.9)

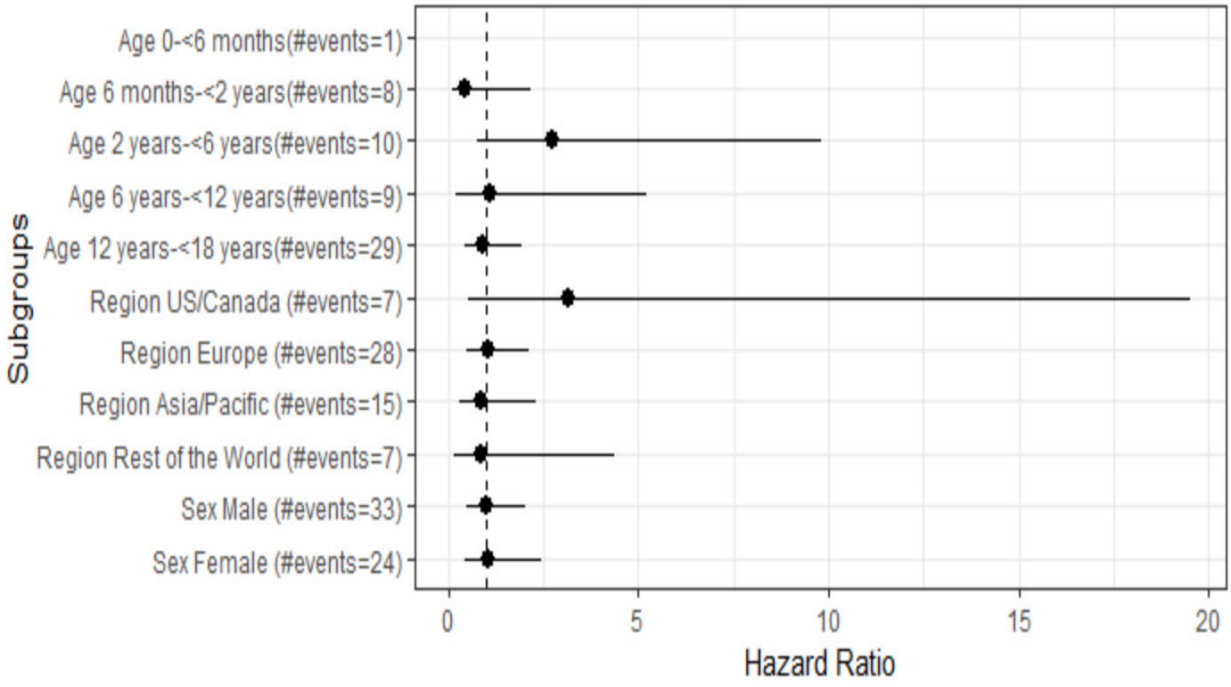
DVT only (n, %)	5 (3.9)	1 (0.9)
Fatal DVT (n, %)	0	0
Nonfatal DVT (n, %)	4 (3.1)	0
Unexplained death which VTE cannot be ruled out (n, %)	1 (0.8)	1 (0.9)
No change or extension of thrombotic burden (n, %)	14 (10.9)	17 (15.5)
Time to first event (days)		
Hazard ratio[a,b]	0.94	
2-sided 95% CI for hazard ratio[b]	(0.50, 1.80)	

Source: Applicant CSR

Subgroup Analysis of Primary Efficacy Endpoint

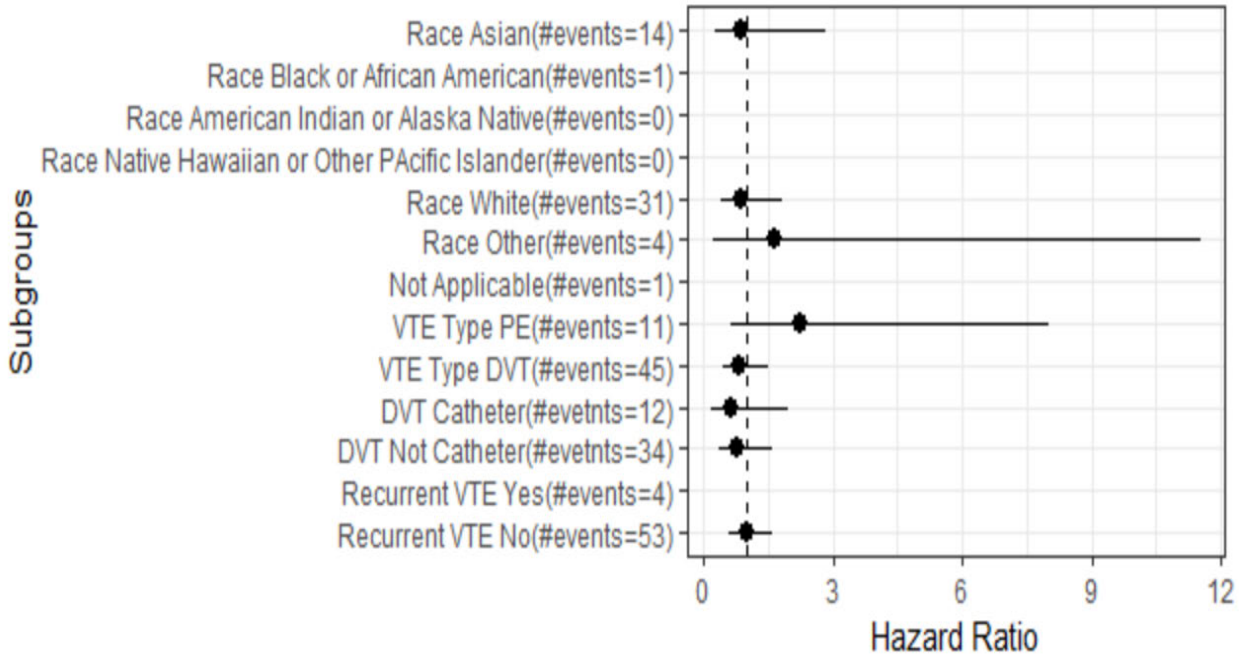
Subgroup analyses of the incidence of the primary efficacy are presented in Figures 3 and 4. Due to the exploratory nature of the analyses and the small number of subjects in these subgroups, it is not adequate to draw any statistical conclusions. The results should be interpreted as descriptive and with caution.

Figure 3: Subgroup Analysis Results by (Age, Region, and Sex) of Primary Efficacy Endpoint (mITT Analysis Set)



Source: FDA Statistical Reviewer Analysis

Figure 4 Subgroup Analysis Results (Race, VTE, DTE, and recurrent VTE) of Primary Efficacy Endpoint (mITT Analysis Set)



Source: FDA Statistical Reviewer Analysis

Secondary Efficacy Endpoints:

Primary Efficacy during Extension Period

A summary of the composite primary efficacy endpoints during the Main Treatment Period plus Extension Period and On-treatment in the mITT Analysis Set is presented in Table 10. The results were considered descriptive and exploratory.

A total of 37 (25.5%) subjects in the edoxaban group and 38 (27.0%) subjects in the SOC group had primary efficacy events during the Main Treatment Period plus Extension Period and On-treatment.

The results were similar to those of the Main Treatment Period. Due to more events observed during the extension period, the HR for the edoxaban group vs. the SOC group in this analysis was 0.86 with narrower 95% CI (0.55,1.34).

Table 10 Adjudicated Composite Primary Efficacy Endpoint – Main Treatment Period Plus Extension Period and On-treatment (mITT Analysis Set)

	Edoxaban (N = 145)	**SOC (N = 141)**
Subjects with events (n, %)	37 (25.5)	38 (27.0)
Symptomatic recurrent VTE (n, %)	6 (4.1)	2 (1.4)
PE with or without DVT (n, %)	0	1 (0.7)
Fatal PE (n, %)	0	0
Nonfatal PE (n, %)	0	1 (0.7)
DVT only (n, %)	6 (4.1)	1 (0.7)
Fatal DVT (n, %)	0	0
Nonfatal DVT (n, %)	5 (3.4)	0
Unexplained death which VTE cannot be ruled out (n, %)	1 (0.7)	1 (0.7)
No change or extension of thrombotic burden (n, %)	31 (21.4)	36 (25.5)
Time to first event (days)		
Hazard ratio[a,b]	0.86	
2-sided 95% CI for hazard ratio[b]	(0.548, 1.342)	
2-sided p-value[b]	0.5021	

CI = confidence interval; DVT = deep vein thrombosis; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism
[a] Edoxaban-to-SOC hazard ratio
[b] Based on Cox proportional hazards regression model including treatment and age group as covariates
Note: Adjudicated composite primary efficacy endpoint includes symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden based on imaging.
Note: Main Treatment Period is defined as from randomization to Month 3 Visit + 3 days.
Note: Extension Period is defined as from Month 3 Visit + 4 days to the date of the last dose of study drug + 3 days.
Note: On-treatment is defined as on study drug, within 3 days of study drug interruption, discontinuation, and the last dose of study drug.
Source: Applicant CSR

Composite Endpoints

The incidence of each component (symptomatic recurrent venous thromboembolic disease, death as a result of VTE, and no change or extension of thrombotic burden) of the composite

primary endpoint that occurred during the Overall Treatment Period and 30-day Follow-up in the mITT Analysis Set is presented in Table 11. The results were considered descriptive and exploratory.

