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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/WS2409

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Lixiana	edoxaban	EMA/H/C/002629/WS2409/0042
Roteas	edoxaban	EMA/H/C/004339/WS2409/0029

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step ¹	Description	Planned date	Actual Date	Need for discussion ²
☐	Start of procedure	30 Jan 2023	30 Jan 2023	☐
☐	CHMP Rapporteur Assessment Report	28 Feb 2023	28 Feb 2023	☐
☐	PRAC Rapporteur Assessment Report	03 Mar 2023	03 Mar 2023	☐
☐	PRAC members comments	08 Mar 2023	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	09 Mar 2023	09 Mar 2023	☐
☐	PRAC endorsed relevant sections of the assessment report ³	16 Mar 2023	16 Mar 2023	☐
☐	CHMP members comments	20 Mar 2023	20 Mar 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Mar 2023	23 Mar 2023	☐
☐	Request for supplementary information	30 Mar 2023	30 Mar 2023	☐
☐	Re-start of procedure	14 Aug 2023		☐
☐	CHMP Rapporteur Assessment Report	12 Sept 2023	23 Aug 2023	☐
☐	PRAC Rapporteur Assessment Report	15 Sept 2023	15 Sept 2023	☐
☐	PRAC members comments	20 Sept 2023	20 Sept 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	21 Sept 2023	21 Sept 2023	☐
☐	PRAC endorsed relevant sections of the assessment report ³	28 Sept 2023	28 Sept 2023	☐
☐	CHMP members comments	02 Oct 2023	28 Sept 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Oct 2023	06 Oct 2023	☐
☒	Opinion	12 Oct 2023	12 Oct 2023	☐

¹ Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

² Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

³ Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

LIST OF ABBREVIATIONS

ADME	absorption, distribution, metabolism, elimination
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC _{0-24h,ss}	Area under the concentration-time curve from time zero to 24 hours after dosing in the steady state
AUC _{0-inf}	Area under the concentration-time curve from time zero to infinity
AUC _{0-last}	Area under the concentration-time curve from time zero to the last measurable concentration
BMI	body mass index
CEC	Clinical Events Committee
CI	confidence interval
C _{max}	Maximum (or peak) plasma concentration
C _{max,ss}	Maximum (or peak) plasma concentration at steady state
CL/F	Clearance
CRB	Clinically relevant bleedings
CRNM	clinically relevant nonmajor
CSR	clinical study report
CT	computed tomography
DVT	deep vein thrombosis
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FXa	activated factor X
GCP	Good Clinical Practice
HR	hazard ratio
INR	international normalised ratio
IS	Internal Standard
ISR	Incurred Sample Reanalysis
ISTH	International Society on Thrombosis and Haemostasis
K _a	absorption rate constant
LLOQ	lower limit of quantitation
LMWH	low-molecular weight heparin
MI	myocardial infarction
mITT	modified intent-to-treat
NA	Not applicable
P-gp	P-glycoprotein
PD	pharmacodynamic(s)
PE	pulmonary embolism
PK	pharmacokinetic(s)
PMA	Postmenstrual age
PopPK/PD	Population pharmacokinetic(s)/pharmacodynamic(s)
PP	per protocol
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
QD	Once daily
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCS	Summary of Clinical Safety
SD	Standard Deviation
SEE	systemic embolic event
SOC	standard of care
SP	synthetic pentasaccharide
STD	standard
TBL	total bilirubin
TE	thromboembolic event

TEAE	treatment-emergent adverse event
Tmax	Time of maximum (or peak) plasma concentration
UFH	unfractionated heparin
ULN	upper limit of normal
ULOQ	upper limit of quantitation
US	United States
Vc/F	apparent central volume
V/F	Central volume
VKA	vitamin K antagonist
Vp/F	apparent peripheral volume
VTE	venous thromboembolic event

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Daiichi Sankyo Europe GmbH submitted to the European Medicines Agency on 24 November 2022 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with available paediatric data based on final results from study DU176b-D-U312; this is a phase 3, open-label, randomised, multicentre, 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 paediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE). The Package Leaflet and Labelling are updated accordingly. The RMP version 17.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to bring the PI in line with the latest QRD template version 10.3.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

GLP/GCP inspections

Not applicable.

2. Overall conclusion and impact on the benefit/risk balance

This variation application intends to update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with available paediatric data based on final results from study DU176b-D-U312. This is a phase 3, open-label, randomised, multicentre, 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 paediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE). The Package Leaflet and Labelling are updated accordingly. The RMP version 17.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to bring the PI in line with the latest QRD template version 10.3.

The pharmacokinetics of edoxaban was evaluated in 208 paediatric subjects across 3 clinical studies (Hokusai VTE PEDIATRICS, ENNOBLE-ATE, and a single-dose PK/PD study) using a population pharmacokinetic (PopPK) model. The pharmacokinetic data of 141 paediatric subjects enrolled in Hokusai VTE PEDIATRICS and ENNOBLE-ATE were included in the PopPK analysis. The median exposure of edoxaban in paediatric subjects patients tended to be within the range of exposures observed in adult patients, but there was a 20-30% underexposure in children adolescents aged 12 to <18 years compared to adults who received the edoxaban 60 mg once daily (QD) dose. In Hokusai VTE PEDIATRICS and ENNOBLE-ATE, the observed geometric mean trough exposures of edoxaban in the paediatric population were 7.8 ng/mL in subjects 0 to <6 months of age (N = 9), 8.6 ng/mL in subjects 6 months to <2 years of age (N = 19), 7.4 ng/mL in subjects 2 to <6 years of age (N = 36), 13.7 ng/mL in subjects 6 to <12 years of age (N = 38), and 10.8 ng/mL in subjects 12 to <18 years of age (N = 39). Overall, the PK-PD relationships were similar between paediatric patients from birth to

18 years of age and adult VTE patients. However, the variability in PD generated considerable uncertainty in the assessment of this relationship.

The applicant did not propose a paediatric indication or posology for edoxaban arguing that study DU176b-D-U312 did not meet the primary objective of showing non-inferiority of edoxaban versus SOC on a primary endpoint including symptomatic and VTE. This approach was not endorsed initially, as the pivotal study did not show apparently a lack of efficacy of edoxaban or safety signal in children, and EMA rules allow extrapolation of the efficacy of a medicinal product from adults to children by means of an extrapolation exercise (EMA/199678/2016). In addition, the Paediatric Addendum on VTE prophylaxis and treatment does not require a formal hypothesis of non-inferiority at the time of designing VTE paediatric phase III trials (EMA/CHMP/763438/2017). Therefore, it was considered during the first round that a paediatric indication and posology might be feasible even if study DU176b-D-U312 did not meet its primary objective.

In the response to CHMP questions, the applicant provided and discussed some key pitfalls of the paediatric development of edoxaban in children. Regarding dose and posology, similar exposure as obtained in adults was NOT achieved using the proposed dose regimen of edoxaban tablets in subjects 12 to <18 years of age (rather, it could lead to an approximately 20% to 30% underexposure). This was translated into a higher annualized rate of recurrent symptomatic VTE with edoxaban vs. SOC in the meta-analysis provided in response to Q10 of the RSI (15.6% vs. 6.4% in the study U312 in children), while in the adult study U305, the trend was the opposite in favour of edoxaban (3.5% vs. 3.9%). In addition, in sensitivity analyses, using the endpoint of symptomatic recurrent VTE as defined in the EINSTEIN-Jr study, edoxaban would have been declared inferior to SOC with statistical significance (HR: 2.34; 95% CI: 0.453 to 12.054) (see also assessment of the MAH answer to Q11). Therefore, a potential lack of efficacy of edoxaban due to underexposure in children at the doses tested in study U312 is a real possibility.

In addition, it is unknown whether the tablet and granule formulations are bioequivalent in patients younger than 12 years. There are inadequate PK/PD, efficacy, or safety data to support the use of the edoxaban 30 mg or 15 mg tablets in patients younger than 12 years of age. As a result, establishing a paediatric posology is challenging and subject to significant uncertainty with the data available, and an extrapolation exercise of the efficacy from adults is fraught with risk. Finally, there are several treatment options for paediatric VTE (i.e.: rivaroxaban, dabigatran, heparins and VKAs). Given the treatment options available for paediatric patients and the uncertainty that edoxaban offers at least an equivalent benefit to SOC in this patient population, the MAH does not consider that a recommendation for formulation development is warranted (see assessment of the MAH answer to Q10 of the RSI).

It is unfortunate that the paediatric PIP has failed in achieving the goal of establishing an appropriate effective and safe dose that provides a similar edoxaban exposure as in adults. Given the uncertainties about the benefit-risk profile of edoxaban in the paediatric population and the difficulties in establishing an appropriate paediatric dose, the CHMP shares the MAH proposal of not recommending the use of edoxaban in children.

Regarding changes to the product information, the CHMP agrees with the MAH proposal of not pursuing a paediatric indication and posology, as well as not proposing a line extension for a paediatric formulation (granules for oral suspension used in paediatric trials in children aged < 12 years). However, some amendments have been implemented by the MAH in sections 4.8, 5.1 and 5.2.

The benefit-risk balance of Lixiana/Roteas, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with available paediatric data based on final results from study DU176b-D-U312; this is a phase 3, open-label, randomised, multicentre, 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 paediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE). The Package Leaflet and Labelling are updated accordingly. The RMP version 17.0 has also been submitted. In addition, the MAH took the opportunity to clarify that edoxaban tablets can be delivered through a nasogastric tube in Section 4.2 of the SmPC, to implement editorial changes in the SmPC and to bring the PI in line with the latest QRD template version 10.3.

☒ is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan for Lixiana/Roteas (Decision number: P/0423/2021) (PIP number: EMEA-000788-PIP02-11-M11) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Following the review of paediatric data it was concluded that edoxaban is not recommended for use in children and adolescents from birth to 18 years of age with confirmed VTE (PE and/or DVT) event as the efficacy has not been established. Available data in VTE patients are described in sections 4.8, 5.1 and 5.2. For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Edoxaban (as tosilate) is an orally active, selective, direct, and reversible inhibitor of activated coagulation factor X (FXa) that was developed as an anticoagulant agent.

The edoxaban (Lixiana®) Marketing Authorisation was granted by the European Commission on 19 Jun 2015. In addition, Roteas® was approved on 19 Apr 2017 as informed consent approval to Lixiana. Lixiana and Roteas are approved for the following indications in the European Union:

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with 1 or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke, or transient ischaemic attack
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

Currently, edoxaban is authorised in 67 countries and is marketed in 59 countries worldwide. Cumulatively, from the international birth date through to the end of first quarter 2022, a total of 884,920 patients are estimated to have received edoxaban for the orthopaedic surgery indication (approved in Japan) and 7,885,754 patient-years of edoxaban exposure for nonvalvular atrial fibrillation and venous thromboembolic event (VTE) indications.

This Clinical Overview Addendum provides data to support the Type II variation application in order to update the Summary of Product Characteristics with clinical paediatric data.

The current standard of care for the treatment of VTE in children is unfractionated heparin (UFH) or low molecular weight heparin (LMWH) administered for 5-7 days usually followed by (at least) three months of LMWH or oral anticoagulation with a vitamin K antagonist (VKA) [4,10,11]. The duration of anticoagulation treatment must take into consideration the differences in risk and benefit that may vary with the cause of the VTE (e.g.: idiopathic versus CVC-associated VTE), the age of the patient, and whether or not the conditions that triggered the VTE are still present (e.g.: removal of the CVC line). In the absence of large randomized controlled trials, and with much of our current understanding of PK extrapolated from adult studies, ideal dosing for anticoagulation in critically ill neonates remains uncertain.

The important disadvantage of LMWHs, particularly in children, is administration by subcutaneous injections [Bidlingmaier et al. *Semin Thromb Hemost.* 2011;37:814-25]. Vitamin K antagonists have a delayed onset of action, narrow therapeutic index, unpredictable pharmacologic response, and multiple food and drug interactions and therefore require frequent therapeutic monitoring [Monagle et al. *Hematology Am Soc Hematol.* 2018;2018:399-404]. Direct oral anticoagulants overcome many of the above limitations. Direct oral anticoagulants, including edoxaban, can be administered orally, are antithrombin independent, have a rapid onset and offset of action, have few drug and food interactions, and have predictable pharmacokinetics (PK) with no need for routine monitoring of anticoagulation activity [Albiseti et al. *Hämostaseologie.* 2020;40:64-73].

Although paediatric patients are at less risk than adults for the development of a VTE, embolic disease does occur and is well described in children and adolescents with or without risk factors. Thrombosis is an increasingly recognised complication occurring primarily in children with serious underlying conditions and most often associated with intravenous catheters [Young et al. *Pediatr Blood Cancer.* 2006].

The description of studies included in this application is shown in Table 1 below.

All studies are included in module 5 of sequence 96 with an exception: study U313 is mentioned several times in the dossier and described in the Summaries of Clinical Efficacy and Safety but the CSR was included in sequence 92 and assessed in a previous P46 procedure. It has not been included in sequence 96 corresponding to current WS procedure.

Table 1. Description of Studies Included in This Application

Study Type	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Extrinsic Factor PK	A-U154 Module 5.3.1.1 (sequence 96)	To characterize the PK, bioavailability, and food effects of a liquid oral formulation of edoxaban	Phase 1, randomised, open-label, 3-treatment, 3-way crossover	Edoxaban PO: 2 × 30 mg 60 mg (granules for oral suspension)	24	Healthy subjects	Single dose × 3	Completed CSR (sequence 96)
PK/PD	A-U157 Module 5.3.4.2 (sequence 96)	To evaluate PK and PD of edoxaban in paediatric subjects	A Phase 1, open-label, single-dose, nonrandomised	Edoxaban PO: 30 mg, 60 mg (2 × 30 mg), Cohort 1; granules for oral suspension up to 60 mg dose, Cohorts 2 to 5	66	Subjects 0 (38 weeks gestational age) to <18 years of age of both sexes, who may require anticoagulation therapy	Single dose	Completed CSR (sequence 96)

Study Type	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, PD, efficacy, and safety	D-U312 Module 5.3.5.1 (sequence 96)	To evaluate PK and PD of edoxaban and to compare the efficacy and safety of edoxaban to standard of care anticoagulant therapy in children from birth <18 years with confirmed VTE	Randomised, open-label, blinded-endpoint-evaluation, parallel-group, multicentre, controlled	Subjects assigned to the edoxaban group were treated after a heparin lead-in phase with the following oral dosage forms: • Edoxaban 15 and 30 mg tablets; or • Edoxaban granules for reconstituted oral suspension (60 mg reconstituted in 8 mL water to provide a 6 mg/mL liquid suspension)	290 Edoxaban: 147 SOC: 143	Male and female children from birth (38 weeks gestational age) to <18 years of age with confirmed VTE	Minimum 4 months and maximum 13 months	Completed CSR (sequence 96)

Study Type	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and efficacy	C-U313 Module 5.3.5.1 (sequence 92)	To evaluate safety and efficacy of edoxaban in paediatric subjects with cardiac disease at risk of thrombosis.	Open-label randomised, multicentre, parallel-group observational trial	Edoxaban tablets or granules for suspension formulation for oral use, weight-dependent doses as follows: • Fixed dose for subjects in age cohort 12 to <18 years of age depending on whether the subject's weight is more or less than 60 kg • Per mg/kg dose for subjects <12 years of age	168 Edoxaban: 110 SOC: 58	Male and female children from birth (38 weeks gestational age) to <18 years of age with underlying cardiac diseases at risk of thromboembolic complications requiring anticoagulation therapy (either primary or secondary prevention) for a minimum of 3 months	A minimum of 3 months of treatment with extension up to at least 12 months	Completed CSR (sequence 92)

6. Clinical Pharmacology aspects

The Paediatric Investigation Plan for edoxaban includes two Phase 3 safety and efficacy studies and one supporting Phase 1 PK/pharmacodynamics (PD) study conducted in paediatric subjects:

- Study DU176b-D-U312 (Hokusai-VTE Paediatrics Study, hereafter referred to as Study U312), a pivotal Phase 3, open-label, event-driven, randomised, multicentre, controlled study aiming to evaluate the PK and PD of edoxaban and to compare the efficacy and safety of edoxaban with standard of care (SOC) anticoagulant therapy in paediatric subjects from birth to <18 years of age with confirmed VTE
- Study DU176b-C-U313 (ENNOBLE-ATE Study, hereafter referred to as Study U313), a supporting Phase 3, open-label, randomised, parallel-group, multicentre, observational study aiming to evaluate the safety and efficacy of edoxaban in children from birth (38 weeks of gestation) to <18 years of age with cardiac diseases at risk of thromboembolic events (TEs).
- Study DU176b-A-U157 (hereafter referred to as Study U157), a supporting Phase 1, open-label, single-dose, nonrandomised, multicentre study in paediatric subjects <18 years of age aiming to

evaluate the PK and PD of edoxaban following a single dose oral administration of edoxaban tablets and granules.

The number of enrolled subjects by age cohort in each of the 3 paediatric studies (U312, U313, and U157) is shown in Table 1.1.

Table 1.1: Enrolment by Age Cohort in Studies U312, U313, and U157

Age Cohorts (age on the day of dosing)	Number of Subjects		
	Study U157	Study U312 ^a	Study U313 ^b
12 to <18 years of age	15	169	44
6 to <12 years of age	13	45	57
2 to <6 years of age	13	31	51
6 months to <2 years of age ^c	13	29	-
1 to <2 years of age	NA	NA	9
6 months to <1 year of age	NA	NA	3
Birth (38 weeks of gestation) to <6 months of age	12	16	4
Total	66	290	168

NA = not applicable

Four randomised subjects did not receive study drug; 2 subjects 12 to <18 years, 1 subject 6 to <12 years, and 1 subject 6 months to <2 years; Module 5.3.5.1 DU176b-D-U312 CSR [Listing 16.2.1.2](#).

One subject 2 to <6 years did not receive study drug (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.1.2.1](#))

In Study U313, age cohort 6 months to <2 years comprised 2 sub-cohorts: age 1 to <2 years of age and 6 months to <1 year of age.

A population pharmacokinetic/pharmacodynamic (PopPK/PD) analyses of paediatric data from 3 clinical studies (DU176b-D-U312, DU176b-C-U313 and DU176b-A-U157,) were conducted to characterise paediatric pharmacokinetic (PK) and PK/pharmacodynamic (PD) and to compare the PK and PK/PD data between paediatric patients and adult VTE patients from Study DU176b-D-U305.

In addition, a bioavailability and food effect study using edoxaban granules for oral suspension and edoxaban tablets was conducted in healthy adult subjects:

- Study DU176b-A-U154, a Phase 1, open-label, randomised, 3-treatment, 3-way crossover study in healthy adult subjects conducted to assess the relative bioavailability and food effect for a novel liquid oral suspension of edoxaban.

6.1. Bioanalytical methods

The bioanalytical method employed in the submitted bioequivalence and food effect study (DU176b-A-U154) is not defined because the bioanalytical report has not been submitted. This deficiency is not relevant at this stage because that formulation is not intended to be marketed.

The conducted population PKPD analyses of edoxaban involves paediatric patients in Studies DU176b-A-U157, DU176b-D-U312, and DU176b-C-U313. In study DU176b-A-U157 (Edoxaban Population Pharmacokinetic Analysis To Support Dose Selection in Pediatric Study) the plasma concentrations of DU-176b (edoxaban) and the metabolite D21-2393 (edoxaban 4-carboxylic acid) were analysed, but also those of other analytes (D21-3231, D21-1402, and D21-2135) that have not been considered in

the PopPK analysis and, therefore, they are not considered relevant and are not described in this report. In studies DU176b-D-U312 and DU176b-C-U313 the plasma concentrations of DU-176b (edoxaban) and the metabolite D21-2393 (edoxaban 4-carboxylic acid) were analysed. Therefore, the bioanalytical method for the measurement of these two analytes is described in the present report.

The plasma concentrations of DU-176b (edoxaban) and the metabolite D21-2393 (edoxaban 4-carboxylic acid) were measured in these three studies with the bioanalytical method no. 140524DEN176HPL_S_V5, which had been validated in the Validation Report 07670VDAC_DEN_R1 and Partial Validation Reports 080091PVKLN_DEN_R2 and 140524PVRM_DEN_R1. The first two reports have been assessed previously during the initial marketing authorisation application. The metabolites D21-3231, D21-1402 and D21-2135 were measured with the bioanalytical (Summary 140523DEN176HPL_S_V4. 09 December 2015, 151259DEN176HPL_S_V1. 12 February 2016 and 151259DEN176HPL_S_V2. 19 April 2017) that had been validated in the Validation Report 080272VDMW_DEN_R1, which was assessed in the initial marketing authorisation application (see Day 80 report).

As the validation of these methods have been previously assessed, the present report describes the in-study validations or the analyses of the study samples in these studies.

Study DU176b-A-U157 (Edoxaban Population Pharmacokinetic Analysis To Support Dose Selection in Pediatric Study)

The bioanalytical report 141052AKR_DEN for the parent and the metabolite D21-2393 is dated on the 15 December 2021. The Quality assurance unit of the CRO conducted audits on this study and the Quality Assurance (QA) Statement is submitted.

The objective of this study was to determine the concentrations of DU-176 (free form of DU-176b) and D21-2393 (M4 main active metabolite) in human plasma samples collected during the clinical study DU176b-A-U157. Lithium heparinized human plasma samples were analysed using a specific solid-phase extraction procedure and turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS) according to method 140524DEN176HPL_S_V5, which is attached as Appendix A. DU-176- d_6 and D21-2393- d_3 were used as Internal Standard (IS).

Twenty-nine runs were employed for the analysis of DU176b and 5 runs were rejected. Thirty runs were employed for the analysis of D21-2393 and 5 runs were rejected. The calibration range was 0.764 to 382 ng/mL for DU-176 and 0.0792 to 7.92 ng/mL for D21-2393, respectively.

All samples of the same subject were assayed in the same batch and in order of ascending time point (PK profile order) when possible. Prior to conducting a sample analysis run, a system suitability test, consisting of a 15- μ L system suitability sample, and a carryover evaluation, consisting of an extracted zero sample, an extracted sample at the lower limit of quantitation (LLOQ), an extracted sample at the upper limit of quantitation (ULOQ), and a double blank sample, were injected to check the chromatographic performance of the system. The injection sequence consisted of one set (complete range of concentrations) of calibration standards at the beginning and one at the end of each analytical batch (i.e., duplicates of each concentration, one at the beginning and one at the end). Quality Control (QC) samples were distributed throughout the study samples. Study samples and QC samples were bracketed between the two sets of calibration standards. Matrix blanks ($n \geq 2$) and matrix blank samples containing internal standard ($n \leq 10$) were included in each run. Selectivity samples were positioned after the carryover samples at the beginning of a run.

The within-run carryover evaluation did not meet acceptance criteria in the following runs: Runs 37, 38, and 56 for DU-176, and Run 51 for D21-2393. In each case, a sample-by-sample carryover assessment was conducted for the relevant analyte. These assessments found no study samples showing $>2.0\%$ possible contribution from the preceding sample.

In Runs 11, 12, and 57, the Carryover LLOQ injection did not meet acceptance for D21-2393 only. Per Bioanalysis Study Plan, sample by sample carryover assessments were performed, and no samples were affected. Overall carry-over for these runs was acceptable.

Per Bioanalysis Study Plan, a sample by sample carryover assessment was performed following the in-run carryover assessment for Run 19. One sample was identified as being impacted by carryover. However, the sample had a BLQ result. Therefore, carryover was considered acceptable and controlled.

The in-run carryover assessment for Run 20 found a sample isolated from impact by carryover with the mitigation zeroes surrounding the sample successfully mitigating carryover to acceptable levels. However, pre- and post- run carryover assessments failed; therefore, a sample by sample carryover assessment was performed, and no study samples were found to be impacted by carryover.

Carryover in the zero sample immediately following the first standard curve in Run 30 was >20.0% of the mean LLOQ response for D21-2393 prompting a sample by sample carryover assessment. No study samples showing >2.0% possible contribution from the preceding sample were identified.

The last five wells of the carryover assessment for Run 35 had no acquired data. As a precaution, a sample by sample assessment was performed assuming worst case scenario based on carryover data produced. No potential impact on study samples was observed.

Assay carryover was appropriately assessed throughout the study and found to be justifiable for batch acceptance. Samples were assayed in the order of PK time points. Thus, there was no significant sample-to-sample concentration change, which helped to limit the impact of any carryover effect.

The average response of the IS was determined for the standards and QC samples in each run. Any study sample with an IS response that was greater than 150.0% of the mean IS response or less than 50.0% of the mean IS response in the standard and QC samples was evaluated to determine if repeat analysis was necessary. No IS-associated repeat analysis was needed.

There were no unexpected experimental results during this study.

There were no modified integrations performed for the current study.

Run 18 was rejected for D21-2393 and DU-176b with assignable cause due to unacceptable chromatography. This run successfully re-extracted and repeated as Run 19, following a column change and instrument troubleshooting.

Run 24 was rejected for DU-176b with unassignable cause due to QC failure. The calibration standard curve exhibited a somewhat exaggerated quadratic fit which may have impacted the QC1 level. Study samples from Run 24 were repeated in Run 25, which was acceptable.

Run 37 was rejected for D21-2393 with unassignable cause. QC5 was unacceptable and the IS failed to adequately track with the analyte. Study samples from Run 37 were repeated with new QC preparations.

Run 39 was rejected for D21-2393 with unassignable cause due to QC failure. The root cause of the failure was unknown. Study samples from Run 39 were repeated in Run 40, which was acceptable.

Run 42 was rejected for DU-176b with assignable cause. The analyte was overly quadratic, causing the failure of QC5. The cause of failure was determined to be due to extraction. Study samples from Run 42 were repeated in Run 43, which was acceptable.

Run 45 was rejected for DU-176b with assignable cause due to a curve preparation error. Additionally, the dilution QCs in the run failed for both analytes. All diluted study samples were deactivated and repeated in a subsequent run.

Run 50 was rejected for D21-2393 with no assignable cause. QC4 failed with no cause of failure determined. Run 52 was rejected for both analytes with no assignable cause. There was a positive curve bias observed for DU-176b relative to pre-qualified QCs. It was hypothesized that a Carryover LLOQ QC may have been aliquoted in place of QC1, contributing to the overall QC failure.

A total of 45 samples for DU-176b and 44 samples for D21-2393 were re-assayed for Incurred Sample Reanalysis (ISR). Results for the parent drug were acceptable, with 43 out of 45 samples (95.6%) providing acceptable ISR results. The results of the incurred sample reanalysis for D21-2393 were acceptable, with 41 out of 44 samples (93.2%) providing acceptable ISR results.

Chromatograms from Runs 1 and 33 for at least 20% of the study subjects (along with the corresponding standards and quality control samples) are shown in Appendix E.

Assessor's comments:

585 samples (including 259 duplicates) were received from 4 May 2017 to 27 Sep 2021 from Samples were stored at -20°C. 320 samples (including 37 samples of cohort 5) were analysed. Samples were analysed as received, within the established freezer stability limit of 793 days at -20 °C. The longest storage duration as calculated on an individual sample basis was: 22 August 2015 (collection date) to 25 July 2017 (sample analysis date) = 703 days.

All lots of compounds used in Study DU176b-A-U157 were used within established expiration dates as noted on the Certificates of Analysis.

The calibration curves of DU-176b contained 10 concentration levels in duplicate. One calibrator failed in two runs (25 and 39) and both calibrators of the standard (STD), 3 failed in run 31. None was the LLOQ or the ULOQ. The Inter-run accuracy and precision of the valid calibrators was acceptable.

The calibration curves of D21-2393 contained 7 concentration levels in duplicate. Both calibrators of the STD 3 failed in two runs (31 and 40). In run 56 one replicate of STD 1 and 2 failed. But the range was not changed since one was acceptable. The Inter-run accuracy and precision of the valid calibrators was acceptable.

The regression was quadratic ($\text{Response} = A * (\text{Concentration}^{**2}) + B * \text{Concentration} + C$) for DU-176b and linear for D21-2393.

The QCs of the valid runs passed the acceptance criteria. Four QC levels were tested with three or four replicates per concentration level. The failed QCs have not been highlighted but it has been checked that not more than 50% per QC level failed (e.g. run 39, 27, 50) and more than 2/3 of QCs are within the 15% acceptance range. However, for dilution QCs there were several failures. In run 6, 2 out of 3 failed. In run 30 and 31, 3 out of 3 Dilution QC failed. In run 50, 4 out of 4 Dilution QC failed. Therefore, the 4-fold dilution is not valid in those runs. In Runs 6, 30, 31, and 50, DilQC4 did not meet acceptance criteria for DU-176b. All diluted samples in the runs were deactivated and repeated at the appropriate dilution in a subsequent run. Therefore, this deficiency was handled appropriately.

The number of samples per run is not defined and in some runs there is mixture of subjects samples, reanalysis and ISR, which makes impossible to know the number of samples per run in all runs. Later on during the procedure, the applicant confirmed that the number of QCs included per run was sufficient to cover the number of study samples analysed per run.

Five samples were repeated for DU-176b because of the concentration was >ULOQ in 2 cases or original diluted concentration <LLOQ in 3 cases. These reasons are considered acceptable. Eighteen samples were repeated for D21-2393 because of the concentration was >ULOQ in 7 cases or original diluted concentration <LLOQ in 11 cases. These reasons are considered acceptable.

The number of samples that needed to be repeated because concentrations were >ULOQ was low. However, this is because dilution of samples was conducted also during the original analysis of study samples. Some of them were <LLOQ because of excessive dilution. The number of samples that were reported after dilution has not been reported. The range may not be optimal for the analytes. It could be questioned if the calibration range covered the concentrations of the study adequately, but this deficiency is not critical as to reject the study. The QC levels were representative of the calibration range since two MQCs were used at 45.8 and 153 ng/ml in addition to the LQC of 2.29 ng/ml and 306 ng/ml for the HQC for the parent and for the metabolite LQC: 0.238 ng/ml, MQC1: 0.950 ng/ml, MQC2: 3.17 ng/ml and HQC: 6.34 ng/ml.

No sample was re-injected or re-integrated in this study.

ISR was conducted in 45 and 44 out of 320 samples, respectively. 14% is more than the 10% required by the guideline. In addition ISR is not necessary in all studies, like this one. 95.6% and 93.2%, respectively, of the samples differed less than 20%, which is more than the acceptance limit of 66.7%.

Runs 1 and 33 contains chromatograms from subjects. 11 subjects are 16.6% of the 66 subjects of study DU176b-A-U157. This value does not represent 20%, but can be considered acceptable because 20% is required only for bioequivalence studies. For other studies only representative chromatograms should be appended to the report. This representative chromatograms have been submitted.

During the procedure, the MAH provided a list of the FDA inspections conducted in the bioanalytical site located at 19 Brown Road, Ithaca, New York. The latest inspection was conducted in June 2018, and concluded with no findings. This is acceptable.

In study DU176b-D-U312 (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)) the plasma concentrations of DU-176 and D21-2393 were measured with the bioanalytical method 140524DEN176HPL_S_V5, which is the same bioanalytical method employed in the previous study.

The bioanalytical report 160607ASMG_DEN for the parent and the metabolite D21-2393 is dated on the 15 July 2022. The Quality assurance unit of the CRO conducted audits on this study and the QA Statement is submitted.

The objective of this study was to determine the concentrations of DU-176 (free form of DU-176b) and D21-2393 in human plasma samples collected during the clinical study DU176b-D-U312. Lithium heparinized human plasma samples were analysed using a specific solid-phase extraction procedure and turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS). according to method 140524DEN176HPL_S_V5, which is attached as Appendix A. DU-176-d₆ and D21-2393-d₃ were used as IS.

Nineteen runs were employed for the analysis of DU176b and D21-2393. The calibration range was 0.764 to 382 ng/mL for DU-176 and 0.0792 to 7.92 ng/mL for D21-2393, respectively.

All samples of the same subject were assayed in the same batch and in order of ascending time point (PK profile order) when possible. Prior to conducting a sample analysis run, a system suitability test, consisting of a 30-µL system suitability sample, and a carryover evaluation, consisting of an extracted zero sample, an extracted sample at the LLOQ, an extracted sample at the ULOQ, and a double blank sample, were injected to check the chromatographic performance of the system. The injection sequence consisted of one set (complete range of concentrations) of calibration standards at the beginning and one at the end of each analytical batch (i.e., duplicates of each concentration, one at the beginning and one at the end). QC samples were distributed throughout the study samples. Study samples and QC samples were bracketed between the two sets of calibration standards. Matrix blanks (n≥2) and matrix blank samples containing internal standard (n≤10) were included in each run. Selectivity samples were positioned after the carryover samples at the beginning of a run.

Extra zero samples (mitigation zero samples) were inserted into the Watson worklist after the high standards and QC samples as a precaution against the impact of carryover on the data. Additionally, the study samples were assayed in pharmacokinetic (PK) order.

The within-run carryover evaluation did not meet acceptance criteria in Runs 7, 9, 14, 16, 18, and 19 for D21-2393. In each case, a sample-by-sample carryover assessment was conducted for the relevant analyte. One sample in Run 16, Day 5 0h, was determined to have >2.0% possible contribution from the preceding sample. This sample was deactivated and repeated in a Run 18.

In Runs 20 and 21, carryover >20.0% of the mean LLOQ response was observed for D21-2393 in the first reconstitution blank in the run, prompting a sample-by-sample carryover assessment. No study samples reported from these runs had >2.0% possible contribution from the preceding sample.

Assay carryover was appropriately assessed throughout the study and found to be justifiable for batch acceptance. Samples were assayed in the order of PK time points. Thus, there was no significant sample-to-sample concentration change, which helped to limit the impact of any carryover effect.

The average response of the IS was determined for the standards and QC samples in each run. Any study sample with an IS response that was greater than 150.0% of the mean IS response or less than

50.0% of the mean IS response in the standard and QC samples was evaluated to determine if repeat analysis was necessary.

In Run 13, one sample, Day 5 0.5h, included as an analytical repeat, had D21-2393 internal standard response >150.0%. This sample was deactivated and repeated in Run 16.

A total of 43 samples for DU-176 and D21-2393 were re-assayed for ISR.

In Run 1, ten pre-dose study samples had >LLOQ results for both analytes. At the request of the sponsor these samples were repeated in duplicate in Run 3, and again using the back-up samples in Run 4. The original results were confirmed and reported.

In Run 6 the QC5 sample did not meet acceptance criteria for D21-2393. This QC had been previously qualified for use in sample analysis but had been showing a trend toward increasing positive bias. A new QC5 sample was prepared and qualified following this run using a preparation scheme that minimized the amount of organic solvent in the preparation. All samples from this run were repeated for D21-2393 in Run 7.

The QC3 sample in Run 10 did not meet acceptance criteria for DU-176. The DU-176 calibration curve was atypically quadratic in this run and this contributed to the QC failure.

In Run 11, the QC5 sample did not meet acceptance criteria for D21-2393 and the run was rejected for this analyte. There was a drop in internal standard response at this QC level which is typical for the method but was more pronounced in this run. The impacted samples were reanalyzed for D21-2393 in Run 13.

In Run 13 it appears the third and fourth replicates of the QC2 and DilQC4 samples were aliquoted in reverse order however this could not be confirmed. The run was analytically acceptable. A similar aliquoting issue appears to have occurred in Run 15 for the fourth replicate of the QC2 sample and the third replicate of the QC3 sample. This run was also analytically acceptable. This had no impact on the results for this study.

In Run 14, review of the run data indicated the calibration standard curve was prepared high for DU-176 and QC samples showed a negative bias. The run was rejected for this analyte. All samples from this run were repeated for this analyte in Run 15.

Run 20 was rejected for DU-176 as the QC1 sample did not meet the acceptance criteria. No cause was determined.

Run 22 was rejected for D21-2393. The QC1 sample did not meet acceptance criteria and no cause was determined. It was noted that overall signal for this analyte was low in the run. All samples from this run were repeated for D21-2393 in Run 22.

All samples were repeated for DU-176 in Run 11.

There were no modified integrations performed for the current study.

The results of the incurred sample reanalysis for DU-176 were acceptable, with 37 out of 43 samples (86.0%) providing acceptable ISR results. The results of the incurred sample reanalysis for D21-2393 were acceptable, with 42 out of 42 samples (100.0%) providing acceptable ISR results.

The total number of ISR included for D21-2393 analysis was 43; however, when ISR was assessed in Run 8, one sample, Day 5, 0.5 hour, which was diluted for the original analysis but analyzed undiluted for the ISR assessment, had a result >ULOQ. This sample was considered unreportable for ISR. The 42 remaining ISR met the total number for assessment as required. Overall ISR was acceptable for both analytes.

Chromatograms from Run 1 for at least 5% of the study subjects (along with the corresponding standards and quality control samples).

Assessor's comments:

196 samples (including 49 duplicates) were received from 26 Apr 2017 to 25 Feb 2023, from 15 Jun 2017 to 24 July 2017 from 15 Aug 2018 to 27 Dec 2018, from 28 Feb 2019 to 17 Dec 2021 from 31

Oct 2019 to 8 Feb 2021, and the 13 Jan 2020, from 13 Oct 2021 to 8 Dec 2021 Samples were stored at -20°C. 147 samples were analysed. Samples were analysed as received, within the established freezer stability limit of 793 days at -20 °C. The longest storage duration as calculated on an individual sample basis was: 23 January 2018 (collection date) to 08 November 2018 (sample analysis date) = 289 days.

All lots of compounds used in Study DU176b-D-U312 were used within established expiration dates as noted on the Certificates of Analysis (see Appendix B) with the exception of internal standard D21-1553, lot D21-1553-01. Internal standard reference compounds do not require expiration or retest dates and may be used beyond any such dates if no interferences are observed in blank and zero samples and chromatographic peak response is adequate for the method. The internal standard reference compound for DU-176 (D21-1553; DU-176-d₆) was used beyond its expiration date to prepare the internal standard working solution used in Runs 23 and 24 of this study. DU-176 internal standard response was typical and no interferences were observed.

The calibration curves of DU-176b contained 10 concentration levels in duplicate. One calibrator was removed due to low analyte response and IS response, but the other replicate of the LLOQ was valid. In run 22 the two replicates of STD 8 failed, which did not affect the range. The Inter-run accuracy and precision of the valid calibrators was acceptable.

The calibration curves of D21-2393 contained 7 concentration levels in duplicate. One of the replicates of the LLOQ failed in 2 runs and in another it was removed due to low analyte and IS response. The other replicate was valid and the range was not altered. The Inter-run accuracy and precision of the valid calibrators was acceptable.

The regression was quadratic ($\text{Response} = A * (\text{Concentration}^2) + B * \text{Concentration} + C$) for DU-176b and linear for D21-2393.

The QCs of the valid runs passed the acceptance criteria both for the analyte and the metabolite. Four QC levels were tested with three or four replicates per concentration level. The failed QCs have not been highlighted but it has been checked that not more than 50% per QC level failed (e.g. run 11, 13, 15, 17) and more than 2/3 of QCs are within the 15% acceptance range. However, for dilution QCs (ten-fold dilution) in run 16, 3 out of 4 QCs failed. In run 13 only 2 out of 4. That run dilution was then acceptable. The inter-run precision failed for the metabolite QC2 and DilQC. This was due to outlier values. After excluding these few values the precision and accuracy was acceptable.

It is not possible to know if the number of QCs are adequate with respect to the total number of study samples because although 12 or 16 QCs are used per run, the number of study samples per run are not defined in the bioanalytical study report. Later on during the procedure, the applicant confirmed that the number of QCs included per run was sufficient to cover the number of study samples analysed per run.

Eleven samples were repeated for DU-176 because of the concentration was >ULOQ in 1 case or 10 because reanalysis was requested by the sponsor due to PK outlier, but the initial values were reported finally. Then, the reported results are considered valid.

Twenty samples were repeated for D21-2393 because of the concentration was >ULOQ in 8 cases or original diluted concentration <LLOQ in 2 cases. In 10m cases the PK repeat was caused by the outlier values, but the initial results were finally reported. This is considered acceptable.

The number of samples that needed to be repeated because concentrations were >ULOQ was low. However, this is because dilution of samples was conducted also during the original analysis of study samples. Some of them were <LLOQ because of excessive dilution. The number of samples that were reported after dilution has not been reported. The range may not be optimal for the analytes. It could be questioned if the calibration range covered the concentrations of the study adequately, but this deficiency is not critical as to reject the study.

The QC levels were representative of the calibration range since two MQCs were used at 45.8 and 153 ng/ml in addition to the LQC of 2.29 ng/ml and 306 ng/ml for the HQC for the parent and for the metabolite LQC: 0.238 ng/ml, MQC1: 0.950 ng/ml, MQC2: 3.17 ng/ml and HQC: 6.34 ng/ml.

No sample was re-injected or re-integrated in this study.

ISR was conducted in 43 of 1968 samples, respectively, which are more than 10% and they passed the acceptance criteria.

Representative chromatograms have been submitted.

In study DU176b-D-U313 (An Open-Label, Randomized, Parallel-Group, Multicentre, Observational Trial to Evaluate Safety and Efficacy of Edoxaban Tosylate in Children from 38 Weeks Gestational Age to Less Than 18 Years of Age with Cardiac Diseases at Risk of Thromboembolic Events) the plasma concentrations of DU-176b (edoxaban tosylate) and the metabolite D21-2393 (edoxaban 4-carboxylic acid) were measured with the bioanalytical method no. 140524DEN176HPL_S_V5, which is the same bioanalytical method employed in the previous studies.

The bioanalytical report 180260AKR_DEN for the parent and the metabolite D21-2393 is dated on the 15 14 April 2022. The Quality assurance unit of the CRO conducted audits on this study and the QA Statement is submitted.

The objective of this study was to determine the concentrations of DU-176 (free form of DU-176b) and D21-2393 in human plasma samples collected during the clinical study DU176b-C-U313. Lithium heparinized human plasma samples were analyzed using a specific solid-phase extraction procedure and turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS) according to method 140524DEN176HPL_S_V5, which is attached as Appendix A. DU-176-d6 and D21-2393-d3 were used as IS.

Eight runs were employed for the analysis of DU176b and D21-2393 and 1 run was rejected. The calibration range was 0.764 to 382 ng/mL for DU-176 and 0.0792 to 7.92 ng/mL for D21-2393, respectively.