A total of 41 (28.3%) subjects in the edoxaban group and 49 (34.8%) subjects in the SOC group had events during the Main Treatment Period plus Extension Period and 30-day Follow-up (see Table 11).

The results were similar to those of the Main Treatment Period plus the Extension Period in the mITT Analysis Set. The HR for the edoxaban group vs. the SOC group in this analysis was 0.71 (95% CI: 0.47 to 1.07).

Table 11 Analysis of Adjudicated Key Secondary Efficacy Endpoints – Main Treatment Period Plus Extension Period and 30-day Follow-up (mITT Analysis Set)

	Edoxaban (N = 145)	**SOC (N = 141)**
Subjects with events (n, %)	41 (28.3)	49 (34.8)
Symptomatic recurrent VTE (n, %)	7 (4.8)	2 (1.4)
PE with or without DVT (n, %)	1 (0.7)	1 (0.7)
Fatal PE (n, %)	0	0
Nonfatal PE (n, %)	1 (0.7)	1 (0.7)
DVT only (n, %)	6 (4.1)	1 (0.7)
Fatal DVT (n, %)	0	0
Nonfatal DVT (n, %)	5 (3.4)	0
Unexplained death which VTE cannot be ruled out (n, %)	1 (0.7)	1 (0.7)
No change or extension of thrombotic burden (n, %)	35 (24.1)	47 (33.3)
Time to first event (days)		
Hazard ratio[a,b]	0.71	
2-sided 95% CI for hazard ratio[b]	(0.47, 1.07)	

CI = confidence interval; DVT = deep vein thrombosis; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

[a] Edoxaban-to-SOC hazard ratio

[b] Based on Cox proportional hazards regression model including treatment and age group as covariates

Note: Adjudicated key secondary efficacy endpoint includes symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden based on imaging.

Note: Main Treatment Period is defined as from randomization to Month 3 Visit + 3 days. Extension Period is defined as from Month 3 Visit + 4 days to the date of the last dose of study drug + 3 days. 30-day Follow-up is defined as 30 days after the last dose of study drug or Discontinuation Visit.

Note: On-treatment is defined as on study drug, within 3 days of study drug interruption, discontinuation, and the last dose of study drug.

Source: Applicant CSR

All-Cause Mortality

All-cause mortality occurred in 2 (1.4%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group. There was 1 (0.7%) VTE-related death in each group. There was 1 (0.7%) VTE related death in each group. The VTE events with fatal outcome were endocarditis in the edoxaban group and pneumococcal sepsis in the SOC group (see Table 12). The results were considered descriptive and exploratory.

Table 12 Incidence of Adjudicated All-cause Mortality – Overall Treatment Period (mITT Analysis Set)

	Edoxaban (N = 145) n (%)	**SOC (N = 141) n (%)**
Subjects with all-cause mortality	2 (1.4)	3 (2.1)
Cause of death as per CEC definition		
VTE-related death	1 (0.7)	1 (0.7)
Unexplained death which VTE cannot be ruled out	1 (0.7)	1 (0.7)
Other known causes of death	1 (0.7)	2 (1.4)
Cancer	0	1 (0.7)
Infectious disease	0	1 (0.7)
Other	1 (0.7)	0

CEC = Clinical Events Committee; mITT = Modified Intent-to-Treat; SOC = standard of care; VTE = venous thromboembolism

Note: Overall Treatment Period is defined as from the day of randomization to the date of the last dose of study drug + 30 days.

Source: Applicant CSR

Incidence of Each Component in Composite Primary Endpoint

The incidence of each component in the composite primary endpoint is summarized for the mITT Analysis Set during the Main Treatment Period in Table 13. The results were considered descriptive and exploratory.

Table 13 Incidence of Adjudication-confirmed Individual Component of Primary Efficacy Endpoints – Main Treatment Period (mITT Analysis Set)

	Edoxaban (N = 145) n (%)	**SOC (N = 141) n (%)**
Symptomatic recurrent VTE	4 (2.8)	1 (0.7)
PE with or without DVT	0	1 (0.7)
DVT only	4 (2.8)	0
Death as a result of VTE	1 (0.7)	1 (0.7)
Unexplained death which VTE cannot be ruled out	1 (0.7)	1 (0.7)
No change or extension of thrombotic burden	21 (14.5)	29 (20.6)

DVT = deep vein thrombosis; mITT = Modified Intent-to-Treat; SOC = standard of care; VTE = venous thromboembolism. Note: Subjects are counted only once within each category.
Note: Main Treatment Period is defined as from randomization to Month 3 Visit + 3 days.

Source: Applicant CSR

Protocol Amendments

Table 14 Summary of Changes Study DU176b-D-U312

Protocol	Version	Change
DU176b-D-U312	Initial Version (1.0) approved 04/21/2016	n/a
DU176b-D-U312	Version 2.0, 19 JAN 2018	-Amend the number of subjects participating in the edoxaban PK evaluation for each age cohort to indicate that the number of participants will be recruited that have the first 12 subjects demonstrating edoxaban exposure levels after analysis. This changes the number of subjects per cohort from N=12 to N≈ 12 -Permitted multiple-month supply dispensing after Month 3 -Excluded subjects taking concomitant strong inducers of P-gp (because this would decrease the exposure) -Excluded subjects who were in another clinical study <30 days prior to the qualifying index VTE. -Adjusted Day 5 PK/PD Visit 2A for approx. first 12 subjects to be 5th day of edoxaban dosing.

		-Excluded subjects not using approved form of contraception. -Allowed tablet crushing for patients unable to swallow whole tablet. -Adjusted edoxaban dosage based on renal function (as calculated by Cockcroft-Gault equation) for pediatric patients >12 years old and modified Schwartz equation for those <12 years old. Other changes: In accordance with ICH guidance, this amendment adds a section on Risk/Benefit (Section 1.3) and defines End of Study (Section 3.3) based on the fact that this is an event-driven study that will continue until approximately 68 primary efficacy endpoints are achieved during the first 3- month treatment period.
	Version 3.0, 07 JUN 2019	-Added dose adjustments for edoxaban with respect to body weight. -Addressed that Day 1 dosing was not required to occur on day of randomization. -Added and updated exclusion criteria (hypersensitivity to active ingredient, pts with h/o thrombosis with antiphospholipid syndrome) New section on re-screening procedures was added. Added requirement to report all bleeding events as an adverse event or SAE
	Version 4.0, 08 JUN 2021	In Cohort 5, subjects ≤28 days old are to be given a reduced dose of edoxaban at 0.4 mg/kg. For Cohort 5, the sample size on Day 5 will be between 5 and 12 for subjects on edoxaban treatment.

The amendments did not likely have an impact on the integrity of the trial/interpretation of results.

6.2 DU176b-A-U157

6.2.1 Study Design

A Phase 1, Open-label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics (PK)

and Pharmacodynamics (PD) of Edoxaban in Pediatric Patients

This was the first pediatric study conducted with edoxaban. The study was not intended to test a hypothesis but rather to generate information that would allow dose selection (comparable to the exposure of efficacious doses in adults) for subsequent clinical efficacy/safety Phase 3 studies in pediatrics. This study was the subject of PMR 2852-1.

Primary Objective:
The primary objective of this study was to characterize the pharmacokinetic (PK) of edoxaban in pediatric patients following single-dose oral administration.

Secondary Objectives
1. To evaluate the pharmacodynamic (PD) effects of edoxaban in pediatric patients following single-dose oral administration.

2. To evaluate the safety and tolerability of single-dose oral administration of edoxaban in pediatric patients.

3. To assess metabolite exposure (D21-2393, D21-3231, D21-1402, and D21-2135) in pediatric patients.

4. To evaluate the palatability (bitterness, sweetness, and overall taste or aroma) of the liquid oral suspension of edoxaban.

Overall Study Design and Plan

This was a Phase 1, open-label, single-dose, non-randomized, multiple-center, PK and PD study in pediatric patients with initially treated deep vein thrombosis (DVT), and to identify recommended pediatric dose(s) for the Phase 3 VTE study (Study 4). In pediatric patients, the proportion of children developing recurrent VTE ranges from 3% in neonates to 8% in older children and as high as 21% in children reported with a first idiopathic VTE. The results of meta-analyses indicate that 11% of children with non-idiopathic thrombosis develop a second VTE. Hence, this study offered a platform by which the identification of patients with non-idiopathic thrombosis or those with potential recurrence could be identified for future therapeutic care.

Treatments Administered
Patients received a single dose of edoxaban only. Edoxaban doses were selected to achieve exposures comparable to adult doses of 30 mg (low dose) and 60 mg (high dose). Patients in the 12 to <18 years of age cohort received multiples of edoxaban tablets of 15 mg or 30 mg strength. Patients younger than 12 years received edoxaban granules for oral suspension (60 mg reconstituted with water to provide a 6 mg/mL suspension for oral administration).

The study included 5 pediatric age cohorts with evaluation of 2 different doses within each age cohort (low and high dose). A total of 66 pediatric patients with DVT initially treated according to current treatment guidelines (e.g., LMWH) were be enrolled into 5 age cohorts. A total of 66 patients were enrolled in Cohorts 1 to 5, as follows:

Cohorts 1a (low dose)/1b (high dose): 15 patients, 12 to <18 years of age on the day of dosing

Cohorts 2a (low dose)/2b (high dose): 13 patients, 6 to <12 years of age on the day of dosing

Cohorts 3a (low dose)/3b (high dose): 13 patients 2 to <6 years of age on the day of dosing

Cohorts 4a (low dose)/4b (high dose): 13 patients 6 months to <2 years of age on the day of dosing

Cohorts 5a (low dose)/5b (high dose): 12 patients 38 weeks gestation to <6 months of age on the day of dosing

Table 15 Pediatric Dosing Table by Age Cohort

Cohort	Age	Edoxaban Dose
1a	12 to <18 yrs	30 mg
1b		60 mg
2a	6 to <12 yrs	24 mg
2b		45 mg
3a	2 to <6 yrs	0.7 mg/kg, cap 24 mg
3b		1.4 mg/kg, cap 45 mg
4a	6 mo to <2 yrs	0.75 mg/kg
4b		1.5 mg/kg
5a	0 to <6 mo	0.4 mg/kg
5b		0.8 mg/kg

Note: Cohorts Xa are the low dose groups and cohorts Xb are the high dose groups.
DSMB = Data and Safety Monitoring Board; Mo = months; yrs = years.
Source: DSMB Meeting Minutes (Appendix 16.1.4.3)

Dosing in this study was conducted sequentially by age groups, beginning with the oldest age cohort (6 to < 18 years) followed by the next oldest age group, but only after the preceding

cohort had completed dosing and data was reviewed. Prior to testing the dose in the subsequent younger pediatric age groups, a thorough review of pharmacokinetics, anti-Xa activity, and safety data for the current dose cohort was performed.

Dosing Process

Patients were dosed orally with a single dose of edoxaban on Day 1. Patients in the 12 to <18 years of age cohort were dosed with multiples of edoxaban tablets of 15 mg or 30 mg strength. Patients younger than 12 years of age received the edoxaban granules for oral suspension according to body weight (mg/kg) (see Table 6-3). If a patient was unable or unwilling to ingest the assigned dosing form (tablet or suspension formulation), the patient was not enrolled and was replaced.

Order of enrollment was from the oldest age cohort to the youngest age cohort. Within each age cohort, enrollment first started in the lower dose group (to achieve exposures comparable to a 30 mg adult dose). After evaluation of PK and safety data from at least half of the patients in the lower dose group, enrollment could then start in the higher dose group (to achieve exposures comparable to a 60 mg adult dose). If the observed exposures were higher than expected in the lower dose group and exceeded the projected 60 mg adult exposure, then a lower dose could have been investigated in the proposed “high dose” group. Enrollment in the next younger age cohorts began when at least half of patients had completed the study in the older age cohort. Enrollment in the younger age cohorts started only after PK and safety data had been evaluated from at least 6 patients (3 low dose and 3 high dose) in the older age cohort. PK and safety data were reviewed by a DSMB who approved the start of the next younger age cohort.

Study duration was approximately 4 weeks for each patient, which included a screening period (within 21 days of dosing), a treatment period, and a follow-up visit conducted within 10 days after dosing. However, a patient was considered to have completed the study if he/she provided the last scheduled PK sample. The treatment period consisted of predose procedures occurring on Day -1 or 1, dosing on Day 1, and postdose procedures occurring postdose on Days 1 and 2 (all cohorts) and Day 3 (all patients enrolled prior to version 5.0 of the Protocol could have had Day 3 PK samples obtained). The treatment period days could have occurred as in-patient or out-patient based on the clinic’s ability/discretion. The overnight stays were not mandatory.

Table 16 Schedule of Events (All Cohorts)

Study Day →	Days -21 to -2	Day -1/1 Predose			Day 1[1]	Day 2[1]	Day 3[1]	Within 10 Days After Dosing
Study Hour →	Screening	Check-in[2]	Predose	Dosing				Follow-up[3]
Study Event ↓								
Informed consent (parent/legal guardian)	X							
Assent form (if applicable)	X							
Eligibility assessment	X	X						
Medical/surgical history	X	X						
Demographics	X							
Physical examination	X	X	X					X
Body weight, height, and BMI	X	X	X					X
Pregnancy test based on local practice (for post-menarchal females)	X	X						
Urine drug screen for patients 12 years of age and older, for newborns, and for patients who are being breastfed	X	X						
Hematology	X[4]							X
Serum chemistry	X[4]							X[5]
Serology	X[4]							
Urinalysis	X	X						
Coagulation (PT, INR, and aPTT)[6]	X							X
Dosing[7]				X				
VAS assessment[8]				X				
AE/SAE monitoring[9]	X	X	X	X	X	X	X[9]	X
Concomitant medication[9]	X	X	X	X	X	X	X[9]	X

Study Day →	Days -21 to -2	Day -1/1 Predose			Day 1[1]	Day 2[1]	Day 3[1]	Within 10 Days After Dosing
Study Hour →	Screening	Check-in[2]	Predose	Dosing				Follow-up[3]
Study Event ↓								
PK blood draw[10]					X	X	X	
PD blood draw[10]	X		X		X	X		

1. The overnight stay on Day 1 or Day 2 was not mandatory. The patient could have left the clinic on Day 1 following the completion of all study procedures and returned to the clinic on Day 2 for the completion of Day 2 procedures (or Day 3 for patients enrolled prior to version 5.0 of the Protocol). Any procedure occurring after hour 8 on Day 1 could have been performed using a home healthcare service, depending on the availability of the service in the patient's country.
2. Check-in could have occurred on Day -1 or 1, depending on the site.
3. Some patients could have been given the option to have a home healthcare service conduct the procedures for this visit in the patient's home, depending on the availability of the service in the patient's country.
4. Blood samples were obtained at screening if not drawn within 2 weeks prior to screening.
5. Serum chemistry was only obtained from patients in Cohorts 1, 2, and 3.
6. Only 1 assessment was required prior to edoxaban dosing at either screening or upon check-in, as appropriate for the patient.
7. Doses were selected based on emerging PK and safety data.
8. Patients receiving the edoxaban granules for oral suspension formulation who were developmentally capable of providing an accurate response were asked to rate several aspects of palatability (including bitterness, sweetness, overall taste, and aroma) using 100-millimeter VAS. Patients who were old enough scored the VAS themselves. For younger children, the parents provided this information, if possible. For the youngest children, there was free text input available to provide information on whether the patient spat it out and may not have liked the flavor, etc.
9. Continuous monitoring after screening procedures was completed.
10. Refer to cohort-specific PK/PD SOE for specific timepoints.