All samples of the same subject were assayed in the same batch and in order of ascending time point (PK profile order) when possible. Prior to conducting a sample analysis run, a system suitability test, consisting of a 30-µL system suitability sample, and a carryover evaluation, consisting of an extracted zero sample, an extracted sample at the LLOQ, an extracted sample at the ULOQ, and a double blank sample, were injected to check the chromatographic performance of the system. The injection sequence consisted of one set (complete range of concentrations) of calibration standards at the beginning and one at the end of each analytical batch (i.e., duplicates of each concentration, one at the beginning and one at the end). QC samples were distributed throughout the study samples. Study samples and QC samples were bracketed between the two sets of calibration standards. Matrix blanks (n≥2) and matrix blank samples containing internal standard (n≤10) were included in each run. Selectivity samples were positioned after the carryover samples at the beginning of a run.

The within-run carryover evaluation did not meet acceptance criteria in the following runs: Run 2 for D21-2393. In each case, a sample-by-sample carryover assessment was conducted for the relevant analyte. These assessments found no study samples showing >2.0% possible contribution from the preceding sample.

A sample by sample carryover assessment was performed following the in-run carryover assessment for Run 8. Three samples were identified as being impacted by carryover in Run 8. The affected samples were repeated in Run 9. Though carryover did not meet acceptance in Run 9 and a sample by sample carryover assessment was performed, none of the repeat samples showed >2.0% possible contribution from the preceding sample.

A sample by sample carryover assessment was performed following the in-run carryover assessment for Run 9. Two samples were identified as being impacted by carryover. The affected samples were repeated in Run 10 in which carryover met acceptance.

Assay carryover was appropriately assessed throughout the study and found to be justifiable for batch acceptance. Samples were assayed in the order of PK time points. Thus, there was no significant sample-to-sample concentration change, which helped to limit the impact of any carryover effect.

Run 6 was rejected for DU-176b (D21-2393 was not assessed in the run) with unassignable cause. The data suggest that the failure was extraction related as instrument parameters and the peak area ratio were consistent with passing runs.

No IS-associated repeat analysis was needed.

There were no unexpected experimental results during this study.

There were no modified integrations performed for the current study.

A total of 20 samples for DU-176b and 32 samples for D21-2393 were reassayed for ISR. The results of the incurred sample reanalysis for DU-176b were acceptable, with 19 out of 20 samples (95.0%) providing acceptable ISR results. The results of the incurred sample reanalysis for D21-2393 were acceptable, with 30 out of 32 samples (93.8%) providing acceptable ISR results.

Chromatograms from Runs 1 for at least 20% of the study subjects (along with the corresponding standards and quality control samples) are shown in Appendix E.

Assessor's comments:

274 samples (including 120 duplicates) were received from 7 Sep 2018 to 22 Jul 2022 from 4 May 2017 to 27 Sep 2021 from, on 04 Apr 2019 and 16 Jul 2021 and on the 29 Jul 2019 and 3 Sep 2019. Samples were stored at -20°C. 152 samples were analysed. Samples were analysed as received, within the established freezer stability limit of 793 days at -20 °C. The longest storage duration as calculated on an individual sample basis was: 17 April 2019 (collection date) to 16 September 2020 (sample analysis date) = 518 days.

All lots of compounds used in Study DU176b-C-U313 were used within established expiration dates as noted on the Certificates of Analysis

The calibration curves of DU-176b contained 10 concentration levels in duplicate. No calibrator failed. The Inter-run accuracy and precision of the valid calibrators was acceptable.

The calibration curves of D21-2393 contained 7 concentration levels in duplicate. The Applicant claimed that there were 8 valid or accepted calibration curves, but 9 are reported. Both calibrators of the STD 3 failed in run 5 and one failed run 8 but the other calibrator of the same concentration was valid. The range was not changed. The Inter-run accuracy and precision of the valid calibrators was acceptable.

The regression was quadratic ($\text{Response} = A * (\text{Concentration}^2) + B * \text{Concentration} + C$) for DU-176b and linear for D21-2393.

The QCs of the valid runs passed the acceptance criteria. Four QC levels were tested with four replicates per concentration level. The failed QCs have not been highlighted but it has been checked that not more than 50% per QC level failed since only Qc failed in total for the parent and none for the metabolite. However, for runs 8 of the parent, all Dilution QCs failed. Two dilution QCs failed in run 2 and 7. During the procedure, the MAH indicated that there were samples analysed with dilution for DU-176b in Run 8. However, due to dilution QC failure in this run, the results for those samples were deactivated (those affected samples were subsequently repeated within Run 9).

The number of samples per run is not defined and in some runs there is mixture of subjects samples, reanalysis and ISR, which makes impossible to know the number of samples per run in all runs. Later on during the procedure, the applicant confirmed that the number of QCs included per run was sufficient to cover the number of study samples analysed per run.

Three samples were repeated for DU-176b and D21-2393 because of the concentration was >ULOQ in 1 case or original diluted concentration <LLOQ in 2 cases. These reasons are considered acceptable.

The number of samples that needed to be repeated because concentrations were >ULOQ was low. However, this is because dilution of samples was conducted also during the original analysis of study samples. Some of them were <LLOQ because of excessive dilution. The number of samples that were reported after dilution has not been reported. The range may not be optimal for the analytes. It could be questioned if the calibration range covered the concentrations of the study adequately, but this

deficiency is not critical as to reject the study. The QC levels were representative of the calibration range since two MQCs were used at 45.8 and 153 ng/ml in addition to the LQC of 2.29 ng/ml and 306 ng/ml for the HQC for the parent and for the metabolite LQC: 0.238 ng/ml, MQC1: 0.950 ng/ml , MQC2: 3.17 ng/ml and HQC: 6.34 ng/ml.

No sample was re-injected or re-integrated in this study.

ISR was conducted in 20 out of 152 samples, respectively. These are more than the 10% required by the guideline. In addition ISR is not necessary in all studies, like this one. ISR passed the acceptance criterion.

Representative chromatograms have been submitted. In addition, the chromatograms of 1 run containing 23 subjects have been submitted. It is not necessary to submit chromatograms of 20% of the subjects since this is not a bioequivalence study.

6.2. Bioequivalence (and food effect)

A Phase 1 relative bioavailability and food effect study (Study DU176b-A-U154) has been conducted in healthy adult subjects for the paediatric formulation, edoxaban oral granules. According to the applicant, the CSR of Study DU176b-A-U154 was included in the application for Marketing Authorisation for Lixiana submitted to the EMA on 07 January 2014. However, in the initial submission only the synopsis was submitted and the full study report was requested on day 120. This study was not described in the assessment report since it was not considered essential for the initial marketing authorisation. In the present submission, this study supports the granulate for oral suspension formulation administered to the paediatric population, but the marketing authorisation of this formulation is not applied for. Therefore, this study is only descriptive and supportive. The deficiencies identified in this study should be solved if this product was applied for marketing. However, these deficiencies are not critical currently.

Study title: An Open-Label, Randomized, 3-Way Crossover Study in Healthy Adult Subjects to Assess the Relative Bioavailability and Food Effect for a Novel Liquid Oral Suspension of Edoxaban.

Study code: Study DU176b-A-U154.

Dates of the clinical phase: First subject first visit date: 09 Jun 2013. Last subject last follow-up date: 10 Jul 2013. Dosing days can be deduced to be 9, 16 and 23 June 2013 based on the check-in dates.

Dates of the bioanalytical phase: Not available.

Primary objective:

- To characterize the pharmacokinetics (PK) of edoxaban when dosed as a liquid oral suspension under fasting conditions
- To evaluate the relative bioavailability of the liquid oral suspension with respect to the 30 mg oral tablet, both dosed at 60 mg under fasting conditions
- To evaluate the effect of food on the rate and extent of exposure of edoxaban dosed as a liquid oral suspension

Design: This was an open-label, 3-treatment, 3-way crossover study. Subjects were randomised to 1 of 6 treatment sequences. Each treatment period was separated by a washout of at least 7 days between dosing days.

Treatments: On Day 1 of each treatment period, following an overnight fast of at least 10 hours, subjects were administered 1 of the following treatments according to the assigned sequence:

- Treatment A: Single oral dose of 2 × 30-mg tablets of edoxaban dosed under fasting conditions; Lot No.: DU176F1H12T10. Expiration Date: Jun 2017.
- Treatment B: Single oral dose of 10 mL of 6-mg/mL edoxaban oral suspension dosed under fasting conditions. Lot No.: 3318V13009. Expiration Date: Mar 2014.
- Treatment C: Single oral dose of 10 mL of 6-mg/mL edoxaban oral suspension dosed after a Food and Drug Administration standard high-fat, high-calorie breakfast (i.e., approximately 800 to 1000 calories total with approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively). Lot No.: 3318V13009. Expiration Date: Mar 2014.

Wash-out period: 7 days.

Sample size: 24 healthy adult subjects. Twenty-three subjects completed the study, and 1 subject withdrew consent prior to completion. Subject 1013 withdrew consent prior to receiving Treatment B. This subject received Treatment C in Period 1 and did not receive Treatments A or B.

Sampling times: at predose (0) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 14, 24, 30, 36, 48, and 52 hours after dosing of each period.

Analytes: Edoxaban and its metabolite D21-2393

PK methods: Plasma concentration time data were analyzed using non-compartmental methods. The following parameters were estimated for edoxaban: C_{max}, t_{max}, AUC_{0-last}, AUC_{0-inf}, t_{1/2}, CL/F, V_z/F, and F_{rel} (Treatment B vs Treatment A; Treatment C vs Treatment B). For D21-2393, the following parameters were calculated using non-compartmental methods, as data permitted: C_{max}, t_{max}, AUC_{0-last}, AUC_{0-inf}, t_{1/2}, and metabolite to parent drug ratio for AUC_{0-inf}. Pharmacokinetic data were analyzed using noncompartmental methods in Phoenix WinNonlin® (Version 6.3, Pharsight Corporation).

Statistical methods: The peak (C_{max}) and total exposures (AUC_{0-last}, AUC_{0-inf}) were compared between Treatments A and B (bioavailability) and Treatments B and C (food effect), using a mixed effect model for the ln-transformed values of C_{max}, AUC_{0-last}, and AUC_{0-inf} with fixed effects for treatment sequence, period and treatment, and subject nested sequence fitted as a random effect. A 90% confidence interval (CI) was constructed for the ratio of geometric least squares means for each comparison.

Assessor's comments:

The suspension is actually a granulate for oral suspension.

The appendices to the clinical study report are not submitted. The Applicant should have submitted all appendices of the clinical study report, including the bioanalytical study report as well as the method validation report of the bioanalytical method employed in study DU176b-A-U154.

Due to the lack of the study appendices it is not possible to confirm the date of the protocol and its potential amendments, the date of IRB approval, the dates of product administration, the dates of the bioanalytical phase, etc.

Version 1.0 of the protocol, dated 28 Mar 2013, was amended and Version 2.0 of the protocol was released on 31 May 2013 (prior to subject dosing).

The Applicant should have submitted the monitoring reports of study DU176b-A-U154 and the list of regulatory inspections conducted in the clinical and bioanalytical centres.

The Applicant should have clarified if the QA unit of the CRO audited this study

The Applicant should have submitted the Certificate of Analysis of the batches investigated in study DU176b-A-U154.

The Clinical study report does not define the non-compartmental method employed to calculate AUC. As the protocol is not submitted, it is not possible to know if at least the protocol identifies the planned method for AUC estimation.

The software employed for PK calculations is considered acceptable.

The mean and individual concentration – time curves have been submitted within the CSR in the original scale and semi-log-scale. The values of the concentration – times profiles as also been submitted in tabulated form.

Concentrations at time zero were BLOQ, but as the BLOQ or sensitivity of the bioanalytical method has not been included in the CSR the adequacy of the bioanalytical method cannot be known. The LLOQ should be lower than 4.72 ng/ml in order to be able to detect concentrations of 5% of the minimum C_{max} of the parent drug.

Sampling frequency was adequate since T_{max} was not observed in the first sampling time and the percentage of extrapolated AUC was lower than 20% in all cases.

Actual sample times were used for calculation of all plasma PK parameters.

The CSR does not define the statistical software employed for the analysis of the study results, but it seems to be SAS. This statistical software is considered adequate.

The ANOVA model included the conventional sources of variation: treatment, period, sequence and subjects(sequence). The PROC MIXED (i.e. mixed effect model) was used. As subjects with missing data were excluded, the obtained results should agree with those obtained with PROC GLM. As the Statistical appendix has not been attached and the CSR does not include the SAS output, it is not possible to know if the correct analysis was conducted. The comparisons (suspension vs. tablet and fed vs. fasted) should have been conducted by excluding the other third treatment of the study.

Results

Twenty-four subjects were enrolled and completed the study, according to the Summary of Clinical Pharmacology Studies, but only 23 completed the study according to the CSR.

The geometric least square means for exposure parameters and statistical comparisons between the 2 × 30-mg reference tablets and 60-mg test oral granules are summarised in Table 3.3. The total exposure (AUC from time zero to the last measurable concentration [AUC_{0-last}] and AUC_{0-inf}) of edoxaban was comparable for the 60-mg oral granules (Treatment B) and the 2 × 30-mg tablets (Treatment A), but the C_{max} was approximately 13% lower, with the lower bound of 90% CI outside the 80% to 125% bioequivalence range.

Table 3.3: Statistical Analysis of the Natural Log-Transformed Systemic Exposure of Edoxaban Comparing 60 mg Edoxaban Oral Suspension Under Fasting Conditions (Treatment B) to 60 mg Edoxaban Tablet Under Fasting Conditions (Treatment A)

Dependent Variable	Ln(Geo LSMean) ^a		Geo LSMean ^b		Ratio (%) ^c (Edoxaban Suspension Fasting/ Edoxaban Tablet Fasting)	90% CI	
	Edoxaban Suspension Fasting	Edoxaban Tablet Fasting	Edoxaban Suspension Fasting	Edoxaban Tablet Fasting		Lower	Upper
C _{max} (ng/mL)	5.323	5.464	205.055	236.108	86.85	72.97	103.37
AUC _{0-last} (ng·h/mL)	7.449	7.489	1718.527	1788.234	96.10	90.30	102.27
AUC _{0-inf} (ng·h/mL)	7.471	7.511	1755.514	1827.488	96.06	90.43	102.04

AUC_{0-inf} = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-last} = area under the plasma concentration-time curve from time zero until the last measurable concentration; C_{max} = maximum plasma concentration; CI = confidence interval

^a Natural log of the geometric mean based on the least squares mean for edoxaban 60-mg suspension/fasting (Treatment B; Test) and edoxaban 60-mg tablet/fasting (Treatment A; Reference)

^b Geo LSMean = geometric mean based on the least squares mean

^c Ratio (%) = Geo LSMean (Test)/Geo LSMean (Reference)

Overall systemic exposure to the metabolite (D21-2393) relative to that observed for the parent (edoxaban), based on AUC_{0-inf}, was 9.64% for Treatment A and 9.65% for Treatment B under fasting conditions.

The geometric least square means for exposure parameters and statistical comparisons between the 60 mg oral granules fed conditions (Treatment C and test product) and fasting conditions (Treatment B and reference product) are summarised in Table 3.4. The geometric mean ratios and 90% CIs for C_{max}, AUC_{0-last}, and AUC_{0-inf} were within the 80% to 125% range, indicating an absence of food effect on edoxaban exposure following administration of the oral granules.

Table 3.4: Statistical Analysis of the Natural Log-Transformed Systemic Exposure of Edoxaban Comparing 60-mg Edoxaban Oral Suspension Under Fed Conditions (Treatment C) to 60-mg Edoxaban Oral Suspension Under Fasting Conditions (Treatment B)

Dependent Variable	Ln (Geo LSMean) ^a		Geo LSMean ^b		Ratio (%) ^c (Edoxaban Suspension Fed/ Edoxaban Suspension Fasting)	90% CI	
	Edoxaban Suspension Fed	Edoxaban Suspension Fasting	Edoxaban Suspension Fed	Edoxaban Suspension Fasting		Lower	Upper
C _{max} (ng/mL)	5.3595	5.3233	212.6143	205.0546	103.69	87.11	123.41
AUC _{0-last} (ng·h/mL)	7.5253	7.4492	1854.4397	1718.5265	107.91	101.40	114.84
AUC _{0-inf} (ng·h/mL)	7.5432	7.4705	1887.8793	1755.5143	107.54	101.24	114.24

AUC_{0-inf} = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-last} = area under the plasma concentration-time curve from time zero until the last measurable concentration; C_{max} = maximum plasma concentration; CI = confidence interval

^a Natural log of the geometric mean based on the least squares mean for edoxaban 60-mg suspension/fed (Treatment C; Test) and edoxaban 60 mg suspension/fasting (Treatment B; Reference)

^b Geo LSMean = geometric mean based on the least squares mean

^c Ratio (%) = Geo LSMean (Test)/Geo LSMean (Reference)

The median t_{max} for Edoxaban 60 mg Suspension under fed conditions (2.50 h) was delayed by 1 h, relative to that for the fasting state (1.50 h).

Overall systemic exposure to the metabolite (D21-2393) relative to that observed for the parent (edoxaban), based on AUC_{0-inf}, was 8.04% for of edoxaban 60 mg suspension Treatment C, which was slightly lower than that observed for Treatments A and B.

Safety: Edoxaban was well tolerated in healthy subjects. There were no deaths, serious AEs (SAEs), or discontinuations due to an AE. All treatment-emergent AEs (TEAEs) resolved without sequelae. A total of 9 TEAEs were reported by 7 (29.2%) of the 24 subjects in this study. Overall, 2 subjects (8.7%) reported 2 TEAEs following Treatment A, 3 subjects (13.0%) reported 3 TEAEs following Treatment B, and 4 subjects (16.7%) reported 4 TEAEs following Treatment C. Most TEAEs were mild in severity with the exception of disturbance of attention (moderate, related to edoxaban) reported in 1 subject following Treatment C. None of the TEAEs reported following Treatment A or Treatment B was considered related to edoxaban; 3 TEAEs reported following Treatment C were considered related to edoxaban. No clinically significant laboratory values, ECG values, or vital sign abnormalities were reported.

Palatability Results: Overall, Treatment B was highly palatable, with mean scores >80 mm for palatability, bitterness, and sweetness, and mean score of 79.3 mm for overall taste. Eleven (47.8%) of the 23 subjects who received Treatment B scored aroma as neutral (approximately 50 mm); with the exception of 1 subject (9.7 mm), all other individual scores were in the upper half of the possible score range.

Protocol deviations: All deviations were considered minor and were not expected to have a significant impact on the clinical and PK assessments. Minor protocol deviations included excursions from the sample collection and sample processing time windows.

Assessor's comments:

The results reported by the company cannot be reproduced in PROC GLM in SAS is employed. No matter if all the data is combined in a single ANOVA or if the comparisons are conducted deleting the data from the other third treatment.

With a single ANOVA the results obtained using the PK data reported by the Applicant are:

<i>C_{max}</i>	<i>Point_estimate</i>	<i>Lower_Limit</i>	<i>Upper_Limit</i>
<i>A vs B</i>	<i>86.85</i>	<i>75.11</i>	<i>100.42</i>
<i>A vs C</i>	<i>90.05</i>	<i>77.88</i>	<i>104.12</i>
<i>B vs C</i>	<i>103.69</i>	<i>89.68</i>	<i>119.88</i>
<i>AUC</i>			
<i>AUC_t</i>	<i>Point_estimate</i>	<i>Lower_Limit</i>	<i>Upper_Limit</i>
<i>A vs B</i>	<i>96.05</i>	<i>91.21</i>	<i>101.15</i>
<i>A vs C</i>	<i>103.76</i>	<i>98.53</i>	<i>109.27</i>
<i>B vs C</i>	<i>108.03</i>	<i>102.58</i>	<i>113.76</i>

With separate ANOVAs

Suspension vs. tablet

<i>Parameter</i>	<i>Point_estimate</i>	<i>Lower_Limit</i>	<i>Upper_Limit</i>
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<i>C_{max} (A vs B)</i>	<i>86.76</i>	<i>74.8</i>	<i>100.64</i>
<i>AUC (A vs B)</i>	<i>96.08</i>	<i>90.86</i>	<i>101.61</i>
<u><i>Suspension fed vs. suspension fasted</i></u>			
<i>Parameter</i>	<i>Point_estimate</i>	<i>Lower_Limit</i>	<i>Upper_Limit</i>
<i>C_{max} (B vs C)</i>	<i>103.53</i>	<i>91.25</i>	<i>117.46</i>
<i>AUC (B vs C)</i>	<i>107.93</i>	<i>102.61</i>	<i>113.53</i>
<i>The results are similar and the conclusions are the same.</i>			
<i>The suspension has shown to be bioequivalent with respect to extent of absorption and exhibits a lower C_{max}. The clinical relevance of this difference should be addressed in the PK/PD or efficacy analysis.</i>			
<i>The high-fat high-calorie meal does not affect the bioavailability of the suspension significantly. The oral suspension could be taken with or without food.</i>			
<i>The deviations do not seem to affect the validity of the study conclusions.</i>			
<i>The limit sample size of a bioequivalence study cannot detect any difference in the safety or tolerability profile. However, due to similar extent of exposure and lower C_{max}, the systemic safety profile is expected to be similar.</i>			

6.3. Pharmacokinetics in the target population

Phase 1 Studies Conducted in Support of Clinical Development

Table 2.1: Summary of Clinical Pharmacology (Phase 1) Studies

Serial No./Section No.	Study Number/ Location in CTD	Objectives of the Studies	Edoxaban Dose (mg)	Metabolites Measured	Biomarkers
BIOAVAILABILITY AND FOOD EFFECT					
1	DU176b-A-U154 Module 5.3.1.1	Relative bioavailability, food effect	60 mg	D21-2393	NA
SINGLE- AND MULTIPLE-DOSE PK, PD STUDIES IN PAEDIATRIC PATIENTS					
2	DU176b-A-U157 Module 5.3.4	To characterize PK and PD of edoxaban in paediatric patients	12 to <18 years, 30 and 60 mg 6 to <12 years, 24 and 45 mg 2 to <6 years, 0.7 mg/kg, cap 24 mg and 1.4 mg/kg, cap 45 mg 6 months to <2 years, 0.75 and 1.5 mg/kg 0 to < 6 months, 0.4 and 0.8 mg/kg	D21-2393, D21-3231, D21-1402, and D21-2135	PT, aPTT, anti- FXa

anti-FXa = anti-factor Xa; aPTT = activated partial thromboplastin time; CTD = common technical document; NA= not applicable; PD= pharmacodynamics; PK = pharmacokinetics; PT = prothrombin time.