AE = adverse event; aPTT = activated partial thromboplastin time; BMI = body mass index; INR = international normalized ratio; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PT = prothrombin time; SAE = serious adverse event; SOE = schedule of events; VAS = visual analog scale.
Source: Study Protocol (Appendix 16.1.1)

Main Inclusion Criteria for DU176b-A-U157 (Study 3)

Male and female pediatric patients ages birth to less than 18 years of age who may require or are currently on anticoagulant therapy.
These could have included the following:

- Patients who had a recently acquired or Investigator determined ongoing risk of
- thromboembolic events (eg, patients with thrombophilia, congenital heart disease, presence of a central venous catheter, and prior VTE).
- Patients who were completing their standard-of-care anticoagulant therapy. Edoxaban could have been initiated 12 hours after cessation of enoxaparin, dabigatran, or apixaban therapy (A-U136, A-U151, and A-E152) and 24 hours after cessation of rivaroxaban therapy (A-U151). Note that the dose of edoxaban should have been at the time of the next scheduled standard-of-care anticoagulant administration:
- At least 4 hours after last dose of unfractionated heparin.
- At least 12 hours after last dose of twice daily (BID) low molecular weight heparin (LMWH).
- At least 24 hours after last dose of QD LMWH and synthetic pentasaccharide FXa inhibitors.
- For patients who had been on a prior vitamin K antagonist (eg, warfarin [C-U122] and any other anticoagulants) therapy, international normalized ratio (INR) value should have been $\leq$2.5 prior
  to edoxaban dosing. If the patient's INR was >2.5, the patient's INR should have been monitored until it was $\leq$2.5.
- Patients who had been currently treated for VTE with at least 5 days of heparin may have interrupted their standard-of-care anticoagulant therapy for edoxaban administration. The dose of edoxaban should have been:
- At least 12 hours from last dose of BID LMWH, with a restart of LMWH 24 hours after edoxaban dose.
- At least 24 hours from last dose of QD LMWH, with a restart of LMWH 24 hours after edoxaban dose.
- Patients with cardiac conditions who may have required anticoagulant therapy.
- Patients with sickle cell disease who may have required anticoagulant therapy.

For any condition, anticoagulant treatment interruption or discontinuation did not take place if the patient was at increased risk and were appropriate as per standard-of-care practices. Patients had to satisfy all of the following criteria to be included in the study. Any temporal changes in the following criteria that may have prohibited patient consideration, but should have normalized for future eligibility, were reassessed for the patient's future participation in the study:

1. Patients/legal guardian(s) had to be able to provide written informed assent (patient, when applicable) and ICFs (signed by parent/legal guardian) prior to participating in the study.
2. Male or female patients 38 weeks gestation to <18 years of age on the day of dosing.
3. Patients 2 to <18 years of age had to have a body mass index (BMI) between the 5th and 95th percentile based on the 2000 Centers for Disease Control and Prevention (CDC) Growth Charts (the maximum number of patients in each dose group that had a BMI between the 85th and 95th percentile should have not been more than 2 patients). Patients <2 years of age had to have a body weight between the 5th and 90th percentile based on the 2000 CDC Growth Charts.
4. Female patients who have had menarche had to test negative for pregnancy, as per local practice, at screening and check-in.
5. Female patients who have had menarche and were sexually active had to agree to use an effective contraception method, per local practice, for at least 30 days prior to edoxaban dose.
6. Patients/legal guardian(s) had to agree to food and drug restrictions during the study.

- Patients had to agree to abstain from and/or legal guardians had to agree not to give the patient cola, tea, coffee, chocolate, and other caffeinated drinks and food from 48 hours before dose administration to until after the last PK sample collection. Mothers who were breastfeeding study patients should have maintained this same dietary restriction for 24 hours prior to edoxaban dosing.
- Patients had to agree to abstain from and/or legal guardian(s) had to agree not to give the patient St. John's Wort and food/supplements and beverages containing grapefruit, grapefruit juice, and Seville oranges from 14 days before the first dose through to until after the last PK sample collection.
- Patients had to agree to abstain from cytochrome P450 (CYP) 3A4 inhibitors/inducers and P-glycoprotein (P-gp) inhibitors/inducers for 14 days prior to the edoxaban dose to until after the last PK sample collection.

7. Patients had to agree to abstain from the use of nonsteroidal anti-inflammatory drugs (such as ibuprofen) and antiplatelet (except for low dose aspirin) from 14 days prior to edoxaban dose until after the last PK sample was collected. Patients on low dose aspirin treatment (1 to 5 mg/kg/day, maximum of 100 mg/day) were permitted to participate in the study per the Investigator's judgment that this did not place the patients at risk. Low dose aspirin on Day 1 should have been withheld until 4 hours post edoxaban dose.

8. Other than signs and symptoms characteristic to their disease state, patients were to be in good health as determined by the absence of clinically significant deviations from normal, with respect to medical and surgical history, physical examination, vital signs, and laboratory reports, as deemed by the Investigator prior to enrollment.

Exclusion Criteria:

Patients who met any of the following criteria were disqualified from entering the study. Any temporal changes in the following criteria that may have prohibited patient consideration, but should have normalized for future eligibility, were reassessed for the patient's future participation in the study:
1. Patients with abnormal coagulation tests during screening, as defined by local laboratory reference ranges (RRs), which were not explained by anticoagulant therapy or temporary concomitant affections.
2. Patients with stroke where anticoagulant therapy was contraindicated.
3. Patients with stage 2 hypertension defined as blood pressure confirmed >99th percentile + 5 mmHg.
4. Patients with renal function less than 50% of normal for age and size as determined by the National Kidney Disease Education Program version of the Schwartz formula.
5. Actively bleeding, had a high risk of bleeding, or had a history of major bleeding
6. Had a currently active gastrointestinal ulceration or a known history of peptic ulcer or gastrointestinal bleeding (including hematemesis, melena, or rectal bleeding including bleeding from hemorrhoids) within the previous 3 months.
7. Had known diabetic retinopathy.
8. Had thrombocytopenia at screening ($<20 \times 10^9$/L).
9. Patients with history of major trauma, or major or invasive procedures within the last month prior to screening. Otherwise, shorter time was permitted depending on the surgery and based on the Investigator's judgment of bleeding risk.
10. Patients with known malabsorption disorders (eg, cystic fibrosis or short bowel syndrome).
11. Hepatic disease which was associated with coagulopathy leading to a clinically relevant bleeding risk, alanine transaminase (ALT) >5 times the upper limit of normal (ULN), or total bilirubin >2 times the ULN with direct bilirubin >20% of the total.
12. Patient was currently enrolled in another investigational device or drug study or was receiving other investigational agents. Patients had to complete the prior clinical study at least 30 days prior to dosing.
13. Patients of childbearing potential (post-menarche) who were sexually active and were not using approved contraception, per local practice; who were pregnant (as based on test results); or were breastfeeding.
14. Females with history of abnormal menses, including history of menorrhagia (heavy menstrual bleeding), metrorrhagia, or polymenorrhea.
15. Patient had known hypersensitivity to the active ingredient or any of the excipients of any compounds of the investigational product (IP).
16. Positive drug or alcohol screen (excluding cotinine) at screening for patients 12 years of age or older, neonates (0 to 28 days old), and for patients who were being breastfed.
Exception to this was if patients were on prescription drug(s). The window to potentially hold and/or resume the prescription drug needed to be determined by DSI based on the information of the prescription drug.
17. Patients who had received a transfusion or any blood products within 30 days prior to the

first dose.
18. Patients with any condition that, as judged by the Investigator, would have placed the patient at increased risk of harm if he/she participated in the study or would have interfered with the conduct of the study or the interpretation of the data.
19. Patients with a history of thrombosis who were diagnosed with antiphospholipid syndrome and were triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies).

Patient Replacement

Dropouts (for reasons other than AEs) could have been replaced, if deemed necessary, upon written approval by the Sponsor. A replacement patient was within the same age cohort range and received the same dose and formulation of study drug as the patient being replaced. Any replacements were made only after receiving the Sponsor's written prior authorization

Patient Rescreening

Rescreening of patients that failed to meet the inclusion and exclusion criteria was allowed if the reason for failure to meet the criteria had resolved and was no longer considered a risk to the patient (eg, temporal laboratory deviations meeting exclusion criteria, treatment with contraindicated medications, non-chronic diagnoses). Rescreening of patients for this reason was to be reviewed on a case-by-case basis and was dependent upon approval from the Medpace and DSI Medical Monitors. However, if a patient was screened but could not dose for personal/logistic reasons within 21 days of screening, he/she needed to be rescreened. The exception was to be made for patients who had previously been on warfarin therapy and needed to be within the acceptable range of INR values. This was considered rescreening, and only INR values were monitored at subsequent testing to ensure that prior to edoxaban dosing, the patient met the inclusion criterion of INR $\leq$2.5.

Method of Assigning Patients to Treatment Groups

This was an open-label, single-dose, non-randomized study. In each age group, patients were assigned to a particular treatment in a manner that allowed for an even distribution of ages across doses (this decision was to be made in consultation with the clinical study lead).

Edoxaban was evaluated in all patients in 1 treatment period. Each patient received a single oral dose on Day 1. In each age cohort, appropriate doses were selected to achieve exposures comparable to adult doses of 30 mg (low dose groups) and 60 mg (high dose groups). The doses given to each age cohort and dose group were adjusted based on emerging data. The doses (mg/kg) for patients younger than 6 years were based on patients' body weight, as presented in Table 7-2.

Table 17 Baseline Characteristics of Patient Population

	Cohorts 1a/1b		Cohorts 2a/2b		Cohorts 3a/3b		Cohorts 4a/4b		Cohort 5a/5b		
Age	12 to <18 yrs		6 to <12 yrs		2 to <6 yrs		6 mo to <2 yrs		0 to <6 mo		
Category	Low Dose (N=8)	High Dose (N=7)	Low Dose (N=7)	High Dose (N=6)	Low Dose (N=7)	High Dose (N=6)	Low Dose (N=7)	High Dose (N=6)	Low Dose (N=6)	High Dose (N=6)	Overall (N=66)
Age at informed consent (yrs)											
n	8	7	7	6	7	6	7	6	6	6	66
Mean (SD)	15.899 (1.139)	15.314 (1.343)	9.551 (1.075)	9.459 (1.927)	4.310 (1.567)	4.316 (1.367)	1.175 (0.530)	0.970 (0.513)	0.167 (0.208)	0.253 (0.169)	6.525 (6.026)
Median	16.129	15.362	9.782	9.903	5.043	4.169	0.819	0.656	0.059	0.277	5.198
Min, max	13.802, 17.525	12.972, 17.153	8.159, 10.823	6.431, 11.436	2.242, 5.900	2.171, 5.925	0.704, 1.947	0.632, 1.807	0.008, 0.435	0.016, 0.433	0.008, 17.525
Sex – n (%)											
Female	5 (62.5)	4 (57.1)	3 (42.9)	4 (66.7)	3 (42.9)	1 (16.7)	3 (42.9)	3 (50.0)	2 (33.3)	3 (50.0)	31 (47.0)
Male	3 (37.5)	3 (42.9)	4 (57.1)	2 (33.3)	4 (57.1)	5 (83.3)	4 (57.1)	3 (50.0)	4 (66.7)	3 (50.0)	35 (53.0)
Race – n (%)											
White	7 (87.5)	6 (85.7)	5 (71.4)	5 (83.3)	5 (71.4)	3 (50.0)	2 (28.6)	5 (83.3)	2 (33.3)	3 (50.0)	43 (65.2)
Black or African American	1 (12.5)	1 (14.3)	2 (28.6)	1 (16.7)	2 (28.6)	1 (16.7)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (15.2)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	3 (42.9)	0 (0.0)	4 (66.7)	3 (50.0)	11 (16.7)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	2 (3.0)

Compliance: No study withdrawals.

Efficacy: Not applicable.

Study Endpoints

Pharmacokinetic/Pharmacodynamic endpoint(s):

PK endpoints included modeled PK parameters such as apparent systemic clearance (CL/F), apparent volume of distribution (V/F), and area under the concentration-time curve (AUC) for edoxaban and metabolites, and metabolite/parent ratios for AUC.

The PD endpoints included observed, change-from-baseline, and percent-change-from baseline PT, aPTT, and anti-FXa.

Secondary endpoint(s): None stated

Safety and tolerability assessments:

Safety assessments included: AEs, physical examination findings, vital signs, standard hematology, clinical chemistry, and urinalysis laboratory tests. Note: urinalysis will be performed with plastic bags with a sticky strip from neonates and infants with diapers. Palatability of the liquid formulation will be assessed using visual analog scale (VAS) scores.

Statistical Methods:

Pharmacokinetic Analysis Set
The PK analysis set comprised all patients who received edoxaban as per protocol and had at least 1 post dose PK measurement with known collection times and date/time of dose administration and who did not have any clinically significant events or protocol deviations that may have compromised the integrity of the PK results.

Pharmacodynamic Analysis Set
The PD analysis set comprised all patients who received edoxaban as per protocol and had at least 1 post dose PD measurement with known collection time and date/time of dose administration and who did not have any clinically significant events or protocol deviations that may have compromised the integrity of the PD results.

Safety Analysis Set
The safety analysis set included all patients who received edoxaban.

Amendments

The following main updates were introduced in amended Protocols:
Protocol version 2.0 (dated 09 May 2014)

1. Changed the doses of study drug given from 15, 30, and 60 mg to 15 and 30 mg.
2. Clarified that the patients <12 years of age would receive reconstituted liquid oral suspension formulations instead of tablets.
3. Clarified that a patient would be considered a completer if they provided the last scheduled PK sample.
4. Added a palatability assessment on Day 1.
5. Clarified that AEs would be recorded from date of the signed ICF to up to 10 days after the last dose of study drug.

Protocol version 3.0 (dated 21 January 2015)

1. Clarified language regarding anticoagulation therapy and thromboembolic events for patient eligibility.
2. Added BMI inclusion criteria.
3. Clarified that both Investigator and Sponsor must deem patients to be in good health.

4. Clarified drug screening language such that cotinine in the urine is not an exclusion criterion and to screen newborns and patients who are being breastfed.
5. Specified patient fasting requirements.
6. Protocol version 4.0 (dated 03 November 2015)
7. Clarified that a patient's age cohort is determined by age on the day of dosing.
8. Clarified inclusion criteria regarding concurrent and prior aspirin therapy.
9. Changed pregnancy test to be based on local practice.
10. Clarified the malabsorption disorders exclusion criteria.

Protocol version 5.0 (dated 14 July 2016)

1. Added a fifth cohort of patients and increased the sample size to 60 patients.
2. Revised the PK/PD time points for all cohorts and added text to indicate reduced blood volume sampling for patients 6 years of age and younger.
3. Removed the Day 3 visit.
4. Allowed for use of home healthcare services, as available.
5. Clarified that the PK model will be refined as new data becomes available.

Protocol version 6.0 (dated 08 August 2018)

1. Changed the age of youngest included patients.
2. Revised the PK/PD schedules for all cohorts.
3. Added back the Day 3 visit for Cohort 1.
4. Revised the study endpoints to include safety as a secondary objective.
5. Protocol version 6.1-IN (dated 14 December 2018)
6. Revised the inclusion and exclusion criteria according to the request of the (b) (4).
7. Protocol version 7.0 (dated 16 September 2019)
8. Updated requirements for enrollment initiation of Cohort 5.
9. Revised and updated exclusion criteria to add hypersensitivity to the active ingredient or to any of the excipients of any components, based on the recommendations from (b) (4).

Protocol version 7.1-FR (dated 11 October 2019)

1. Updated requirements for enrollment initiation of Cohort 5 for France.
2. Revised and updated exclusion criteria to add hypersensitivity to the active ingredient or to any of the excipients of any components, based on the recommendations from (b) (4)

Protocol version 4.0 (dated 03 November 2015)

1. Clarified that a patient's age cohort is determined by age on the day of dosing.
2. Clarified inclusion criteria regarding concurrent and prior aspirin therapy.
3. Changed pregnancy test to be based on local practice.

4. Clarified the malabsorption disorders exclusion criteria.

Protocol version 5.0 (dated 14 July 2016)

1. Added a fifth cohort of patients and increased the sample size to 60 patients.
2. Revised the PK/PD time points for all cohorts and added text to indicate reduced blood volume sampling for patients 6 years of age and younger.
3. Removed the Day 3 visit.
4. Allowed for use of home healthcare services, as available.
5. Clarified that the PK model will be refined as new data becomes available.

Protocol version 6.0 (dated 08 August 2018)

1. Changed the age of youngest included patients.
2. Revised the PK/PD schedules for all cohorts.
3. Added back the Day 3 visit for Cohort 1.
4. Revised the study endpoints to include safety as a secondary objective.