Population Model-based Analyses Supporting Development

Table 2.2: Population Model-based Reports

Study Number/ Location in CTD	Objectives of the Studies	Studies Included in PopPK Analysis
PopPK/PD report Module 5.3.5.3	- To characterise the population PK and PK/PD in paediatric patients. - To evaluate the effect of intrinsic and extrinsic factors on the PK and PD of edoxaban in paediatric patients. - To compare the PK, PK/PD, and exposure-response relationships of edoxaban in paediatric and adult patient populations. - To use population PK and PK/PD analyses to evaluate dosing options in the paediatric patients.	DU176b-A-U157, DU176b-D-U312, and DU176b-C-U313
PopPK report Module 5.3.4.2	- To estimate the PK parameters for the paediatric patients enrolled in Study DU176b-A-U157. - To inform edoxaban doses to be administered in pivotal studies.	DU176b-A-U157 and DU176b-A-U312

CTD = common technical document; PD = pharmacodynamic(s); PopPK = population pharmacokinetic(s); PK = pharmacokinetic(s)

Pharmacodynamics

The PD blood samples were collected in the 3 paediatric studies (DU176b-A-U157, DU176b-D-U312, and DU176b-C-U313) for estimation of biomarkers of coagulation (prothrombin time [PT], activated partial thromboplastin time [aPTT], and anti-FXa). Two Phase 3 studies with PK and PD data available are listed in Table 2.3.

Table 2.3: Phase 3 Studies with PK and Biomarker Data

Study No./ Location in CTD	Study Title	Phase	Biomarkers Evaluated
DU176b-D-U312 Module 5.3.5	A Phase 3, open-label, randomised, 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 paediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE)	3	PT, aPTT, anti-FXa
DU176b-C-U313 Module 5.3.5	An open-label, randomised, parallel-group, multicenter, observational trial to evaluate safety and efficacy of edoxaban tosylate in children from 38 weeks gestational age to less than 18 years of age with cardiac diseases at risk of thromboembolic events	3	PT, aPTT, anti-FXa

aPTT = activated partial thromboplastin time; CTD = common technical document; anti-FXa = anti-factor Xa; PK = pharmacokinetics; PD = pharmacodynamics; PT = prothrombin time

Pharmacokinetics and pharmacodynamics of Single-Dose Edoxaban in Paediatric Patients (DU176b-A-U157)

Study DU176b-A-U157 was a Phase 1, open-label, single-dose, nonrandomised, multiple centre, PK, and PD study in paediatric patients.

The goal of Study DU176b-A-U157 was to provide information related to the following objectives:

Primary:

- To characterize the PK of edoxaban in pediatric patients following single-dose oral administration

Secondary:

- To evaluate the PD effects of edoxaban in pediatric patients following single-dose oral administration
- To evaluate the safety and tolerability of single-dose oral administration of edoxaban in pediatric patients
- To assess metabolite exposure (D21-2393, D21-3231, D21-1402, and D21-2135) in pediatric patients
- To evaluate the palatability (bitterness, sweetness, and overall taste or aroma) of the liquid oral suspension of edoxaban

The study included 5 paediatric age cohorts with evaluation of 2 different doses within each age cohort (low and high doses), as listed below (Table 3.6). 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 (mg/kg) for patients younger than 6 years were based on patients' body weight. Patients in 12 to <18 years of age cohort received multiple edoxaban tablets of 15- or 30-mg strength. Patients younger than 12 years received edoxaban granules for oral suspension. Patients were asked to fast for at least 4 hours before dosing and for an additional 2 hours after dosing.

Table 3.6: Edoxaban Dose by Cohort in Study DU176b-A-U157

Cohort	Age	Edoxaban Dose
1a (n = 8)	12 to <18 years	30 mg
1b (n = 7)		60 mg
2a (n = 7)	6 to <12 years	24 mg
2b (n = 6)		45 mg
3a (n = 7)	2 to <6 years	0.7 mg/kg, no more than 24 mg
3b (n = 6)		1.4 mg/kg, no more than 45 mg
4a (n = 7)	6 months to <2 years	0.75 mg/kg
4b (n = 6)		1.5 mg/kg
5a (n = 6)	0 to <6 months	0.4 mg/kg
5b (n = 6)		0.8 mg/kg

Seven serial blood PK samples were collected from Cohort 1 on the basis of a sampling window approach: 0.25 to 1, 1.5 to 3, 3.5 to 6, 6.5 to 8, 8.5 to 14, 24 to 36, and 48 to 54 hours after dosing.

Five sparse blood PK samples were collected from Cohorts 2 and 3. Four and three blood PK samples were collected from Cohorts 4 and 5, respectively. Sampling scheme could have been adjusted for various age cohorts based on emerging PK and safety data. PD sampling was concurrent with PK sampling.

Edoxaban was absorbed rapidly and the highest plasma concentration of edoxaban was observed within 0.5 to 3 hours after oral administration in all age cohorts in both the high- and low-dose groups. The plasma concentration-time profiles for different age cohorts were found to be visually similar (Figure 3.1 and Figure 3.2).

Figure 3.1: Plasma Concentrations of Edoxaban Versus Time on Linear and Semilogarithmic Scales – High-dose Group

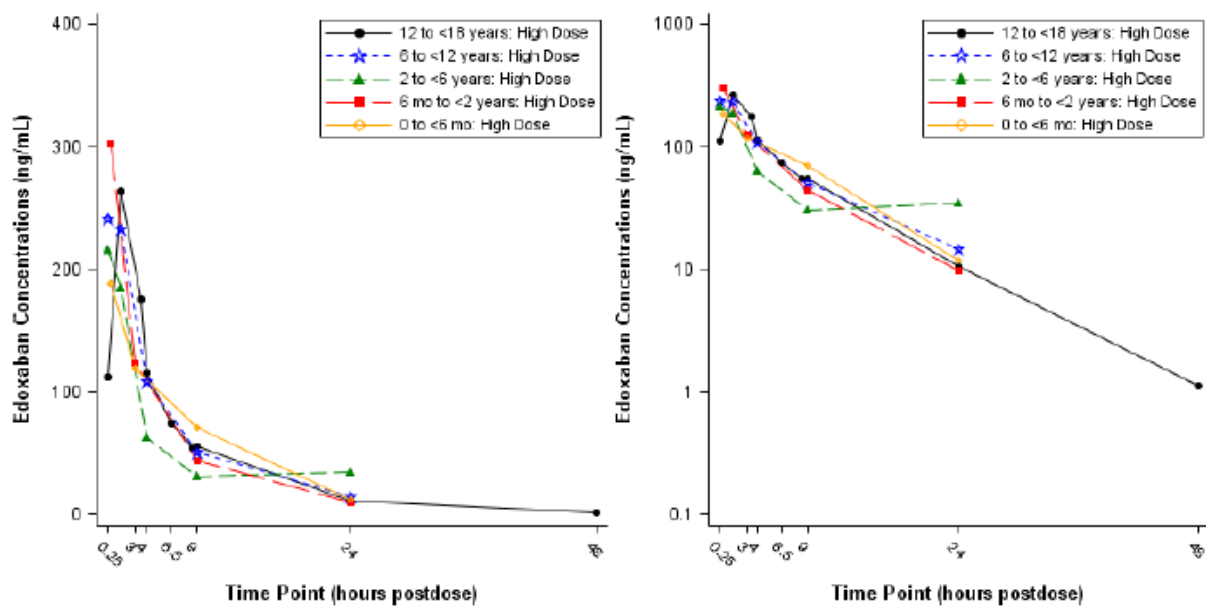
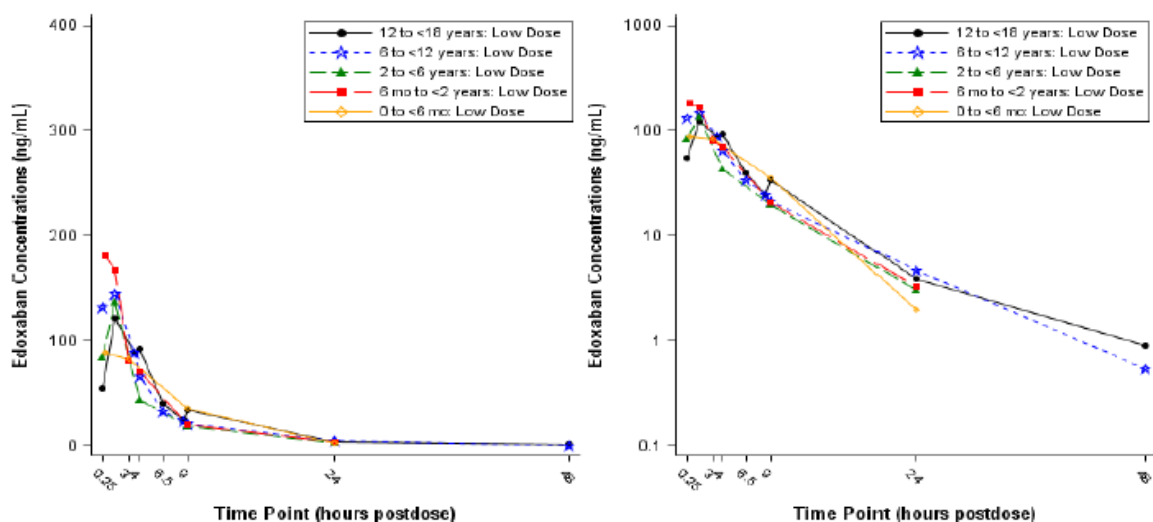


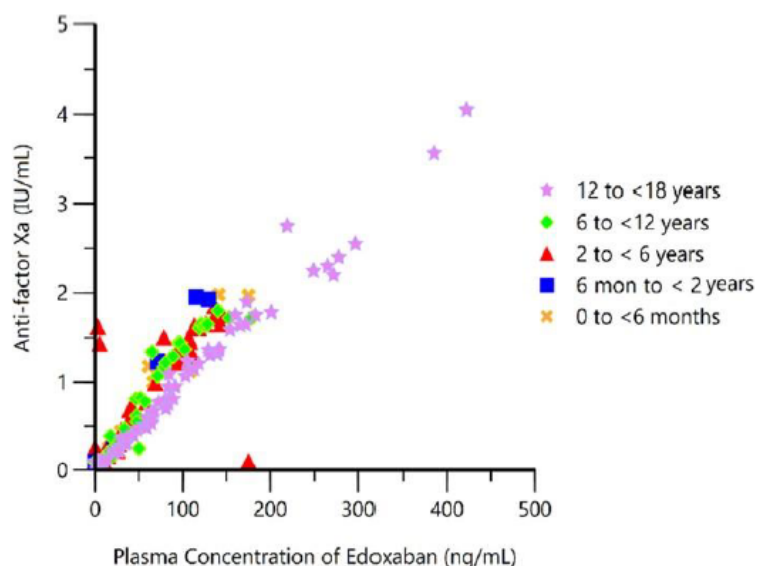
Figure 3.2: Plasma Concentrations of Edoxaban Versus Time on Linear and Semilogarithmic Scales – Low-dose Group

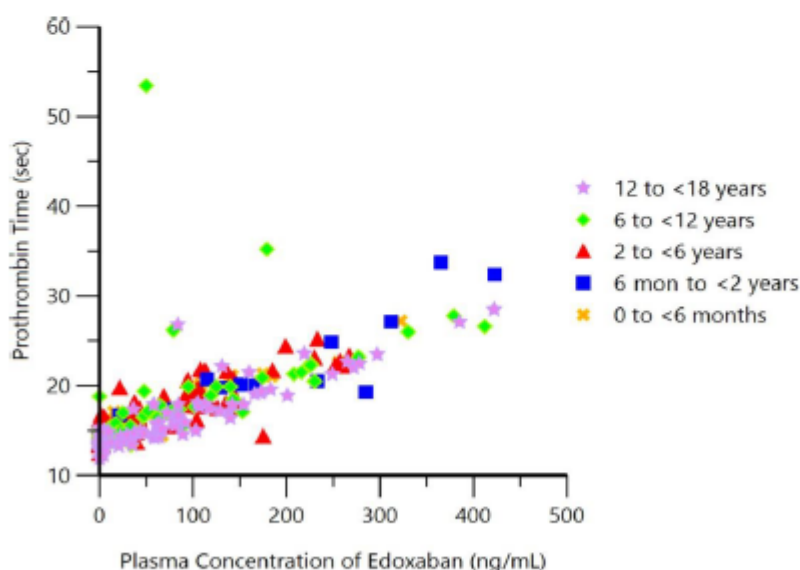
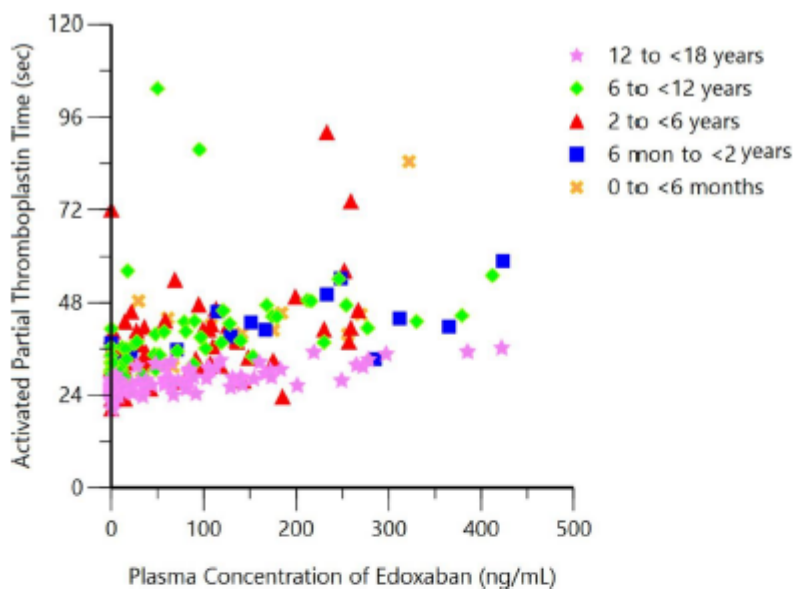


Across all cohorts, mean PT, aPTT, and anti-FXa values increased following edoxaban administration with peak values observed approximately 1.5 to 3 hours after dosing followed by a rapid decrease until 4 to 8 hours after dosing and a slower decline after 8 hours.

The PD (anti-FXa, aPTT, and PT) versus edoxaban plasma concentration relationships were compared among 5 paediatric cohorts (Figure 3.4).

Figure 3.4: Pharmacokinetic and Pharmacodynamic (anti-FXa, aPTT, and PT) Relationships of Edoxaban in Paediatric Patients (Study DU176b-A-U157)





Note: One subject had a predose aPTT value of 255 seconds. The aPTT value was excluded to support proper visualization of the PK-PD relationship. aPTT = activated partial thromboplastin time.

PopPK analysis

Analysis objectives:

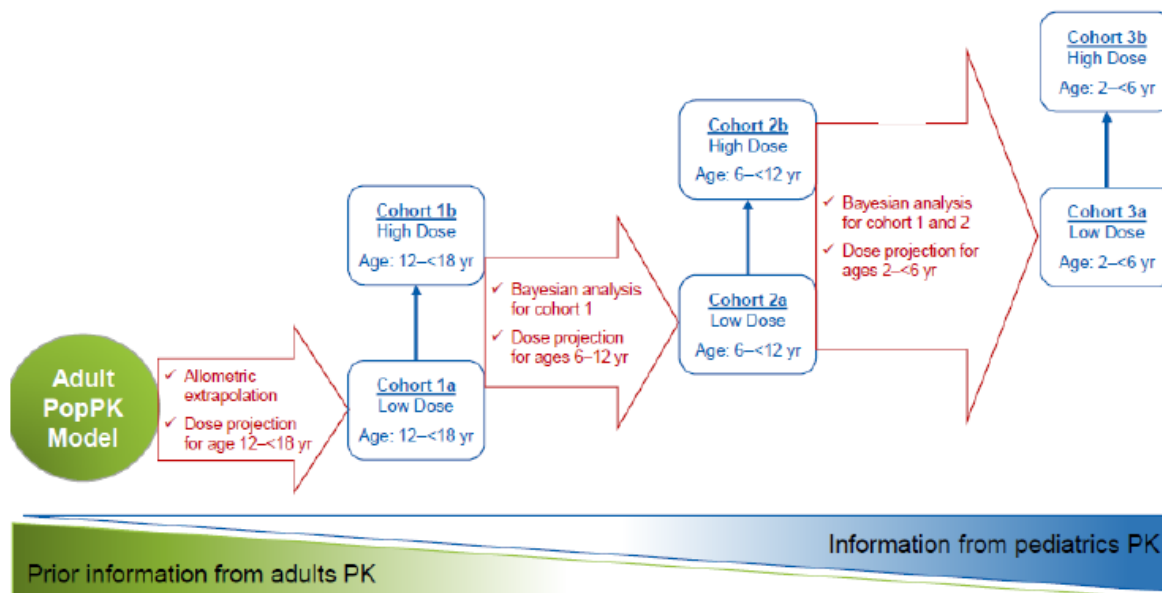
- To establish a preliminary edoxaban population PK (PopPK) model in pediatric patients aged 0 - <18 years of age
- To conduct PK simulations and propose dose regimens for each subsequent dose cohort and also for the same age cohort in study DU176b-A-U312

A PopPK model has been established previously for edoxaban in the adult patient population. The current PK analysis for the ongoing pediatric studies used a Bayesian estimation approach [software Stan® with Torsten, a collection of Stan functions to facilitate analysis of pharmacometrics data (2, 3)] by incorporating the information from the edoxaban adult PK model as well as the experts' cumulative

belief in certain PK parameters (Figure 1). Initially the adult PopPK model was modified to derive the PK model for pediatric subjects age 2– <18 years.

Subsequently, the model was further modified to fit the data from younger subjects. Using Stan, Markov Chain Monte Carlo (MCMC) sampling of the posterior distribution of the PopPK model parameters was implemented. Diagnostics such as trace plots were used to determine if convergence was reached.

Figure 1: Iterative steps for dose determination in DU176b-A-U157



Based on the adult exposure response analysis, it was proposed that the pediatric dose for a specific age cohort will be considered appropriate if the median estimated exposure at the pediatric dose is within the 0.5 to 1.5-fold of the median predicted exposure in adult VTE subjects at 60 mg QD dose.

Table 3 presents that number of subjects in each age cohort by study. Table 4 presents the summary of the continuous covariates of interest.