Protocol version 6.1-IN (dated 14 December 2018)

1. Revised the inclusion and exclusion criteria according to the request of (b) (4) .

Protocol version 7.0 (dated 16 September 2019)

1. Updated requirements for enrollment initiation of Cohort 5.
2. Revised and updated exclusion criteria to add hypersensitivity to the active
3. ingredient or to any of the excipients of any components, based on the
4. recommendations from the (b) (4) .
5. Protocol version 7.1-FR (dated 11 October 2019)
6. Updated requirements for enrollment initiation of Cohort 5 for France.
7. Revised and updated exclusion criteria to add hypersensitivity to the active ingredient or to any of the excipients of any components, based on the recommendations from the (b) (4)

Administrative Structure

An independent Data and Safety Monitoring Board (DSMB) consisting of a panel of clinicians or therapeutic area experts was convened to provide independent review to assure patient safety and integrity of the study were being upheld. Responsibilities of the DSMB were set forth in the DSMB Charter. Information on the DSMB, including committee members, curriculum vitae, charter, and minutes can be found in Appendix 16.1.4.3.

The study was sponsored by Daiichi Sankyo, Inc. (DSI) and conducted at 32 clinical sites in the United States, Canada, France, India, Italy, Jordan, Lebanon, Spain, Turkey, and the United Kingdom. DSI and Medpace, Inc. (hereinafter Medpace), a contract research organization, performed safety monitoring. Five Investigators' Meetings were held during this study.

Medpace also performed project management, clinical monitoring, data management, statistical analysis, and Clinical Study Report (CSR) preparation. Medpace Reference Laboratories (Cincinnati, Ohio) and Q2 Solutions (Ithaca, New York) performed clinical laboratory analyses. Medpace Reference Laboratories was able to perform the drug screen upon request. Safety laboratory analyses were performed locally.

A Steering Committee consisting of a panel of study Investigators or therapeutic area experts was convened to provide clinical and scientific expertise to DSI on the design, execution, and analysis of this Phase 1 pediatric study. Responsibilities of the Steering Committee were set forth in the Steering Committee Charter.

6.2.2 Study Results DU176b-A-U157

Compliance with Good Clinical Practices

- The studies were conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s):
- European Commission Directive (2001/20/EC Apr 2001)
- European Commission Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- Food and Drug Administration GCP Regulations: CFR Title 21, parts 11, 50, 54, 56 and 312;
- The Health Insurance Portability and Accountability Act as appropriate and/or other applicable local regulations.

  Adequate provisions were made for soliciting the assent of the children and the consent of their parents or legal guardians. The safety monitoring practices employed by the Protocol (i.e., physical examinations, vital signs, adverse events [AEs], and clinical laboratory assessments) in addition to periodic data review by the DSMB were considered adequate to protect the patients' safety.

  Results
- PK/PD:
  In the pediatric population of 38 weeks gestation (0 months) to <18 years of age, edoxaban was absorbed rapidly after oral administration in all age cohorts in both high dose and low dose groups and produced similar plasma concentration-time profiles for different age cohorts. Rapid clearance after achieving peak concentration was observed

for all age cohorts.

- Safety and tolerability of single-dose oral administration of edoxaban in pediatric patients:

  Edoxaban was safe and well tolerated when administered orally in a single low dose or single high dose to pediatric patients from 38 weeks gestation (0 months) to <18 years of age.

- Four patients in Cohorts 1a/1b, 6 patients in Cohorts 2a/2b, 1 patient in Cohorts 3a/3b, and 4 patients in Cohorts 4a/4b experienced TEAEs, of which the majority were mild, resolved without any sequelae, and did not require any medical intervention. No patients in Cohorts 5a/5b experienced any TEAEs.
  Given the small number of patients in each group, the number of TEAEs in the low and high dose groups in each cohort was comparable. No severe TEAEs were observed.

  By System Organ Class (SOC), the most frequently reported TEAEs were gastrointestinal disorders
  (4 [6.1%] patients overall:
  2 patients in the low dose group of Cohort 2 [2a] and
  1 patient each in the low dose groups of Cohort 1[1a] and Cohort 4 [4a]); skin and subcutaneous tissue disorders (3 [4.5%] patients overall: 1 patient each in the high dose groups of Cohort 2 [2b] and Cohort 4 [4b], and 1 patient in the low dose group of Cohort 4 [4a]); and respiratory, thoracic, and mediastinal disorders
  (3 [4.5%] patients overall: 2 patients in the low dose group of Cohort 4 [4a] and
  1 patient in the low dose group of Cohort 2 [2a]).

  The following changes in coagulation were observed:

- In the 12 to <18 years age cohort, 1 patient treated with high dose of edoxaban (Cohort 1b) had PT prolonged (mild, without bleeding), which was considered to be related to edoxaban.
- In the 6 to <12 years age cohort, 1 patient treated with high dose of edoxaban (Cohort 2b) had aPTT prolonged (mild, without clinical impact), which was considered to be related to edoxaban.
- There were no deaths during the study. No patients experienced TESAEs or study drug-related SAEs during the study, and there were no TEAEs leading to discontinuation of study drug.
- Two patients experienced 3 SAEs in the screening phase and did not receive the study drug.
- No clinically meaningful changes in chemistry or hematology laboratory evaluations

or vital signs were observed

The majority of TEAEs were mild, resolved without any sequelae, and did not require any medical intervention. No SAEs or study drug-related SAEs occurred during the study. No deaths occurred during the study. There were no AEs of special interest during the study.

- Palatability Assessment using a Visual Analog Score (VAS)

  The mean (SD) overall palatability score ranged from 53.6 (35.78) millimeters in the low dose group of Cohort 2 to 83.3 (20.41) millimeters in the high dose group of Cohort 3. The overall palatability score, the overall taste score, the sweetness score, and the aroma score were higher in the high dose groups compared to the low dose groups for Cohorts 2, 3, and 5. The bitterness score was higher in the high dose groups compared to the low dose groups for Cohorts 3 and 5.

  Reviewer Comment: This PREA PMR was conducted as specified and may be considered fulfilled.

Efficacy Results –N/A; there were no efficacy endpoints in the trial.

7. Integrated Review of Effectiveness

Not applicable; single pivotal trial failed to demonstrate efficacy.
The Applicant has not submitted evidence of effectiveness that meets the statutory evidentiary standard. No indication is requested or recommended.

8. Review of Safety

8.1. Safety Review Approach

This is a safety review of the results of the Phase 3 study conducted to fulfil PMR 2852-2, "A phase 3 multicenter, randomized, active control study of edoxaban in pediatric patients with documented venous thromboembolism". The review found that overall, edoxaban showed similar safety in comparison to SOC agents in the pediatric population studied.

The safety analysis is comprised of all subjects in the Randomized Analysis Set who received at least 1 dose of study drug actually taken. The Safety Analysis Set comprised 286 subjects (145 in the edoxaban group and 141 in the SOC group). The study included 5 pediatric age cohorts with evaluation of 2 different doses within each age cohort (low and high dose). Age cohorts and dose groups are described in Section 6.1. In general, all data were summarized by age cohort and dose group, and all evaluable data were included in the analyses.

8.2. Review of the Safety Database

Safety Drug Exposure (Safety Analysis Set)

Overall, the number of days of treatment exposure for edoxaban was greater than that for SOC subjects. The mean treatment exposure for subjects on edoxaban was 186 days (+ 120 days) and for subjects receiving SOC was 157 days (+102 days).

The median treatment exposure for edoxaban was 147 days, and for SOC treatments then median treatment exposure was 107 days. Table 18 below delineates treatment exposure fully.

Table 18 Treatment Exposure by Arm/Treatment

	Edoxaban (N = 145)	SOC (Total) (N = 141)	SOC		
			Heparin (N = 116)	SP-FXa Inhibitor (N = 5)	VKA (N = 41)
Study treatment duration (days)					
Mean (± SD)	187.6 (± 120.95)	158.7 (± 102.50)	133.6 (± 106.34)	84.6 (± 56.44)	160.1 (± 109.04)
Median	147.0	110.0	95.5	87.0	112.0
Minimum, maximum	1, 400	1, 412	1, 412	3, 162	2, 368
Study duration (days)					
Mean (± SD)	223.5 (± 119.32)	196.8 (± 110.68)	194.6 (± 109.47)	151.6 (± 53.17)	213.2 (± 117.98)
Median	176.0	152.0	149.5	120.0	206.0
Minimum, maximum	25, 477	0, 562	0, 543	104, 210	7, 562
Treatment exposure (days)					
Mean (± SD)	186.1 (± 120.14)	157.0 (± 102.38)	132.9 (± 106.13)	84.6 (± 56.44)	156.6 (± 108.92)
Median	147.0	107.0	94.5	87.0	102.0
Minimum, maximum	1, 394	1, 412	1, 412	3, 162	2, 368

FXa = activated Factor X; SD = standard deviation; SOC = standard of care; SP = synthetic pentasaccharide; VKA = vitamin K antagonist

Study drug interruptions for any reason during the Main Treatment Period were required in 16.6% (24/145) in the Savaysa arm versus 20.6% (29/141) in the SOC arm. Dose interruptions due to adverse events were similar across all arms (Edoxaban 6.9%, versus SOC 7.1%). Dose discontinuation overall was 7.6% in the edoxaban arm, 15.6% SOC arm, and 16.4% LMWH arm. Reasons for discontinuation were due to adverse event, death, withdrawal by subject, lost to follow up, protocol violation, subject discontinued by PI discretion, or other.

8.2.1. Relevant characteristics of the safety population:

The safety and efficacy populations are essentially the same. See Table of Demographic and Baseline Characteristics (mITT Analysis Set).

8.2.2. Adequacy of the safety database:

The size of the safety database is adequate and was previously agreed upon with the Agency. The youngest cohort of patients, 0 to ≤ 6 months enrolled the fewest number of patients, and while the numbers were balanced between study drug 9 (6.2%) and SOC 7 (5%), it would have been helpful to have a few more neonates enrolled. It is likely difficult to recruit participants to the very youngest cohort. The duration of treatment is according to standard medical practice for the treatment of VTE.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Clinical evaluations were conducted appropriately to assess the safety of edoxaban versus SOC.

8.3.2. Categorization of Adverse Events

- Applicant provided accurate definitions of AEs and serious adverse events (SAEs) in the protocol. Adverse events were coded according to MedDRA Version 23.0.

8.3.3. Routine Clinical Tests

See Section 6, Table 5 Schedule of Events for the frequency, time points and specification of routine laboratory tests.

In general, blood draws were not fasting, except for the assay for edoxaban exposure verification: The first 8 to 12 subjects participating in the Day 5 PK/PD assessment of subjects randomized to edoxaban should have been fasting for 1 hour prior to the uptake of edoxaban dose and a maximum of 2 hours after taking edoxaban dose. If this was not feasible because of the subject's age or other needs, milk, or an equivalent substitute liquid (but not fruit juices or caffeinated drinks) was allowed until 1 hour before and starting at 1 hour after dosing, laboratory studies drawn on day 5.

The original study procedure was for all blood draws to be obtained at the accredited lab used by the subject, however due to the COVID-19 pandemic, changes were required. These are described in the section 6.8.2 of the study report. Changes in the Conduct of the Study Related to COVID-19. If it was not possible to obtain protocol-specified laboratory tests at the usual labs, then the tests could be performed in another, more accessible but accredited lab. The results along with normal reference ranges were to be conveyed to the site as soon as possible (at least via phone interview). Results review needed to be documented in the subject medical records with a copy of the laboratory report filed therein. In cases where bloodwork was to be sent to labs not previously qualified for the study, a laboratory accreditation certificate was to be obtained, and a list of laboratory normal ranges collected.

If possible, vital signs were to be collected by a medical professional familiar with the procedure. A written copy of the measurements could serve as a source document.

The measures taken to obtain required labs and vital signs seem reasonable.

8.4. Safety Results

8.4.1. Deaths

Three subject deaths were reported in the edoxaban group, and 3 subject deaths were reported in the SOC group. The deaths in the edoxaban group included cardiogenic shock and endocarditis (1 subject), respiratory failure (1 subject), and pleural effusion and respiratory failure (1 subject). The deaths in the SOC group included adrenal insufficiency and metastatic cancer (1 subject); pneumococcal sepsis (1 subject); and cardiopulmonary failure, systemic inflammatory response syndrome, acute respiratory distress syndrome, and noncardiogenic pulmonary edema (1 subject). None of the deaths were considered related to study drug.

Reviewer Comment: The narratives were reviewed and none of the deaths appeared to be related to study drug.

8.4.2. Serious Adverse Events

During the Overall Treatment Period, the percentage of subjects who experienced serious TEAEs was 30.3% (44/145) of subjects in the edoxaban group and 26.2% (37/141) of subjects in the SOC group (Table 14.3.2.20).

Serious TEAEs that occurred in ≥2 subjects in either group were febrile neutropenia (4.1% [6/145]); pneumonia (2.8% [4/145]); urinary tract infection (2.1% [3/145]); and thrombocytopenia, headache, intracranial pressure increased, cerebral venous sinus thrombosis, vomiting, suicidal ideation, and PE (1.4% [2/145] each) in the edoxaban group and febrile neutropenia (4.3% [6/143]); thrombocytopenia and headache (2.1% [3/141] each); and gastroenteritis, cellulitis, rhinovirus infection, dehydration, and vomiting (1.4% [2/141] each) in the SOC group. Serious TEAEs are provided by subject for the Safety Analysis Set in Listing 16.2.7.2.

Reviewer Comment: The incidence of serious TEAEs was slightly higher in the edoxaban arm but the types of events were similar between arms.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Overall, 5.5% (8/145) of subjects in the edoxaban group experienced TEAEs leading to discontinuation of study treatment during the Main Treatment Period. The TEAEs leading to discontinuation of study treatment included venous embolism, DVT, peripheral embolism, cerebral venous sinus thrombosis, hemorrhagic stroke, intracranial pressure increased, hematochezia, and pruritus. Three (2.1%) subjects in the SOC group during the Main Treatment Period experienced TEAE leading to study discontinuation.

Compliance with edoxaban was excellent at 91% for the Main Treatment Period. In contrast, for SOC with warfarin, less than 50% of subjects were within the INR therapeutic range of 2.0 to 3.0. Subjects in the SOC group were monitored for enoxaparin compliance by measuring anti-FXa levels. Compliance with enoxaparin was considered low.

8.4.4. Significant Adverse Events

Table 19 Treatment Emergent Adverse Events by SOC, Preferred Term and Severity

		Mild		Moderate		Severe	
		Edoxaban	SOC	Edoxaban	SOC	Edoxaban	SOC
Subjects with TEAE	n (%)	46 (31.7)	54 (38.3)	43 (29.7)	26 (18.4)	14 (9.7)	15(10)
Thrombocytopenia	n (%)	1 (0.7)	0	2 (1.4)	5 (3.5)	3 (2.1)	1 (0.7)
Anemia	n (%)	2 (1.4)	0	1 (0.7)	2 (1.4)	2 (1.4)	2 (1.4)
Neutropenia	n (%)	1 (0.7)	2 (1.4)	0	0	2 (1.4)	1 (0.7)
Febrile neutropenia	n (%)	2 (1.4)	0	5 (3.4)	4 (2.8)	1 (0.7)	2 (0.7)
Headache	n (%)	16 (11.0)	(2.8)	1 (0.7)	11 (7.8)	3 (2.1)	0

Source: Applicant's Table 14.3.2.29: Safety Analysis Set

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent AEs occurred in 71% (103/145) of subjects in the edoxaban group and 67.4% (95/141) of subjects in the SOC group. The most frequently (≥4% of subjects in either group) reported TEAEs were headache, vomiting, and pyrexia. The TEAEs of headache, vomiting, nasopharyngitis, cough, dizziness, rash, and urinary tract infection occurred more frequently in the edoxaban group. The TEAEs of oropharyngeal pain, metrorrhagia, anxiety, drug hypersensitivity, ecchymosis, ear pain, pancytopenia, rhinovirus infection, and stomatitis occurred more frequently in the SOC group. The incidences of all other reported TEAEs differed between the groups by <2%. Overall, no new safety signals related to edoxaban use were observed.

The percentage of subjects who experienced treatment-related TEAEs was 16.6% (24/145) in the edoxaban group and 14.2% (20/141) in the SOC group. The most frequently reported treatment-related TEAEs (≥2%) in the edoxaban group were epistaxis (3.4% [5/145]) and

headache (2.1% [3/145]). The most frequently reported treatment-related TEAEs (≥2%) in the SOC group were epistaxis (2.8% [4/141]) and metrorrhagia (2.1% [3/141]).

The frequency of treatment related AEs was similar between the edoxaban and SOC groups. The most frequently reported TEAE's are related to bleeding, which is the most important safety issue with anticoagulant drugs.

8.4.6. Laboratory Findings

Mean values for the serum chemistry and hematology parameters evaluated were similar between the 2 groups at baseline, and mean changes from baseline for each parameter were generally similar between the groups during the study.