Table 3: Summary of Edoxaban Observations in PopPK Analysis Dataset

Description	Number of Samples	
	Study U312	Study U157
PopPK dataset	118	320
BLQ samples excluded	0	5
Post-dose samples with lower concentrations than pre-dose samples	4	0
Trough samples with peak-like concentrations	0	1
Total excluded from PopPK analysis	4	6
Total included in PopPK analysis	114	314

Table 4: Continuous covariates for subjects in PopPK analysis

A. DU176b-A-U312

	12 to <18 years (N=21)	6 to <12 years (N=12)	2 to <6 years (N=14)	0.5 to <2 years (N=10)	<0.5 years (N=2)	Overall (N=59)
Age (years)						
Mean (SD)	15.7 (1.66)	9.86 (1.72)	3.87 (1.31)	0.986 (0.359)	0.180 (0.113)	8.67 (6.17)
Median (CV%)	15.9 (10.6)	9.96 (17.4)	4.13 (33.8)	0.925 (36.4)	0.180 (62.9)	8.78 (71.2)
[Min, Max]	[12.1, 17.9]	[6.85, 11.8]	[2.15, 5.99]	[0.620, 1.80]	[0.100, 0.260]	[0.100, 17.9]
Postmenstrual age (weeks)						
Mean (SD)	855 (86.6)	552 (90.0)	240 (68.2)	89.5 (18.7)	47.5 (6.36)	490 (322)
Median (CV%)	867 (10.1)	557 (16.3)	254 (28.5)	86.5 (20.9)	47.5 (13.4)	496 (65.7)
[Min, Max]	[669, 970]	[395, 654]	[150, 351]	[70.0, 132]	[43.0, 52.0]	[43.0, 970]
Body Weight (kg)						
Mean (SD)	68.1 (22.0)	34.7 (17.9)	15.3 (4.17)	8.36 (2.26)	2.65 (0.0707)	36.4 (29.6)
Median (CV%)	61.7 (32.3)	29.0 (51.7)	13.1 (27.3)	8.40 (27.0)	2.65 (2.7)	24.2 (81.4)
[Min, Max]	[40.5, 138]	[21.3, 86.8]	[11.0, 21.7]	[5.00, 12.5]	[2.60, 2.70]	[2.60, 138]

B. DU176b-A-U157

	12 to <18 years (N=15)	6 to <12 years (N=13)	2 to <6 years (N=13)	0.5 to <2 years (N=13)	<0.5 years (N=12)	Overall (N=66)
Age (years)						
Mean (SD)	15.6 (1.21)	9.51 (1.46)	4.32 (1.42)	1.06 (0.511)	0.200 (0.186)	6.52 (6.03)
Median (CV%)	15.9 (7.8)	9.80 (15.4)	4.30 (32.8)	0.800 (48.1)	0.150 (92.9)	5.20 (92.5)
[Min, Max]	[13.0, 17.5]	[6.40, 11.4]	[2.20, 5.90]	[0.600, 1.90]	[0, 0.400]	[0, 17.5]
Postmenstrual age (weeks)						
Mean (SD)	855 (63.3)	536 (75.6)	264 (73.6)	95.2 (26.6)	49.6 (9.85)	380 (315)
Median (CV%)	874 (7.4)	549 (14.1)	266 (27.8)	81.0 (27.9)	47.5 (19.9)	311 (82.9)
[Min, Max]	[722, 953]	[374, 636]	[152, 348]	[71.0, 140]	[38.0, 62.0]	[38.0, 953]
Body Weight (kg)						
Mean (SD)	66.4 (27.3)	31.0 (7.02)	17.1 (3.65)	9.06 (1.66)	4.82 (1.68)	27.2 (26.6)
Median (CV%)	59.2 (41.1)	27.9 (22.6)	17.8 (21.4)	8.90 (18.3)	4.65 (35.0)	18.2 (97.9)
[Min, Max]	[35.4, 157]	[22.0, 47.2]	[11.3, 23.5]	[7.00, 12.3]	[2.70, 6.60]	[2.70, 157]

The edoxaban pediatric PK was best described by a 2-compartment model with allometric body weight exponents (0.75 for clearances and 1 for volumes). The model that incorporated a maturation function for clearance (via a post-menstrual age (PMA) effect on CL) demonstrated an improved fit to the data (Table 2). The final population PK parameters are presented in Table 5.

Table 5: Final Model Parameter Estimates for Edoxaban PK

Parameter	Median (90% CrI)
CL (clearance, L/h)	42.9 (40.3, 45.6)
Q (inter-compartment clearance, L/h)	12.5 (9.76, 16.1)
V1 (Central compartment volume, L)	198 (180, 219)
V2 (Peripheral compartment volume, L)	178 (143, 241)
Ka (Absorption rate, 1/hr)	2.74 (2.14, 3.56)
tLag (lag time in absorption, hr)	0.225 (0.214, 0.228)
WTonCL (weight effect on CL)	0.75 FIX
TM50 (PMA effect on CL, weeks)	52.6 (47.8, 57.3)
Hill Coefficient (PMA effect on CL)	3.4 FIX
Sigma (residual error, CV%)	19% (16%, 24%)
omega[1] (IIV on CL, CV%)	30% (25%, 35%)
omega[2] (IIV on Q, CV%)	79% (56%, 103%)
omega[3] (IIV on V1, CV%)	29% (20%, 40%)
omega[4] (IIV on V2, CV%)	67% (48%, 88%)
omega[5] (IIV on ka, CV%)	107% (78%, 141%)

Note that estimates are given with the 90% credible interval (CrI) in parenthesis, 2000 MCMC samples were used in the estimation.

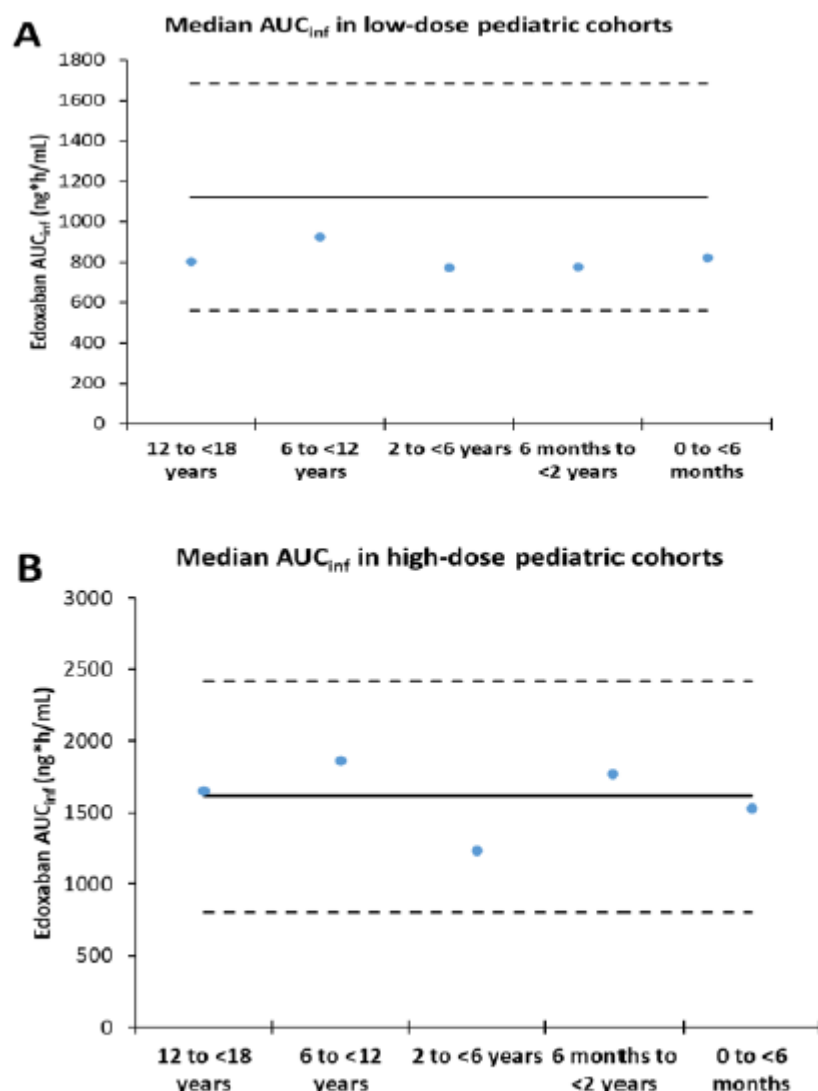
The individual estimates of AUC_{0-inf} are summarised by cohort and dose level in Table 3.7. The CL/F increased with age/body weight and the mean PK exposures for different age cohorts were similar. For each age cohort, the mean exposure increased proportionally with dose in a dose range of 30 to 60 mg in patients of 12 to <18 years, 24 to 45 mg in patients of 6 to <12 years, 0.7 to 1.4 mg/kg in patients of 2 to <6 years, 0.75 to 1.5 mg/kg in patients of 6 months to <2 years, and 0.4 to 0.8 mg/kg in patients of 0 to < 6 months old. Across all cohorts, the median exposure was within the 0.5- to 1.5-fold of the exposure in adults VTE patients receiving corresponding doses (30 mg QD for low dose and 60 mg QD for high dose) (Figure 3.3).

Table 3.7: Estimated AUC_{0-inf} of Subjects Enrolled in Study DU176B-A-U157 by Age Cohort and Dose Level

Cohort	Age	Body Weight Mean $\pm$ SD (kg)	Edoxaban Dose	CL/F Mean $\pm$ SD (L/h)	AUC _{0-inf} Mean $\pm$ SD (ng·h/mL)
1a (n = 8)	12 to <18 years	71.7 $\pm$ 34.9	30 mg	36.33 $\pm$ 8.13	861 $\pm$ 186
1b (n = 7)		60.3 $\pm$ 15.5	60 mg	36.70 $\pm$ 11.76	1778 $\pm$ 538
2a (n = 7)	6 to <12 years	31.4 $\pm$ 5.56	24 mg	25.31 $\pm$ 3.37	963 $\pm$ 133
2b (n = 6)		30.5 $\pm$ 8.97	45 mg	23.68 $\pm$ 5.65	1998 $\pm$ 499
3a (n = 7)	2 to <6 years	16.6 $\pm$ 3.66	0.7 mg/kg, cap 24 mg	16.55 $\pm$ 6.54	746 $\pm$ 139
3b (n = 6)		17.7 $\pm$ 3.89	1.4 mg/kg, cap 45 mg	19.78 $\pm$ 6.97	1295 $\pm$ 259
4a (n = 7)	6 months to <2 years	9.21 $\pm$ 1.46	0.75 mg/kg	8.85 $\pm$ 3.79	865 $\pm$ 310
4b (n = 6)		8.88 $\pm$ 1.99	1.5 mg/kg	7.90 $\pm$ 3.54	1765 $\pm$ 297
5a (n = 6)	0 to <6 months	4.35 $\pm$ 1.72	0.4 mg/kg	2.26 $\pm$ 1.63	899 $\pm$ 406
5b (n = 6)		5.28 $\pm$ 1.67	0.8 mg/kg	2.70 $\pm$ 1.15	1709 $\pm$ 516

AUC_{0-inf} = area under the plasma concentration-time curve from time zero extrapolated to infinity; CL/F = apparent total clearance

Figure 3.3: Comparison of Median Exposure in the Paediatric Subjects vs Median Exposure in Adult Subjects at 30 mg QD (Reference for Low-dose Group) 60- mg QD (Reference for High-dose Group) Dose



AUC_{0-inf} = area under the plasma concentration-time curve from time zero extrapolated to infinity; QD = once daily; VTE = venous thromboembolism. Note: The dash lines represent 0.5-fold and 1.5-fold of median AUC_{inf} in adult VTE patients enrolled in Study HOKUSAI-VTE receiving 30 mg QD (A) and 60 mg QD (B). The solid line represents median AUC_{inf} in adult VTE patient receiving 30 mg QD (A) and 60 mg QD (B). The solid dots represent the median AUC_{inf} in paediatric cohorts.

Pharmacokinetics and Pharmacodynamics of Edoxaban in Paediatric Patients with Confirmed Venous Thromboembolism (DU176b-D-U312)

Study DU176b-D-U312 was an event-driven Phase 3, prospective, randomised, open-label, blinded endpoint evaluation (PROBE), parallel-group study in paediatric subjects with confirmed VTE. This study was designed to evaluate the PK and PD of edoxaban and to compare the efficacy and safety of edoxaban with standard of care (standard of care, including LMWH, vitamin K antagonist, or synthetic pentasaccharide Xa inhibitors) in paediatric subjects with confirmed VTE.

Sequential enrollment of age cohorts was used for randomisation. The order of enrolment was from the oldest age cohort to the youngest age cohort. Starting doses of edoxaban for each age cohort in this study (Table 3.8) was selected on the basis of edoxaban exposure for age-matched subjects and safety data from DU176b-A-U157 study and on PopPK analyses. Edoxaban was supplied on a 1-month treatment interval as tablets (15- and/or 30-mg strengths) or granules for oral suspension 60 mg (6

mg/mL). Subjects were instructed to take edoxaban (tablets or granules) orally once a day, at the same time every day, with or without food.

Table 3.8: Edoxaban Dose for All 5 Cohorts (12 to <18 years, 6 to <12 years, 2 to <6 years, 6 months to <2 years, and birth to <6 months)

Age	Body Weight	Dose (tablet)	Dose (suspension) (6-mg/mL Concentration) ^{c,e}	Dose Reduction ^a
12 to <18 Years ^b (At date of consent)	≥60 kg	60 mg QD	NA	45 mg QD
	≥30 and <60 kg	45 mg QD	NA	30 mg QD
	<Fifth percentile for age ^c	30 mg QD	NA	NA
6 to <12 Years (At date of consent)	<60 kg Dosed on the basis of milligrams per kilogram ^d	NA	1.2 mg/kg with a maximum dose of 45 mg	0.8 mg/kg, with a maximum dose of 45 mg
2 to <6 Years (At date of consent)	Dosed on the basis of milligrams per kilogram	NA	1.4 mg/kg with a maximum dose of 45 mg	0.7 mg/kg, with a maximum dose of 24 mg
6 months to <2 years (At date of consent)	Dosed on the basis of milligrams per kilogram	NA	1.5 mg/kg with a maximum dose of 45 mg	0.75 mg/kg with a maximum dose of 24 mg
>28 days to <6 months (At date of consent)	Dosed on the basis of milligrams per kilogram	NA	0.8 mg/kg with a maximum dose of 12 mg	0.4 mg/kg, with a maximum dose of 6 mg
38 weeks' gestation to <28 days (At date of consent)	Dosed on the basis of milligrams per kilogram	NA	0.4 mg/kg with a maximum dose of 6 mg	0.4 mg/kg, with a maximum dose of 6 mg

eGFR = estimated glomerular filtration rate;

NA = not applicable; P-gp = P-glycoprotein; QD = once a day

^a 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 randomisation as determined by the age-appropriate formula: Cockcroft-Gault equation for paediatric subjects ≥12 years of age and modified Schwartz equation for paediatric subjects <12 years of age). Refer to Appendix 17.7 of the protocol for eGFR values below which dose reduction should have been implemented.

If a subject experienced a change in renal function from normal to eGFR ≥30% to ≤50% after randomisation, the measurement will be repeated within 1 week to 10 days after correction of the underlying factors causing preazotemia. 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.

- ^b 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.
- ^c Edoxaban dosage regimen was reduced permanently for subject with body weight <fifth percentile for age.
- ^d Edoxaban granulation was diluted with 8 mL of water to provide a concentration of 6-mg/mL dosing suspension. 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.
- ^e Edoxaban granules were for subjects <12 years of age only. Subjects 12 to <18 years of age used crushed edoxaban tablets. For those subjects could not swallow whole tablets, edoxaban tablets may have been crushed and mixed with 2 to 3 ounces of water and immediately administered by mouth or through a gastric tube. The crushed tablets could also be mixed into applesauce and immediately administered.
- Note: Dose was based upon weight at corresponding visit.

Sparse PK/PD samples were collected on the day of the fifth dose of edoxaban (Day 5 + 3 days). Predose PK samples were collected from all participating subjects. Postdose PK samples were taken at either any time between 0.5 to 3 hours after dosing or any time between 3 to 8 hours after dosing. The PD sampling time on Day 5 for measurement of PT, aPTT, and anti-FXa was the same time as the PK sampling time.

Plasma concentrations for edoxaban are summarised in Table 3.9.

Table 3.9: Summary of Plasma Concentrations of Edoxaban (Study DU176b-D-U312)

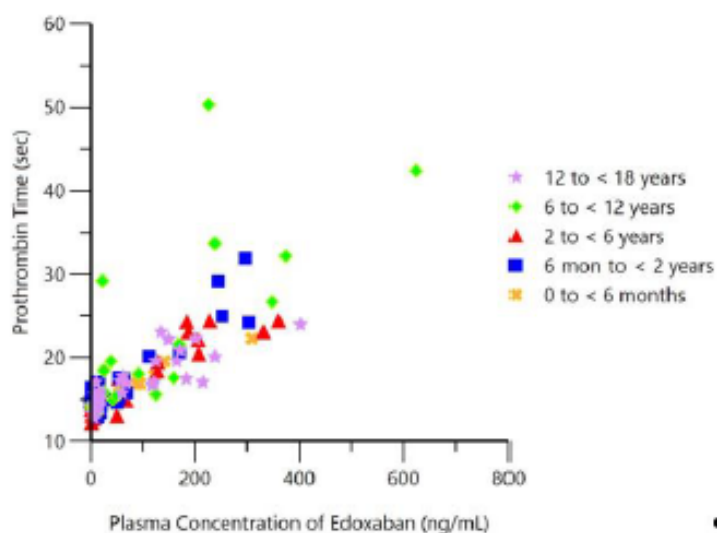
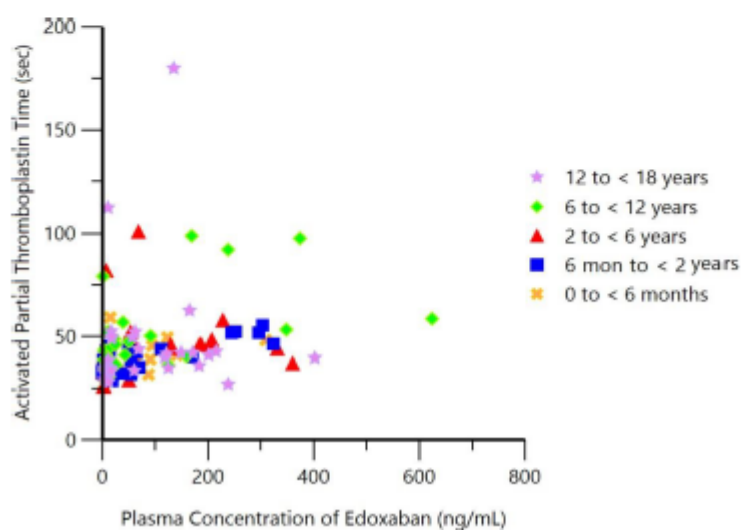
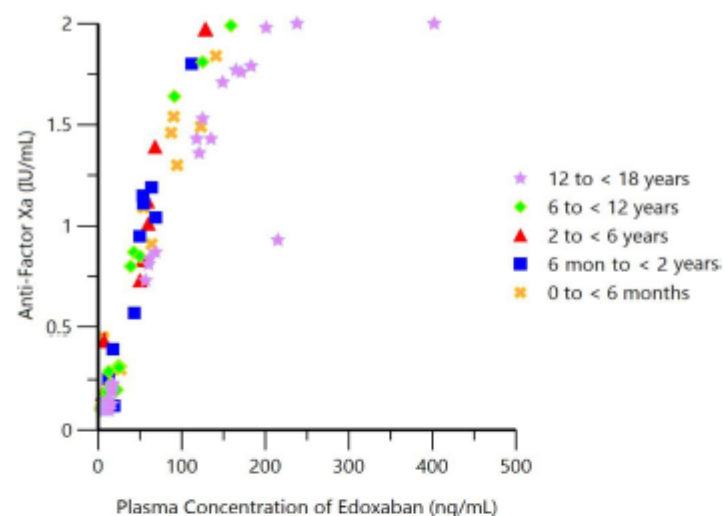
Age Group	Dosage	Statistic	Plasma Concentration of Edoxaban (ng/mL) ^a		
			Predose (t=0)	0.5 to 3 Hours	3 to 8 Hours
12 to <18 Years	30 mg	n	1	1	0
		Mean $\pm$ SD	10.70	10.50	NA
	45 mg	n	9	5	4
		Mean $\pm$ SD	8.62 $\pm$ 5.09	145.20 $\pm$ 84.79	109.50 $\pm$ 52.77
	60 mg	n	11	8	3
		Mean $\pm$ SD	14.76 $\pm$ 16.15	139.67 $\pm$ 124.93	152.66 $\pm$ 54.09
6 to <12 Years	All	n	12	5	7
		Mean $\pm$ SD	13.30 $\pm$ 11.09	319.36 $\pm$ 219.14	125.02 $\pm$ 69.95
2 to <6 Years	All	n	14	4	10
		Mean $\pm$ SD	7.10 $\pm$ 5.12	281.25 $\pm$ 75.66	112.60 $\pm$ 62.39
6 Months to <2 Years	All	n	12	5	7
		Mean $\pm$ SD	17.03 $\pm$ 20.11	215.00 $\pm$ 104.42	144.48 $\pm$ 105.84
0 to <6 Months	All	n	9	4	5
		Mean $\pm$ SD	15.38 $\pm$ 19.75	213.75 $\pm$ 95.32	80.70 $\pm$ 16.04

CV = coefficient of variation; Min = minimum; Max = maximum; SD = standard deviation; SE = standard error.

^a Sampling time points as per protocol, Version 1, are Baseline, 0.5 to 2 hours or 3 to 8 hours. Sampling time points as per protocol, Versions 2 and 3, are Baseline, 1 to 3 hours, or 3 to 8 hours.

Compared with predose levels, edoxaban treatment increased the levels of PT, aPTT, and anti-FXa in patients from birth to <18 years old. A plot of plasma edoxaban concentration and anti-FXa demonstrated a linear relationship between the 2 across 5 paediatric cohorts and the curves were overlaid among 5 paediatric cohorts (Figure 3.5).

Figure 3.5: Pharmacokinetic and Pharmacodynamic (anti-FXa, aPTT and PT) Relationships of Edoxaban in Paediatric Patients (Study DU176b-D-U312)



Pharmacokinetics and Pharmacodynamics of Edoxaban in Paediatric Patients with Cardiac Diseases at Risk of Thromboembolic Events (DU176b-C-U313)

Study DU176b-C-U313 was a Phase 3, open-label, randomised, parallel-group, multicenter, observational study to evaluate and to compare the safety and efficacy of edoxaban against SOC anticoagulants [LMWH, unfractionated heparin, and vitamin K antagonists] in subjects with cardiac conditions at risk of thromboembolic events who require anticoagulation.

The doses of edoxaban for each age cohort in this study were selected based on edoxaban exposure for age-matched subjects and safety data from DU176b-A-U157 study and on PopPK analyses. The age- and body weight-based doses were the same as that used in Study DU176b- D-U312 (Table 3.8). Edoxaban was supplied in 1-month treatment intervals as tablets (15 mg and/or 30 mg strengths) or granules for oral suspension (60 mg, 6 mg/mL). Subjects were instructed to take edoxaban (tablets or granules) orally once a day (QD), at the same time every day, with or without food.

Predose PD samples for measurement of PT, aPTT, and anti-FXa were collected from study participants on Day 1. Sparse PK/PD samples were collected during Month 1 visit (Day 30 $\pm$ 5 days). During the visit, one predose PK sample was collected and one postdose PK sample was taken at any time between 1 to 3 hours after dosing. For an individual subject, PD samples and PK samples were collected at the same time points during Month 1 visit.

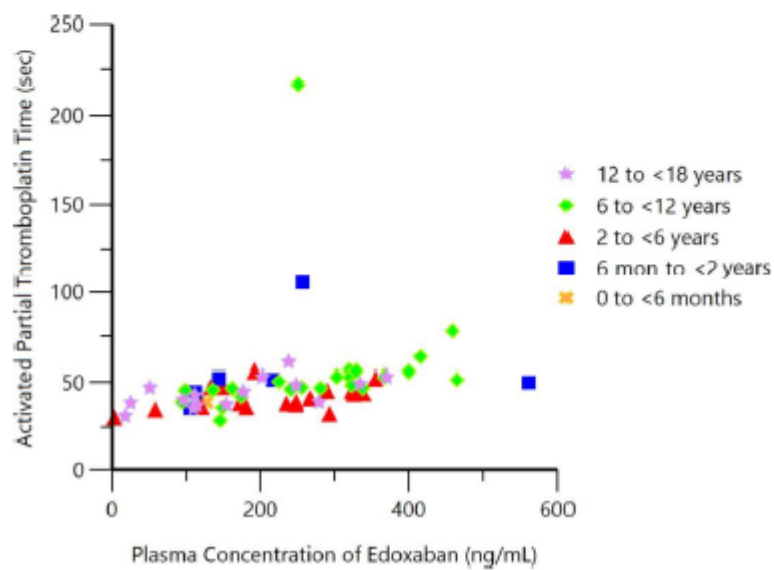
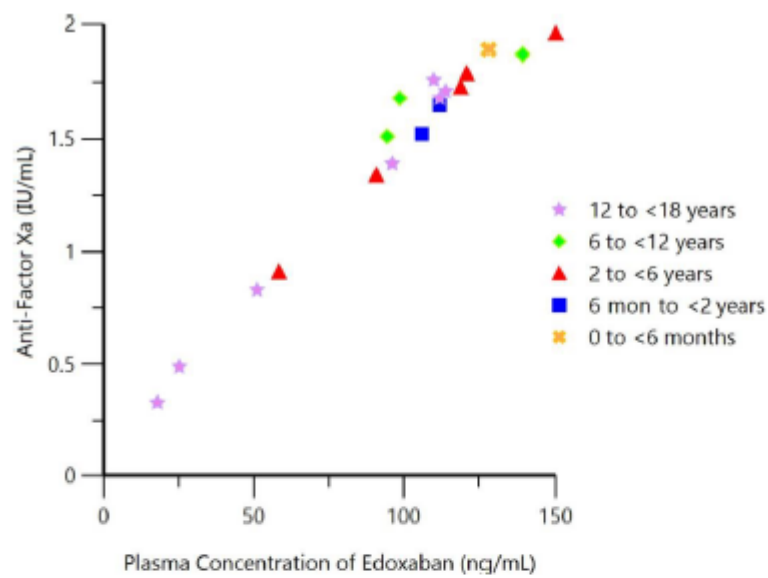
Plasma concentrations for edoxaban are summarised in Table 3.11.

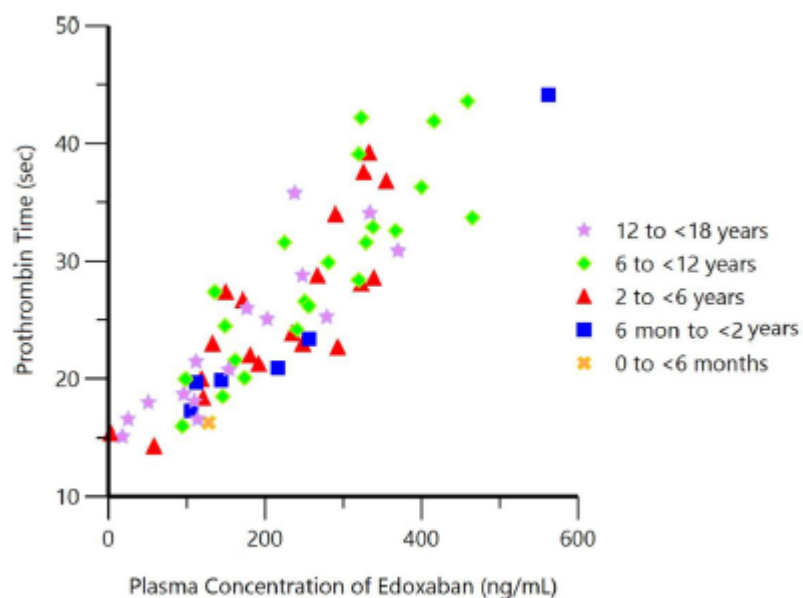
Table 3.11: Summary of Plasma Concentrations of Edoxaban (Study DU176b-C-U313)

Age Group	Dosage	Statistic	Plasma Concentration of Edoxaban (ng/mL)	
			Predose (t = 0)	1 to 3 Hours After Dose
12 to <18 Years	All	n	18	17
		Mean $\pm$ SD	16.40 $\pm$ 11.72	183.02 $\pm$ 110.48
6 to <12 Years	All	n	25	25
		Mean $\pm$ SD	38.59 $\pm$ 85.70	266.25 $\pm$ 109.50
2 to <6 Years	All	n	23	23
		Mean $\pm$ SD	13.85 $\pm$ 12.75	218.85 $\pm$ 109.83
6 Months to <2 Years	All	n	6	6
		Mean $\pm$ SD	22.58 $\pm$ 23.46	233.00 $\pm$ 171.91
0 to < 6 Months	All	n	1	1
		Mean $\pm$ SD	2.00	128.00

Compared to predose levels, edoxaban treatment increased the levels of PT and anti-FXa across the five age cohorts from birth to <18 years. Although the sample size of each cohort was small, a plot of plasma edoxaban concentration and anti-FXa demonstrated a linear relationship between the two across five paediatric cohorts and the curves were overlaid among 5 paediatric cohorts (Figure 3.6).

Figure 3.6: Pharmacokinetics and Pharmacodynamics (anti-FXa, aPTT and PT) Relationships of Edoxaban in Paediatric Patients (Study DU176b-C-U313)





Population PK-PD and Exposure-Response Modeling with Simulations of Edoxaban

The objectives of the analysis were as follows:

- To develop a population PK model for edoxaban that describes data pooled from pediatric patients
- To compare the exposure of edoxaban in pediatric and adult patient populations
- To develop a population PKPD model to describe activated partial thromboplastin time (APTT) behavior due to edoxaban administration in pediatric patients
- To develop a population PKPD model to describe prothrombin time (PT) behavior due to edoxaban administration in pediatric patients
- To develop a population PKPD model to describe anti-activated factor X (AFXA) behavior due to edoxaban administration in pediatric patients
- To compare the PK-PD relationships in pediatric and adult patient populations
- To use population PK, PKPD, and exposure-response analyses to evaluate dosing options in the pediatric patients

The following clinical studies were included in the pharmacometrics analyses of edoxaban:

Table: Clinical Studies Included in the Analysis

Study Number, Phase, Type	Number of Subjects with PK data	Edoxaban Dose and Regimen	[PK and/or PD] Sampling
DU176B-A-U157	N=66	Weight adjusted single dose or flat dose depending on age	0.25-1hr, 1.5-3hr, 3.5-6hr, 6.5-8hr, 8.5-14hr, 24-36hr, 48-54hr
DU176B-D-U312	N=69	Weight adjusted once-daily dose or flat dose depending on age	0hr, Day 5+3 days 1-3hr or 5-8hr
DU176B-C-U313	N=73	Weight adjusted once-daily dose or flat dose depending on age	Predose, between 1 and 3 hour postdose

Abbreviations: PK = pharmacokinetic; PD = pharmacodynamic

For the population PK analysis, an individual was defined as evaluable if both of the following criteria were satisfied:

1. Received at least one dose of Edoxaban
2. Had at least one measurable Edoxaban concentration observation with associated sampling time and dosing information

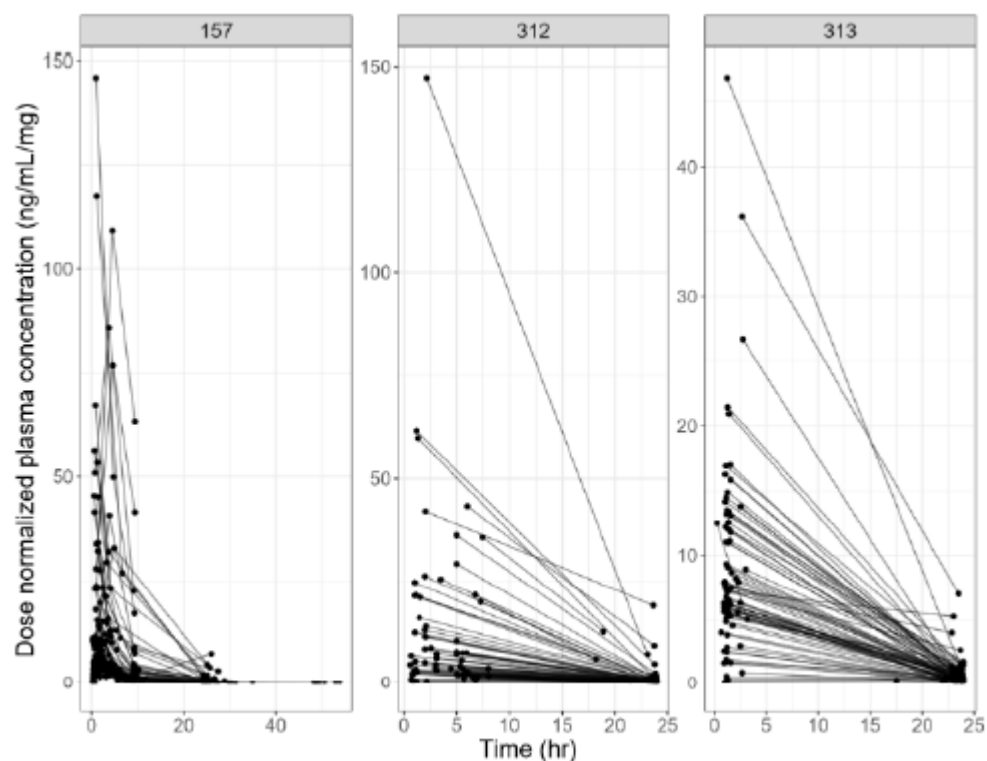
For the pharmacokinetic-pharmacodynamic (PK-PD) analysis, an individual was defined as evaluable if both of the following criteria were satisfied:

1. Had at least one PD measurement with associated sampling time
2. Had individual PK parameter estimates from the population PK analysis

The PK analysis of edoxaban data included 208 subjects with 589 measurable PK observations.

The edoxaban dose was adjusted depending on age. In the U157 study, patients were each given a single dose, while U312 and U313 utilized QD dose regimens. The dose normalized concentration-time profiles are presented in Figure 1.

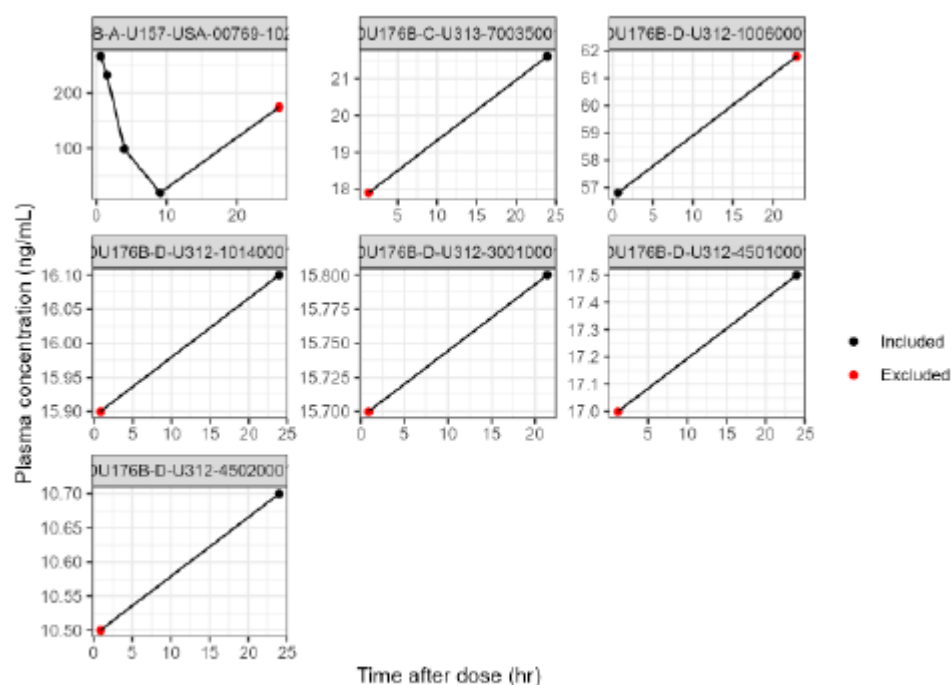
Figure 1 Dose-Normalized Observed Concentration-Time Profiles of Edoxaban



Source: [Edoxaban-Popk-Model-summary-17oct2022.html](https://www.ema.europa.eu/en/documents/assessment-report/edoxaban-popk-model-summary-17oct2022_en.pdf)

There were 7 PK observations that were unrealistic and were excluded from the analysis. The excluded PK points are shown in Figure 2, where the red points indicate the excluded observations.

Figure 2 PK Observations that are Excluded from the Analysis



Source: [Edoxaban-Popk-Model-summary-17oct2022.html](https://www.ema.europa.eu/en/documents/assessment-report/edoxaban-popk-model-summary-17oct2022_en.pdf)

Statistical summaries of the categorical covariates are presented in Table 5.

Table 5 Categorical Covariate Summary

Study	U157 (N=66)	U312 (N=69)	U313 (N=73)	Overall (N=208)
Formulation				
Suspension	51 (77.3%)	48 (69.6%)	54 (74.0%)	153 (73.6%)
Tablet	15 (22.7%)	21 (30.4%)	19 (26.0%)	55 (26.4%)
Fed status				
Fasted	66 (100%)	61 (88.4%)	67 (91.8%)	194 (93.3%)
Fed	0 (0%)	8 (11.6%)	6 (8.2%)	14 (6.7%)
Sex				
Female	31 (47.0%)	29 (42.0%)	23 (31.5%)	83 (39.9%)
Male	35 (53.0%)	40 (58.0%)	50 (68.5%)	125 (60.1%)
Race				
Asian	11 (16.7%)	11 (15.9%)	6 (8.2%)	28 (13.5%)
Black	10 (15.2%)	6 (8.7%)	4 (5.5%)	20 (9.6%)
Other	2 (3.0%)	10 (14.5%)	10 (13.7%)	22 (10.6%)
White	43 (65.2%)	40 (58.0%)	43 (58.9%)	126 (60.6%)
Unknown	0 (0%)	2 (2.9%)	10 (13.7%)	12 (5.8%)
Ethnic				
Hispanic or latino	6 (9.1%)	16 (23.2%)	4 (5.5%)	26 (12.5%)
Not hispanic or latino	58 (87.9%)	51 (73.9%)	59 (80.8%)	168 (80.8%)
Unknown	2 (3.0%)	2 (2.9%)	10 (13.7%)	14 (6.7%)
PGP Inhibitors				
No	65 (98.5%)	67 (97.1%)	69 (94.5%)	201 (96.6%)
Yes	1 (1.5%)	2 (2.9%)	4 (5.5%)	7 (3.4%)
PGP Inducers				
No	65 (98.5%)	69 (100%)	73 (100%)	207 (99.5%)
Yes	1 (1.5%)	0 (0%)	0 (0%)	1 (0.5%)
Antiplatelets				
No	59 (89.4%)	68 (98.6%)	50 (68.5%)	177 (85.1%)
Yes	7 (10.6%)	1 (1.4%)	23 (31.5%)	31 (14.9%)
Proton pump inhibitors				
No	64 (97.0%)	69 (100%)	73 (100%)	206 (99.0%)
Yes	2 (3.0%)	0 (0%)	0 (0%)	2 (1.0%)
NSAIDs				
No	66 (100%)	69 (100%)	73 (100%)	208 (100%)

Source: Edoxaban-Popk-Model-summary-17oct2022.html

Abbreviations: N = Number of subjects; NSAIDs = Non-steroidal anti-inflammatory drugs; PGP = P-glycoprotein

Statistical summaries of the continuous covariates are presented in Table 6.

None of the continuous covariates had >20% of missing values; hence, all continuous covariates were included as planned in the analysis.

Table 6 Continuous Covariate Summary

Study	U157 (N=66)	U312 (N=69)	U313 (N=73)	Overall (N=208)
Alanine Aminotransferase (ukat/L)				
Mean (SD)	0.440 (0.331)	0.672 (0.570)	0.339 (0.188)	0.485 (0.420)
Median [Min, Max]	0.365 [0.0830, 2.24]	0.536 [0.0835, 2.86]	0.301 [0.0835, 1.32]	0.365 [0.0830, 2.86]
Missing	1 (1.5%)	0 (0%)	4 (5.5%)	5 (2.4%)
Aspartate Aminotransferase (ukat/L)				
Mean (SD)	0.561 (0.213)	0.660 (0.463)	0.482 (0.141)	0.560 (0.297)
Median [Min, Max]	0.548 [0.199, 1.10]	0.518 [0.150, 2.59]	0.468 [0.200, 0.768]	0.504 [0.150, 2.59]
Missing	1 (1.5%)	16 (23.2%)	5 (6.8%)	22 (10.6%)
Bilirubin (umol/L)				
Mean (SD)	16.2 (20.5)	9.52 (8.77)	9.95 (10.6)	11.8 (14.3)
Median [Min, Max]	9.58 [1.71, 113]	6.67 [2.00, 55.6]	8.55 [1.71, 61.6]	8.00 [1.71, 113]
Creatinine (umol/L)				
Mean (SD)	0.431 (0.201)	0.446 (0.226)	0.473 (0.192)	0.451 (0.206)
Median [Min, Max]	0.395 [0.170, 0.850]	0.400 [0.0400, 1.21]	0.420 [0.160, 1.12]	0.410 [0.0400, 1.21]
Estimated glomerular filtration rate (mL/min/1.73 m²)				
Mean (SD)	116 (43.0)	131 (101)	115 (29.4)	121 (65.5)
Median [Min, Max]	110 [29.5, 258]	110 [34.1, 774]	115 [53.3, 219]	111 [29.5, 774]
Hemoglobin (g/L)				
Mean (SD)	126 (25.4)	111 (23.7)	134 (19.9)	124 (24.8)
Median [Min, Max]	126 [80.0, 189]	112 [55.0, 169]	135 [81.0, 180]	125 [55.0, 189]
Missing	0 (0%)	6 (8.7%)	7 (9.6%)	13 (6.3%)
Body weight (kg)				
Mean (SD)	27.2 (26.6)	31.9 (29.5)	29.3 (20.6)	29.5 (25.7)
Median [Min, Max]	18.2 [2.70, 157]	21.3 [2.60, 138]	21.8 [6.20, 90.0]	21.1 [2.60, 157]
Age (years)				
Mean (SD)	6.58 (6.05)	7.51 (6.43)	7.98 (4.98)	7.38 (5.83)
Median [Min, Max]	5.24 [0.0110, 17.6]	5.59 [0.0769, 17.9]	7.09 [0.503, 17.9]	6.06 [0.0110, 17.9]
Post-menstrual age (weeks)				
Mean (SD)	380 (315)	429 (334)	453 (259)	422 (303)
Median [Min, Max]	311 [38.6, 954]	329 [42.0, 970]	407 [64.1, 968]	353 [38.6, 970]

Source: Edoxaban-Popk-Model-summary-17oct2022.html

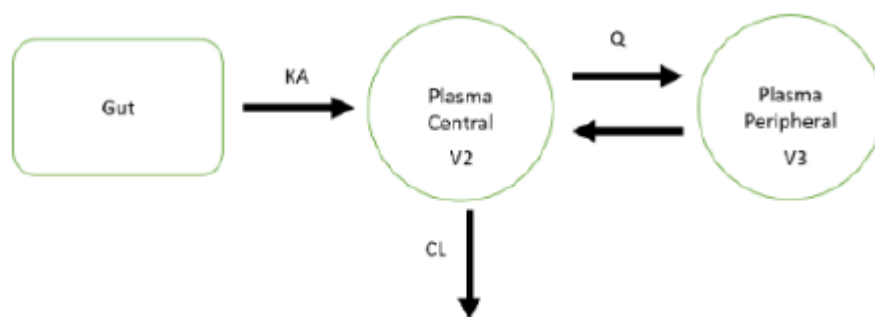
Note: This table includes imputation of Bilirubin according to the rules discussed.