8.4.7. Vital Signs

The mean values for each of the vital sign parameters (SBP and DBP, pulse, and body temperature) were similar between the two groups at baseline, and no clinically meaningful mean changes from baseline were observed for any of these parameters in either of the groups during the study. During the Main Treatment Period, the percentage of subjects who had a post baseline SBP value in the category of ≤90 mm Hg and a decrease of ≥20 mm Hg was 7.6% (11/145) in the edoxaban group and 5.0% (7/141) in the SOC group (Table 10.9). The percentage of subjects who had a postbaseline weight decrease of ≥7% was 13.1% (19/145) in the edoxaban group and 7.1% (10/141) in the SOC group.

8.4.8. Electrocardiograms (ECGs)

ECGs were not routinely obtained.

8.4.9. QT

ECGs were not routinely obtained.

8.4.10. Immunogenicity

Not applicable; not a protein.

8.5. Analysis of Submission-Specific Safety Issues

The most important safety issue for edoxaban is bleeding. The primary safety objective of this trial was adjudicated conformed major and clinically relevant non-major bleeding during the Main Treatment Period and On-treatment periods.

8.5.1. Bleeding

In terms of the primary safety objective, results were comparable between the edoxaban and SOC groups. A total of 3 (2.1%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudicated confirmed major and CRNM bleeding event during the Main Treatment Period and On-treatment (HR:0.60, 95% CI: 0.139 to 2.597).

Reviewer Comment: More bleeding occurred in the control arm (SOC) (5 vs 3 patients).

8.5.2 Liver Test Abnormalities

Elevated liver related labs occurring in greater than 5 subjects:

- ALT >3 x ULN 10.3% in the Edoxaban group and in 8.5% of subjects in the SOC group
- ALT > 5x ULN: 2.1% in the edoxaban group and 4.3% in the SOC group

AST > 3x ULN: 4.1% and 2.8% of subjects in the edoxaban and SOC groups, respectively
ALT or AST 5 > ULN 11% and 8.5% of subject in the edoxaban and SOC groups, respectively (Table 10.8).

On treatment, an adjudicated hepatic event (hepatocellular liver injury occurred in 2 (1.4%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group during the Main Treatment Period plus Extension period

There were no major differences between the groups with regard to elevated liver enzymes and total bilirubin. On treatment during the main treatment and extension periods, 2 (1.4%) subjects in the edoxaban group and 3 (2.1%) in the SOC group had an adjudicated hepatic event (liver injury). During the overall treatment periods, 4 (2.8%) of subjects in the edoxaban group and 3 *(2.1)%) subjects in the SOC group had a hepatic event.

Reviewer Comment: There were no major differences between treatment arms in elevation of liver enzymes and total bilirubin.

8.6.Safety Analyses by Demographic Subgroups

Subgroup Analyses:

During the Main Treatment Period and On-treatment, the adjudicated major and CRNM bleeding event rate was 0.7% higher in the SOC group for subjects 12 to <18 years of age, 2 to <6 years of age, rest of the world region, and index DVT (Table 14.3.1.39). The adjudicated major or CRNM bleeding event rate was 1.4% higher in the SOC group for subjects in the US/Canada region, females, White race, noncritical site of bleeding, and index PE. Numbers in

these subgroups are small and should be interpreted with caution.

During the Main Treatment Period and On-treatment, the adjudicated confirmed major bleeding event rate was 0.7% higher in the edoxaban group for subjects in the Asia/Pacific region, males, Asians, noncritical site of bleeding, and index PE with DVT (Table 14.3.1.40). Numbers in these subgroups are small and should be interpreted with caution

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Cancer was the cause of death for one patient in the SOC arm and no patients in the edoxaban arm.

A 12-year-old male, was randomized to the SOC group. On Day 23, the subject died due to septic shock and its consequences, as a result of chemotherapy-induced neutropenia. Sepsis and respiratory distress syndrome were associated with metastatic endodermal sinus tumor. The final adjudication outcome was reported as death due to infectious disease. This patient entered the trial with a yolk sac tumor (endodermal sinus tumor).

A 17-year-old male randomized to the SOC group also had metastatic cancer. On Day 227, the subject died due to adrenal insufficiency and metastatic adrenocortical carcinoma. The final outcome was death due to cancer. This patient entered the study with adrenocortical carcinoma.

Reviewer Comment: There is no safety signal for tumor development from this trial.

8.8.2. Human Reproduction and Pregnancy

There were no drug exposures to pregnant or lactating women during this study.

8.8.3. Pediatrics and Assessment of Effects on Growth

Assessment of the effect of edoxaban on growth was not performed.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no known abuse potential for anticoagulant agents. There is no data provided for withdrawal or rebound effects in this trial.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

On 4/21/2023, the Applicant submitted labelling supplement S20 where they proposed to incorporate anticoagulant-related nephropathy (secondary to severe bleeding) in the post-marketing experience section 6.2 of the label. This supplement will be acted on separately from this efficacy supplement.

8.9.2. Expectations on Safety in the Postmarket Setting

No indication is being requested or granted. N/A

8.9.3. Additional Safety Issues From Other Disciplines

N/A

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not planned as an indication was not requested.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Section 8.4 of the USPI was revised to reflect the pediatric study conduct and lack of demonstrated efficacy. No new safety issues were identified during the review of this trial, so no new Warnings and Precautions are justified.

10.2. Nonprescription Drug Labeling

N/A.

11. Risk Evaluation and Mitigation Strategies (REMS)

No new REMS appear necessary based upon review of this trial.

12. Postmarketing Requirements and Commitments

This efficacy supplement was the subject of two PMRs:

PMR 2852-1: Perform, complete and submit the full study report for a single-dose study of pharmacokinetics and pharmacodynamics (PK/PD) of edoxaban in pediatric patients at risk for venous thromboembolism (VTE), requiring anticoagulation or recently completing standard of care anticoagulation in accordance with your October 31, 2013 agreed upon Initial Pediatric Study Plan (iPSP).

PMR 2852-2: Perform, complete and submit the full study report for a phase 3 multicenter, randomized, active control study of edoxaban in pediatric patients with documented venous thromboembolism in accordance with your October 31, 2013 agreed upon Initial Pediatric Study Plan (iPSP)

The clinical and clinical pharmacology teams agree that the Applicant fulfilled the requirements of PMR 2852-1 with completion of the single-dose PK/PD study in pediatric patients.

Regarding PMR 2852-2, The Applicant did not follow their SAP or the recommendations from their DMC with regards to enlarging the study based upon the interim analysis that recommended a sample size recalculation to n=422. They terminated the study at 286 patients, thus leaving the study underpowered with a very wide 95% CI with an upper bound that exceeded the NI margin of 1.5.

Additionally, on 03/08/23, the Applicant submitted their Annual Report with PMR/PMC status. In this report, the "explanation of study status" for PMR 2852-1 stated "Study complete" and "submitted" while the status of PMR 2852-2 did not state "study complete" but just "submitted" and described the first subject dosed date and last subject completed date along with the final enrollment numbers. This may indicate that the Applicant understood that they did not complete the trial.

This situation was discussed with the PerC on 09/12/23. The Division asked PerC if they would support our recommendation to not fulfill PMR 2852-2 due to the failure of the Applicant to complete the trial as agreed upon in the PSP and the PMR which reads "Perform, complete, and submit…". The PerC agreed unanimously that they agreed with the conclusion that PMR 2852-2 was not fulfilled. The recommendation is to issue a letter stating that the PMR was not fulfilled.

There appear to be two options with regards to the unfulfilled PMR 2852-2:

1. If feasible, the Applicant could reopen the trial and enroll enough patients to reach 422 subjects (n=136).
2. If not feasible, then the Applicant will need to conduct another study and they should submit a meeting request to discuss their proposed new trial to fulfill the PMR.

13. Appendices

13.1. References

N/A

13.2. Financial Disclosure

The financial disclosure data was reviewed.

Covered Clinical Study (Name and/or Number): DU176b-D-U312

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 661		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 (investigators [redacted] (b) (4)) Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the	Yes ☐	No ☐ (Request explanation

reason:		from Applicant)

Reviewer Comment: The financial disclosures do not appear to impact the results of the trial. Also, since the trial failed to demonstrate the efficacy of edoxaban, the financial disclosures have no impact on the conclusion. No indication is being granted.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIRGINIA E KWITKOWSKI
09/21/2023 10:54:40 AM

JULIA C FRIEND
09/21/2023 12:02:16 PM

SARABDEEP SINGH
09/21/2023 12:13:28 PM

LOLA LUO
09/21/2023 12:15:57 PM

YEH FONG CHEN
09/21/2023 12:43:15 PM