Abbreviations: Min = minimum; Max = maximum; SD = standard deviation

Base model

The selected Base model is a two-compartment model with linear elimination as represented in Figure 3.

Figure 3 Two Compartment Model with Linear Elimination



Source: [Edoxaban-Popk-Model-summary-17oct2022.html](#)

Since all the studies in the analysis included only pediatric subjects, the effects of postmenstrual age (PMA) on clearance were tested for possible inclusion in the population PK (popPK) model. The effects of PMA and eGFR on clearance were each significant. Therefore, both the PMA and eGFR effects on clearance were added to the base model.

The effects of body weight on CL, Q, V2, and V3 were also tested in the model, both by estimating the exponents and by using body weight allometric exponents (V2 and V3 body weight exponents were fixed to 1; CL and Q body weight exponents were fixed to 0.75). The change in the fit and the change in the OFV (decrease of 4 pts) from estimating the body weight exponents to using the fixed allometric model exponents was negligible. Adding allometric exponents of body weight to the model represents an overall improvement to the model. Additionally, there is a physiological and historical precedent of allometry, and therefore, the parsimonious reduced allometric model was taken forward.

Covariate selection

A systematic univariate search was performed.

The fed status was not tested as a covariate in the univariate search because of the 208 subjects with PK data only 14 (6.7%) received edoxaban under fed state. In the univariate search only one covariate effect (formulation on KA) was shown to be statistically significant at the 0.01 level, with a P-value of 0.000692. Since the Pvalue is < 0.001, this covariate was added to the final model. The univariate search results are presented in the Table 7. Since only one covariate effect had a P-value < 0.001, a full stepwise covariate modeling was not run.

Final Model

The parameter estimates for the final popPK model are presented in Table 8.

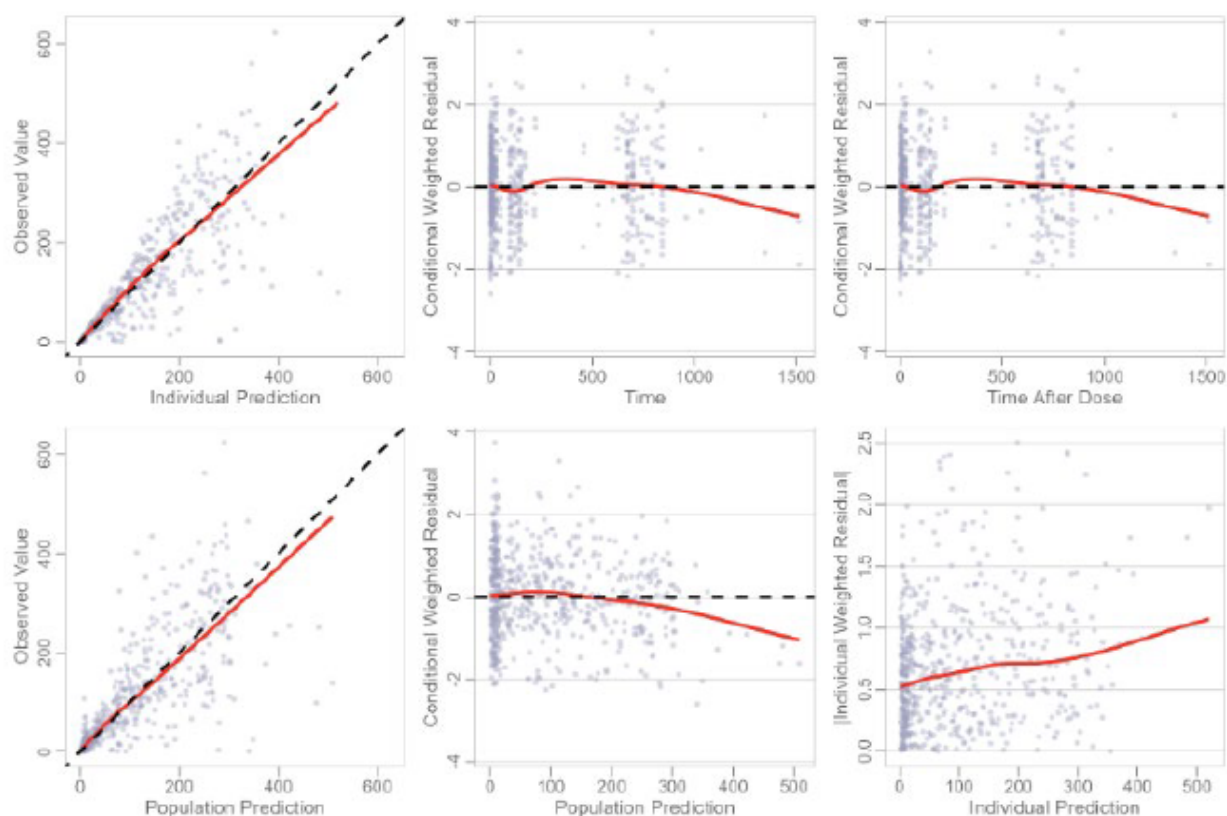
Table 8 Population PK Model Estimates in a Pediatric Patient (body weight = 70 kg and eGFR = 110 mL/min/1.73 m²)

PK parameter	Estimate	RSE	Bootstrap median	Bootstrap 95% CI
Apparent clearance, CL/F (L/h)*	44.19	3%	44.0	41.5 – 46.9
Absorption rate constant, KA (1/h)	0.365	10%	0.35	0.27 - 0.45
Apparent central compartment volume, V2/F (L)	44	22%	42.1	18.1 - 70
Apparent inter-compartmental clearance, Q2/F (L/h)	15.7	16%	15.2	9.45 – 21.26
Apparent peripheral compartment volume, V3/F (L)	262.1	11%	271	216 - 504
Hill coefficient of maturation function, HILL	3.4 (Fixed)	-	-	-
Post-menstrual age at half max of the maturation function, TM50 (weeks)	47.7 (Fixed)	-	-	-
eGFR effect on clearance	0.264	27%	0.265	0.12 – 0.41
Formulation effect on absorption	-0.232	24%	-0.245	-0.37 – 0.11
Inter individual variability (IIV)	Estimate	RSE		
IIV Clearance	34%	7%	34%	28% - 38%
IIV Central compartment volume	36%	25%	36%	13% - 83%
IIV Inter-compartmental clearance	49%	30%	51%	25% - 90%
Residual variability	Estimate	RSE		
Proportional error	0.41	5%	0.40	0.33 – 0.44
Additive error (ng/mL)	0.69	78%	0.57	0.138 – 1.28

Source: Edoxaban-Popk-Model-summary-17oct2022.html

* $CL/F = CL/F_{TYP} * (WT/70)^{0.75} * (eGFR/110)^{0.246} * [PMA^{3.4}/(47.7^{3.4} + PMA^{3.4})]$; CL/F_{TYP} is the estimated CL/F for a patient with eGFR = 110 mL/min/1.73 m² and body weight = 70 kg;
PMA= post-menstrual age in weeks

Figure 4 Goodness of Fit Plots Demonstrating Edoxaban Observations vs. Population and Individual Predictions and CWRES vs. Time



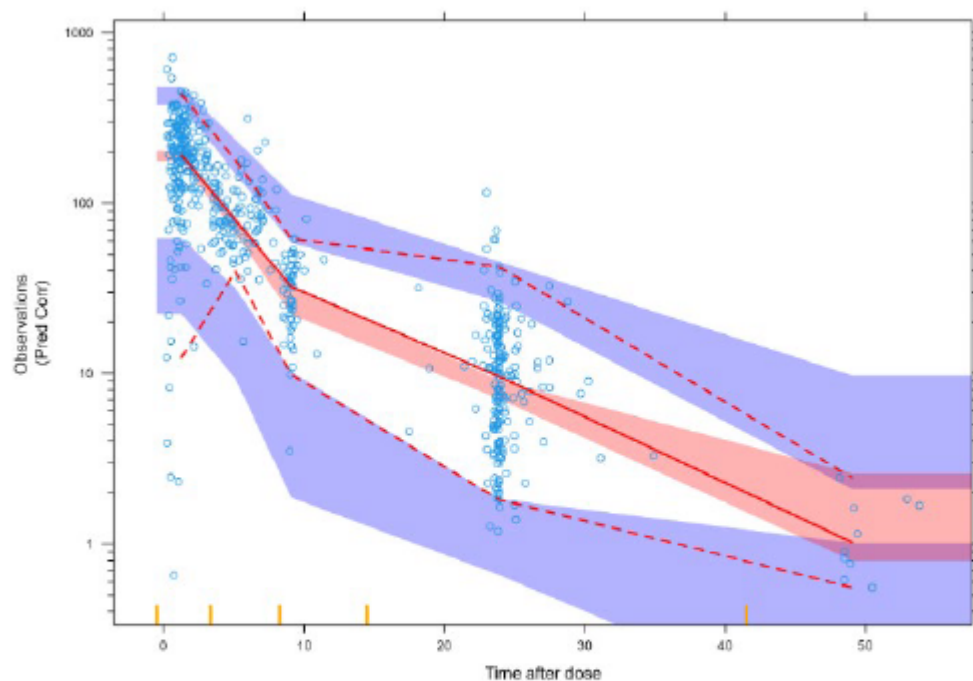
Source: [Edoxaban-Poppk-Model-summary-17oct2022.html](https://www.ema.europa.eu/en/documents/assessment-report/edoxaban-poppk-model-summary-17oct2022_en.pdf)

Abbreviation: CWRES = conditional weighted residuals

Notes: The dashed black lines represent the line of unity in the observations versus predictions plots and $y = 0$ in the Conditional Weighted Residuals plots. The solid orange lines are smooth regression lines.

A prediction-corrected visual predictive check (pcVPC) for the popPK model was performed and is displayed in Figure 5. A pcVPC stratified by age groups for the popPK model was performed and is displayed in Figure 6.

Figure 5 Prediction-Corrected Visual Predictive Check of Observations vs. Time After Dose (Semilogarithmic Scale)

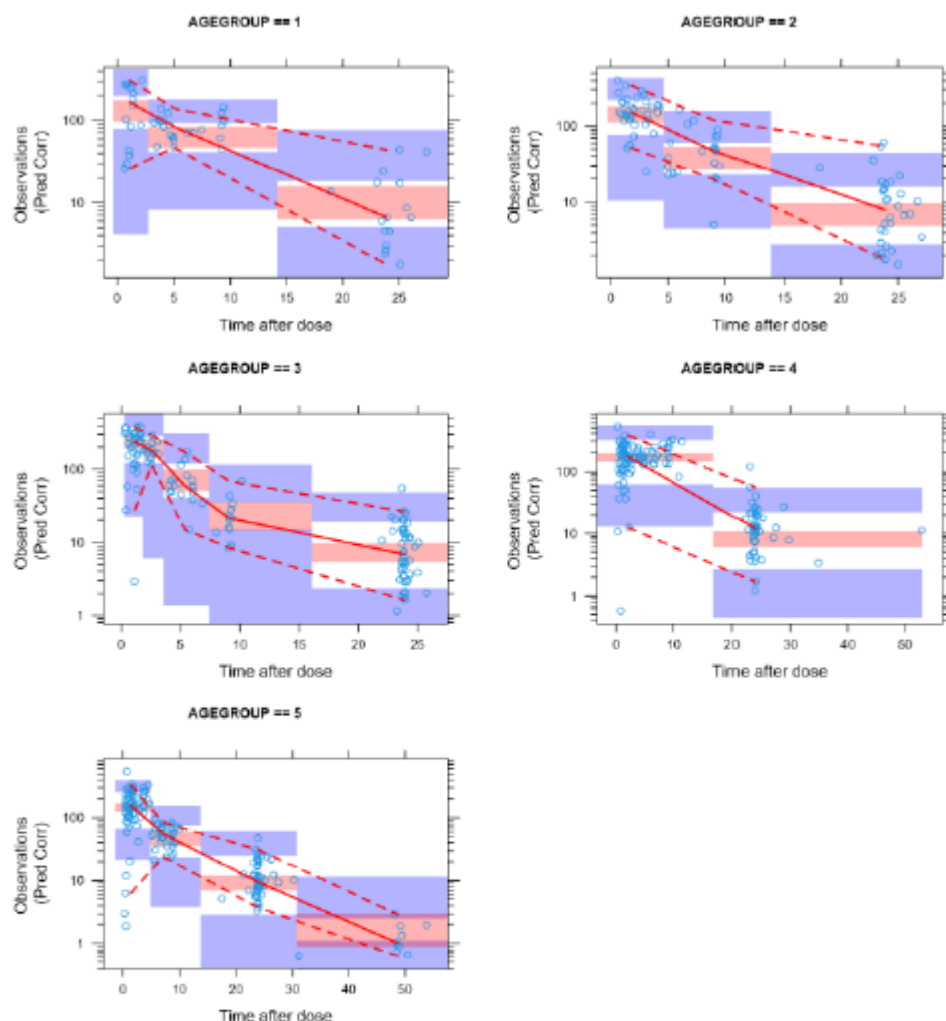


Source: [Edoxaban-Popk-Model-summary-17oct2022.html](#)

Abbreviation: CI = confidence interval

Notes: The solid red line is the simulated median, and the dashed red lines are the simulated 5th and 95th percentiles, respectively. The red-shaded area is the 95% CI of the simulated median, and the blue-shaded areas are the 95% CIs of the simulated 5th and 95th percentiles.

Figure 6 Prediction-Corrected Visual Predictive Check of Observations vs. Time After Dose, by Age Group (Semilogarithmic Scale)



Source: [Edoxaban-Popk-Model-summary-17oct2022.html](https://www.edoxaban.com/Model-summary-17oct2022.html)

Notes: The solid red line is the simulated median, and the dashed red lines are the simulated 5th and 95th percentiles, respectively. The red-shaded area is the 95% CI of the simulated median, and the blue-shaded areas are the 95% CIs of the simulated 5th and 95th percentiles.

AGEGROUP = 1: Population of subjects with age ≤ 0.5 years; AGEGROUP = 2: Population of subjects with age > 0.5 years and ≤ 2 years; AGEGROUP = 3: Population of subjects with age > 2 years and ≤ 6 years; AGEGROUP = 4: Population of subjects with age > 6 years and ≤ 12 years; AGEGROUP = 5: Population of subjects with age > 12 years and ≤ 18 years

Population PK simulations

The source data was used to establish a covariance matrix to obtain a minimum of 1000 participants from each age group (0 to <0.5 years, 0.5 to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years) including the covariates like age, body weight, and eGFR.

The purpose of the simulations is to compare the pediatric exposures with the adult exposures and to assess if the age-, weight-, and eGFR-based pediatric doses are appropriate. The dosing regimen used for simulations is described in Table 9.

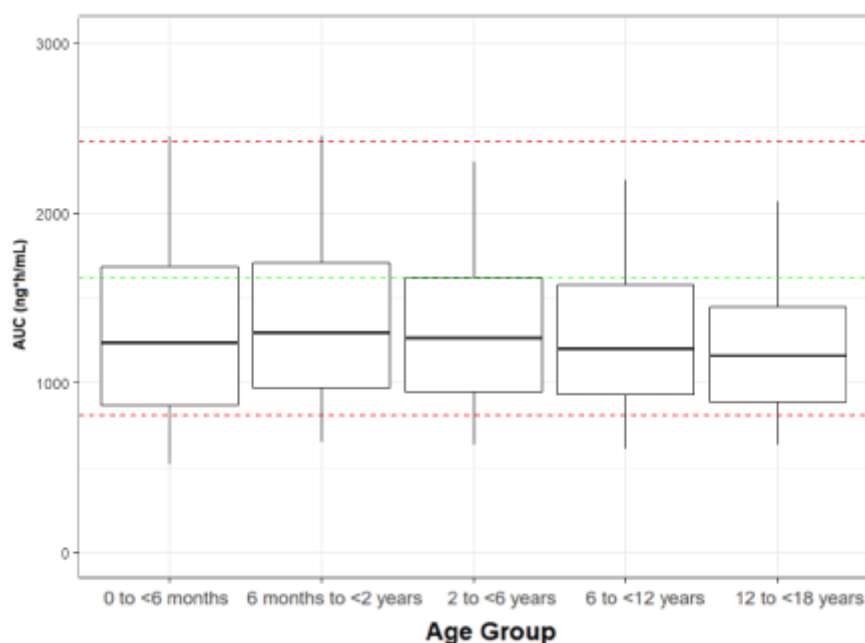
Table 9 Dosing Regimen for Simulations

Age	Body Weight	Dose (Tablet)	Dose (Suspension) (6 mg/mL concentration)	eGFR-based Dose Reduction ^a
12 to <18 years (At date of consent)	≥60 kg	60 mg QD	NA	45 mg QD
	≥30 and <60 kg	45 mg QD	NA	30 mg QD
	<30 kg	30 mg QD	NA	NA
6 to <12 years (At date of consent)	≥60 kg	NA	60 mg QD	45 mg QD
	≥60 kg	NA	60 mg QD	45 mg QD
	<60 kg Dosed based on mg/kg	NA	1.2 mg/kg with a maximum dose of 45 mg	0.8 mg/kg, with a maximum dose of 45 mg
2 to <6 years (At date of consent)	Dosed based on mg/kg	NA	1.4 mg/kg with a maximum dose of 45 mg	0.7 mg/kg, with a maximum dose of 24 mg
6 months to <2 years (At date of consent)	Dosed based on mg/kg	NA	1.5 mg/kg with a maximum dose of 45 mg	0.75 mg/kg with a maximum dose of 24 mg
0 to <6 months (At date of consent)	Dosed based on mg/kg	NA	0.8 mg/kg with a maximum dose of 12 mg	0.4 mg/kg, with a maximum dose of 6 mg

^a Edoxaban dosage regimen is reduced permanently for subjects with moderate renal impairment (eGFR 30% to ≤50% of normal for the subject's age and size).

The simulations were performed following the proposed clinical doses and the simulated AUC_{0-24h,ss} of the five age cohorts were compared with 0.5-fold and 1.5-fold median AUC_{0-24h,ss} of adult VTE patients receiving 60 mg QD dose (Figure 7).

Figure 7 Simulations by Age Group Using Dose Regimen Tested in Clinical Studies



Note: The upper and lower red lines represent 50% and 150% of the adult median patients, the green line represents the median of the adult patients.

Across the five age groups, the simulated 1st quartile, median, and 3rd quartile of AUC_{0-24h,ss} values with the proposed clinical dose fell within the adult reference range (0.5- to 1.5-fold of median AUC_{0-24h,ss} of adult VTE patients receiving 60 mg QD dose). The median AUC_{0-24h,ss} values for 0 to <0.5 year, 0.5 to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years cohorts are 1250, 1310, 1270, 1210, and 1160 ng*h/mL, respectively, which are lower than the median AUC_{0-24h,ss} (1613 ng*h/mL) of adult VTE patients receiving 60 mg QD dose.

The body weight-based dose adjustments for adolescent patients were assessed by simulations (Table 10). The 30 mg QD dose generated a steady-state exposure (median AUC_{0-24h,ss} = 1470 ng*h/mL) comparable to that of adult VTE patients receiving 60 mg QD dose. The proposed doses for adolescents with body weight of 30 kg to <60 kg and ≥60 kg resulted in median AUC_{0-24h,ss} values, 27% and 31%, respectively, lower than that of adult VTE patients receiving 60 mg QD dose. The eGFR-based dose adjustments for paediatric patients were also assessed by simulations (Table 11).

Table 10 Summary of Simulated AUC_{0-24,ss} of Edoxaban for Adolescent Patients by Body Weight Using Dose Regimen Tested in Clinical Studies

Body Weight	< 30 kg	30 kg to < 60 kg	≥ 60 kg
N	70	391	556
Mean ± SD (ng*h/mL)	1690 ± 1030	1240 ± 449	1190 ± 441
Median [Min, Max] (ng*h/mL)	1470 [516, 5470]	1170 [457, 3080]	1120 [337, 3510]

Note: Subjects with body weight <30 kg received 30 mg QD. Subjects with body weight between 30 kg to <60 kg received 45 mg QD (eGFR > 50% of normal) or 30 mg QD (eGFR between 30% to 50% of normal). Subjects with body weight ≥60 kg received 60 mg QD (eGFR > 50% of normal) or 45 mg QD (eGFR between 30% to 50% of normal).

Table 11 Summary of Simulated AUC_{0-24,ss} of Edoxaban for Paediatric Patients by Age and eGFR Using Dose Regimen Tested in Clinical Studies

	0 to <6 months		6 months to <2 years		2 to <6 years		6 to <12 years		12 to <18 years	
% of eGFR of Normal (%)	30-50	>50	30-50	>50	30-50	>50	30-50	>50	30-50	>50
Dose	0.4 mg/kg	0.8 mg/kg	0.75 mg/kg	1.5 mg/kg	0.7 mg/kg	1.4 mg/kg	0.8 mg/kg	1.2 mg/kg	45 or 30 mg ^a	60, 45 or 30 mg ^a
N	61	1184	19	1017	8	1014	10	1000	19	998
Mean (SD) ng*h/mL	660 (242)	1390 (634)	883 (331)	1430 (617)	754 (371)	1340 (527)	1220 (522)	1310 (521)	916 (269)	1250 (522)
Median [Min, Max] ng*h/mL	632 [231, 1470]	1280 [176, 4540]	888 [277, 1730]	1320 [367, 4460]	586 [439, 1520]	1270 [294, 4050]	1280 [400, 1980]	1210 [251, 3550]	811 [598, 1590]	1170 [337, 5470]

^aDose is adjusted by body weight.

6.4. PK/PD Modelling

Population PK-PD Analysis

The PD data used for population PK-PD analysis are summarized in Tables 12 – 17. The effects of intrinsic and extrinsic factors (race, gender, age, weight, eGFR, studies, and concomitant use of antiplatelets) on the PK/PD relationships were explored by using correlational plots of PD endpoints against plasma edoxaban concentrations. No obvious effect of these factors on the PK/PD relationships of edoxaban was observed. Furthermore, the PK/PD relationships of edoxaban were compared among five paediatric groups and adult VTE patients (Figures 15 - 17).

Table 12 Records in the PD Dataset Used for Analysis of AFXA

Study	U157 (N=297)	U312 (N=186)	U313 (N=112)	Total (N=595)
Record status				
Baseline record	7 (2.4%)	0 (0%)	2 (1.8%)	9 (1.5%)
Post-treatment record	118 (39.7%)	87 (46.8%)	19 (17.0%)	224 (37.6%)
Excluded - Missing Value	147 (49.5%)	55 (29.6%)	53 (47.3%)	255 (42.9%)
Excluded - No edoxaban concentration	25 (8.4%)	44 (23.7%)	20 (17.9%)	89 (15.0%)
Excluded - Below limit of quantification	0 (0%)	0 (0%)	18 (16.1%)	18 (3.0%)

Source: edoxaban-pkpd-eda-20221003.html

AFXA = anti-activated Factor X; N = number of records

Table 13 Subjects in the PD Dataset Used for Analysis of AFXA

Study	U157 (N=66)	U312 (N=69)	U313 (N=72)	Total (N=207)
Subject status				
At least 1 baseline and 1 post-treatment analyzed record	3 (4.5%)	0 (0%)	0 (0%)	3 (1.4%)
At least 1 baseline analyzed record	4 (6.1%)	0 (0%)	2 (2.8%)	6 (2.9%)
At least 1 post-treatment analyzed record	37 (56.1%)	57 (82.6%)	19 (26.4%)	113 (54.6%)
Excluded	22 (33.3%)	12 (17.4%)	51 (70.8%)	85 (41.1%)

Source: edoxaban-pkpd-eda-20221003.html

AFXA = anti-activated Factor X; N = number of subjects

Table 14 Records in the PD Dataset Used for Analysis of APTT

Study	U157 (N=298)	U312 (N=184)	U313 (N=112)	Total (N=594)
Record status				
Baseline record	57 (19.1%)	0 (0%)	19 (17.0%)	76 (12.8%)
Post-treatment record	170 (57.0%)	119 (64.7%)	66 (58.9%)	355 (59.8%)
Excluded - Missing Value	33 (11.1%)	13 (7.1%)	7 (6.3%)	53 (8.9%)
Excluded - No edoxaban concentration	38 (12.8%)	52 (28.3%)	20 (17.9%)	110 (18.5%)

Source: edoxaban-pkpd-eda-20221003.html

Abbreviations: APTT = activated partial thromboplastin time; N = number of records

Table 15 Subjects in the PD Dataset Used for Analysis of APTT

Study	U157 (N=66)	U312 (N=69)	U313 (N=72)	Total (N=207)
Subject status				
At least 1 baseline and 1 post-treatment analyzed record	43 (65.2%)	0 (0%)	17 (23.6%)	60 (29.0%)
At least 1 baseline analyzed record	14 (21.2%)	0 (0%)	2 (2.8%)	16 (7.7%)
At least 1 post-treatment analyzed record	8 (12.1%)	64 (92.8%)	49 (68.1%)	121 (58.5%)
Excluded	1 (1.5%)	5 (7.2%)	4 (5.6%)	10 (4.8%)

Source: edoxaban-pkpd-eda-20221003.html

Abbreviations: APTT = activated partial thromboplastin time; N = number of subjects

Table 16 Records in the PD Dataset Used for Analysis of PT

Study	U157 (N=298)	U312 (N=184)	U313 (N=112)	Total (N=594)
Record status				
Baseline record	58 (19.5%)	0 (0%)	19 (17.0%)	77 (13.0%)
Post-treatment record	171 (57.4%)	119 (64.7%)	65 (58.0%)	355 (59.8%)
Excluded - Missing Value	28 (9.4%)	14 (7.6%)	8 (7.1%)	50 (8.4%)
Excluded - No edoxaban concentration	41 (13.8%)	51 (27.7%)	20 (17.9%)	112 (18.9%)

Source: edoxaban-pkpd-eda-20221003.html

Abbreviations: N = number of records; PT = prothrombin time

Table 17 Subjects in the PD Dataset Used for Analysis of PT

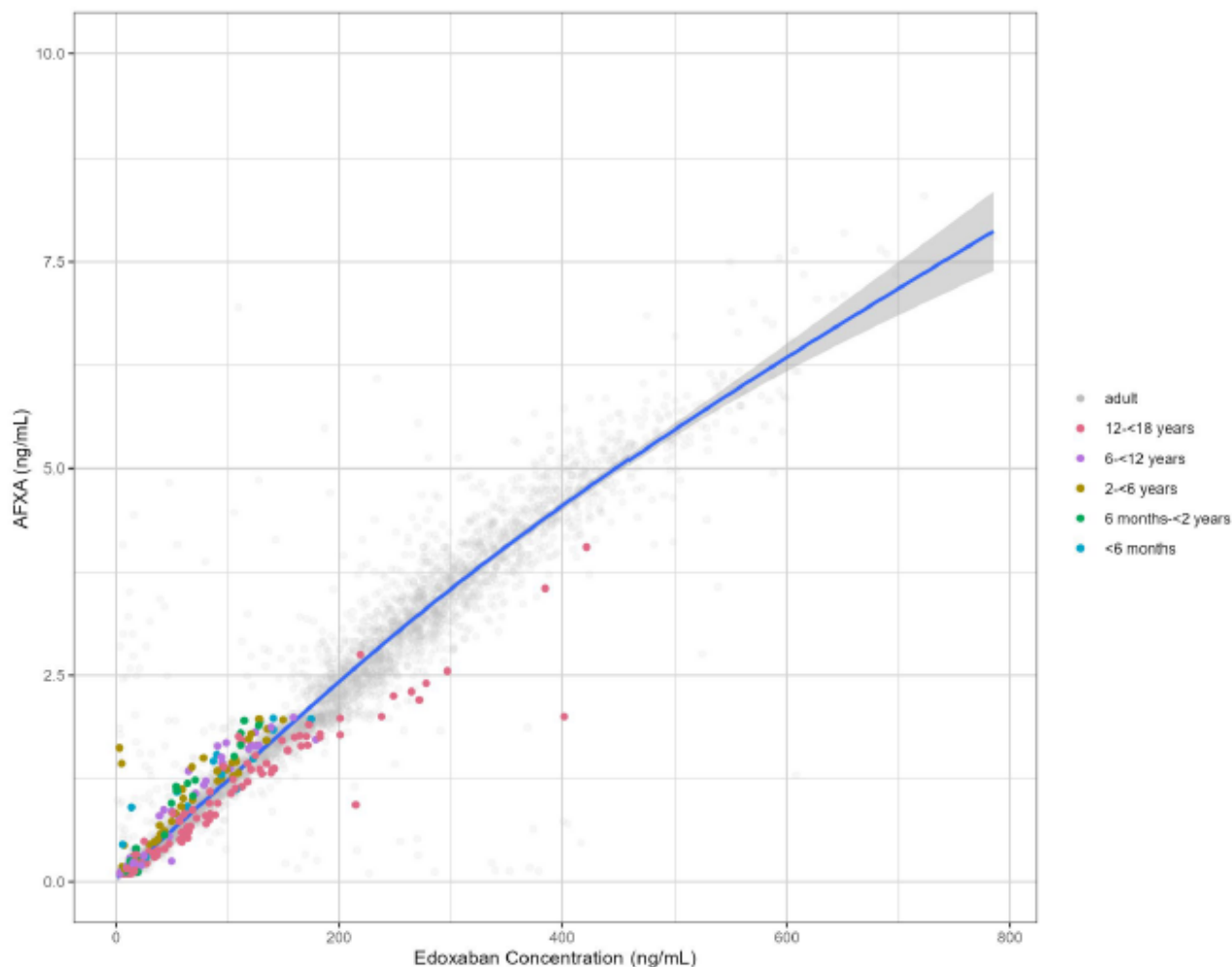
Study	U157 (N=66)	U312 (N=69)	U313 (N=72)	Total (N=207)
Subject status				
At least 1 baseline and 1 post-treatment analyzed record	44 (66.7%)	0 (0%)	16 (22.2%)	60 (29.0%)
At least 1 baseline analyzed record	14 (21.2%)	0 (0%)	3 (4.2%)	17 (8.2%)
At least 1 post-treatment analyzed record	7 (10.6%)	65 (94.2%)	49 (68.1%)	121 (58.5%)
Excluded	1 (1.5%)	4 (5.8%)	4 (5.6%)	9 (4.3%)

Source: edoxaban-pkpd-eda-20221003.html

Abbreviations: N = number of subjects; PT = prothrombin time

Furthermore, the PK/PD relationships of edoxaban were compared among five paediatric groups and adult VTE patients (Figures 15 - 17).

Figure 15 Comparison of AFXA vs. Observed Edoxaban Concentration in Adults and Children

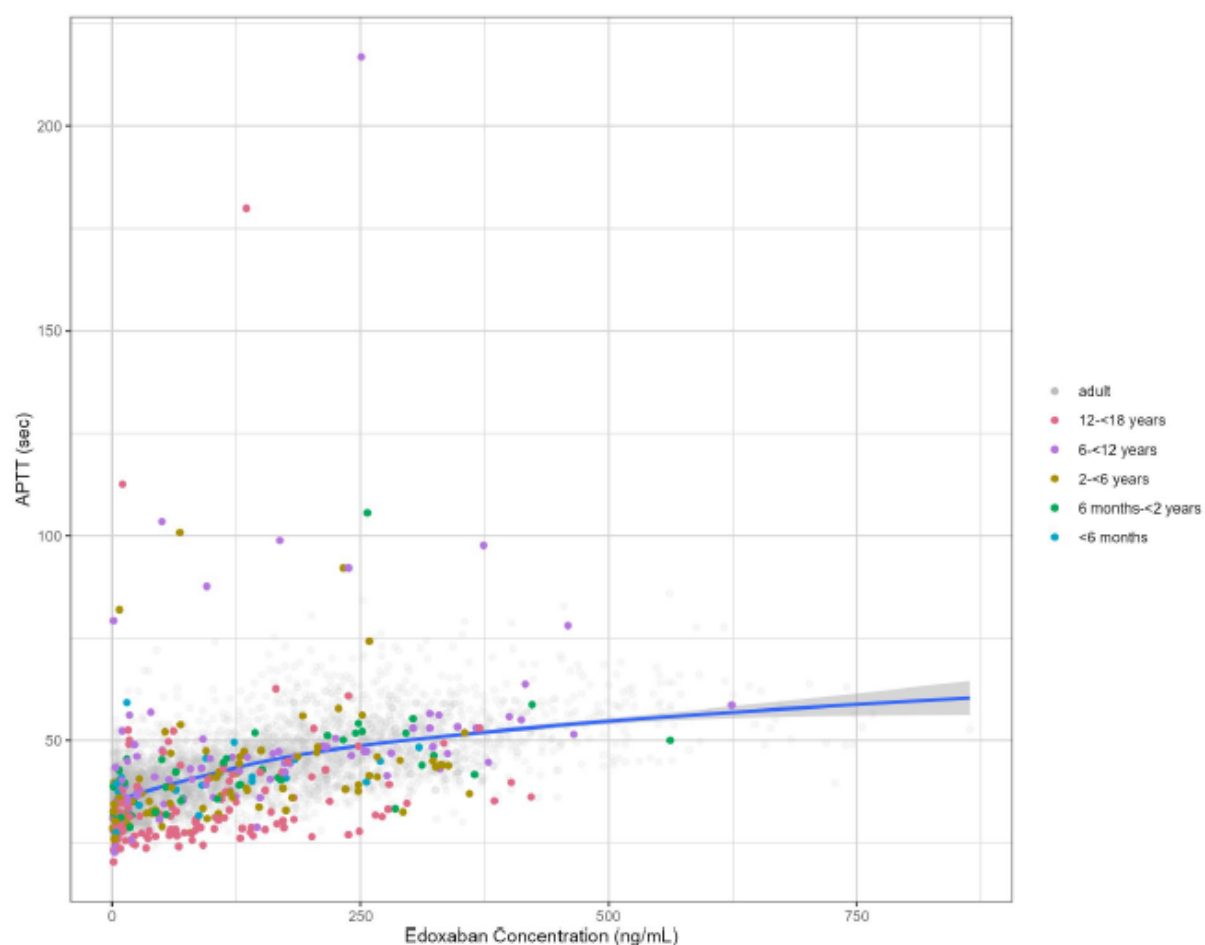


Source: edoxaban-pkpd-eda-20221003.html

Abbreviation: AFXA = anti-activated Factor X

Note: The blue line represents the LOESS fit of adult data

Figure 16 Comparison of APTT vs. Observed Edoxaban Concentration in Adults and Children

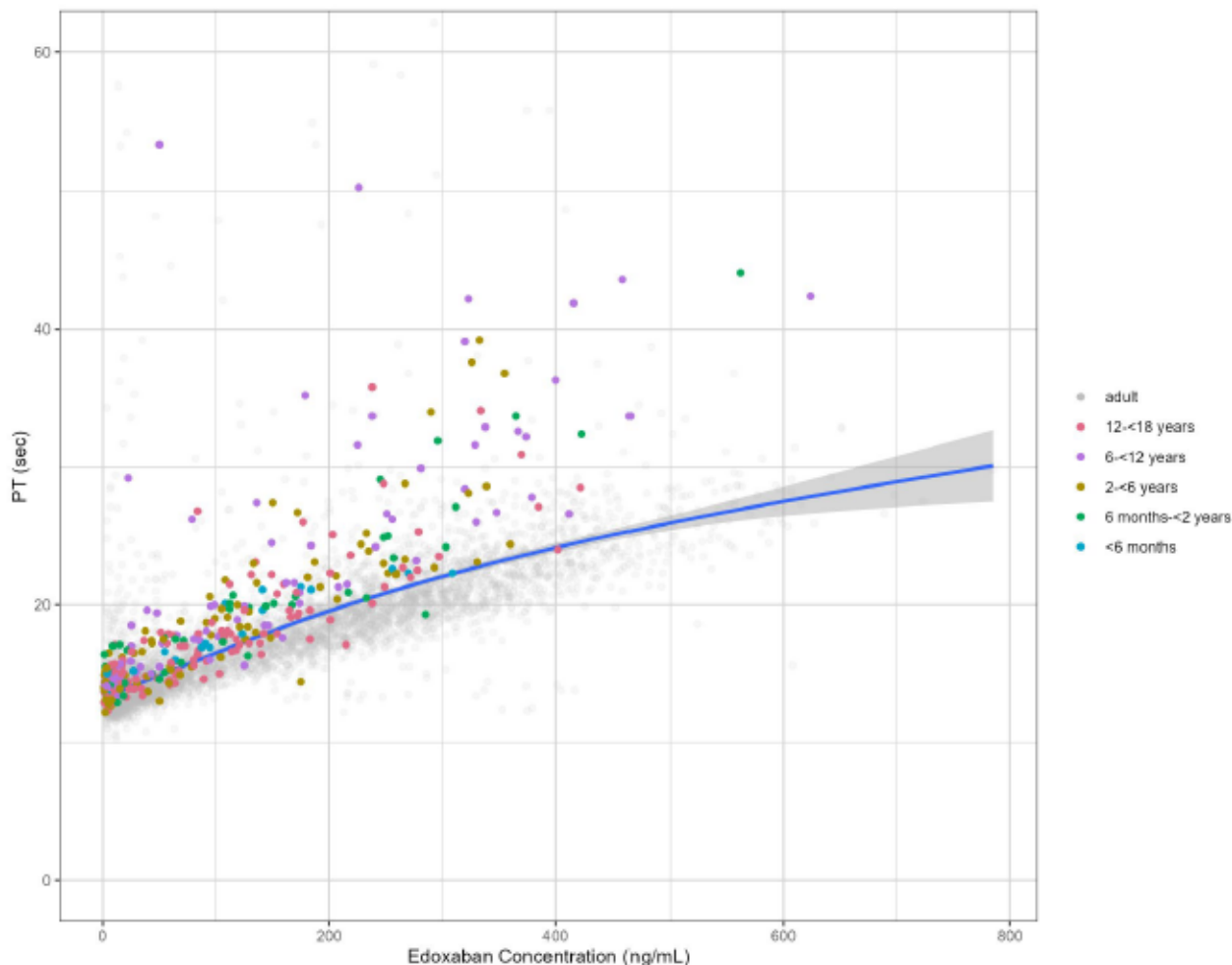


Source: edoxaban-pkpd-eda-20221003.html

Abbreviation: APTT = activated partial thromboplastin time

Note: The blue line represents the LOESS fit of adult data

Figure 17 Comparison of PT vs. Observed Edoxaban Concentration in Adults and Children



Source: edoxaban-pkpd-eda-20221003.html

Abbreviation: PT = prothrombin time

Note: The blue line represents the LOESS fit of adult data

AFXA model

Base Structural Model

AFXA data were best fit with an Emax model with IIV on intercept (E0). E0 was fixed to 0.1 IU/mL. The residual model for AFXA is an additive error model.

Parameter estimates for the AFXA base model are presented in Table 18. Goodness-of-fit plots for this model are shown in Figure 18.

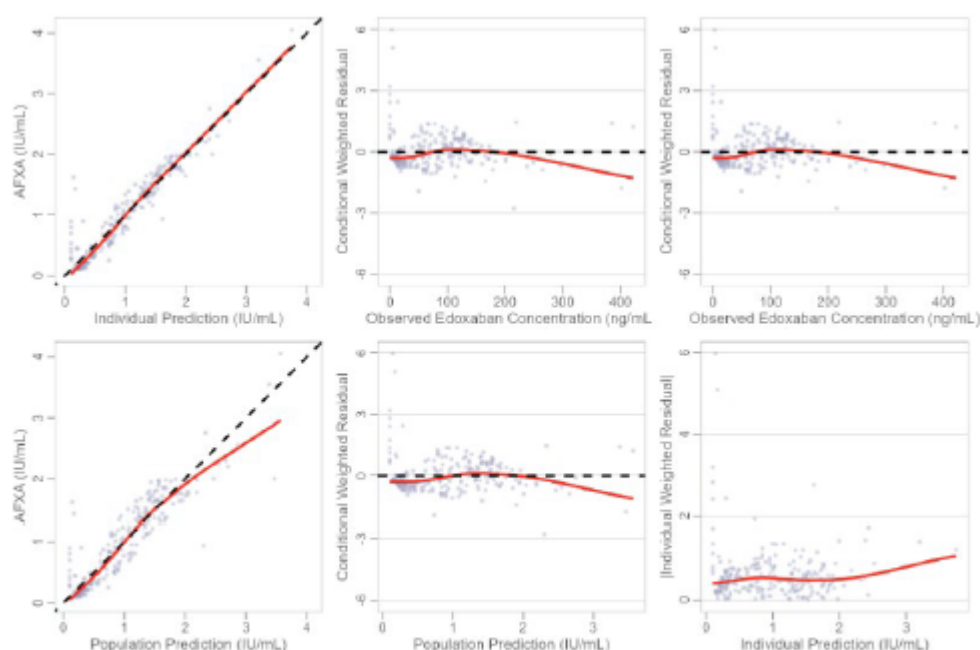
Table 18 Parameter Estimates for the AFXA Base Model

Parameter	Estimate	RSE%	Shrinkage
Typical Values			
Baseline Anti-Factor Xa Activity (IU/mL)	0.100 Fixed	n/a	
Maximum effect of Edoxaban (IU/mL)	8.65	42.3	
Edoxaban concentration at half max (ng/mL)	631	50.0	
Between Subject Variability			
On Baseline Anti-Factor Xa	14.8	28.9	42.5%
Residual Error			
Additive Error (IU/mL)	0.247	15.9	

Source: Edoxaban-PKPD-base-model-summary-26oct2022.html

Abbreviations: AFXA = anti-activated Factor X; CV = coefficient of variation; RSE = relative standard error

Figure 18 Goodness-of-Fit Plots for the AFXA Base Model



Source: Edoxaban-PKPD-base-model-summary-29oct2022.html

Abbreviation: AFXA = anti-activated Factor X

Covariate selection

A univariate search with $p < 0.05$ revealed that PMA, Race, Sex, and body weight were significant on AFXA model parameters. After forward addition ($p < 0.05$) and backward elimination ($p < 0.01$), body weight was significant on EMAX and EC50. Because of the high uncertainty of body weight effect on EMAX (41% RSE), it was removed. Body weight effect on EC50 was included in the final AFXA model.

Final Model

AFXA data was best fit with an Emax model with IIV on EMAX. E0 was fixed to 0.1 IU/mL as there were only 9 of 207 that had evaluable pre-treatment measurements. Body weight effect on EC50 was included in the final model. The covariate effect of body weight on EC50 is generally minimal (15%) and is not expected to be clinically relevant.

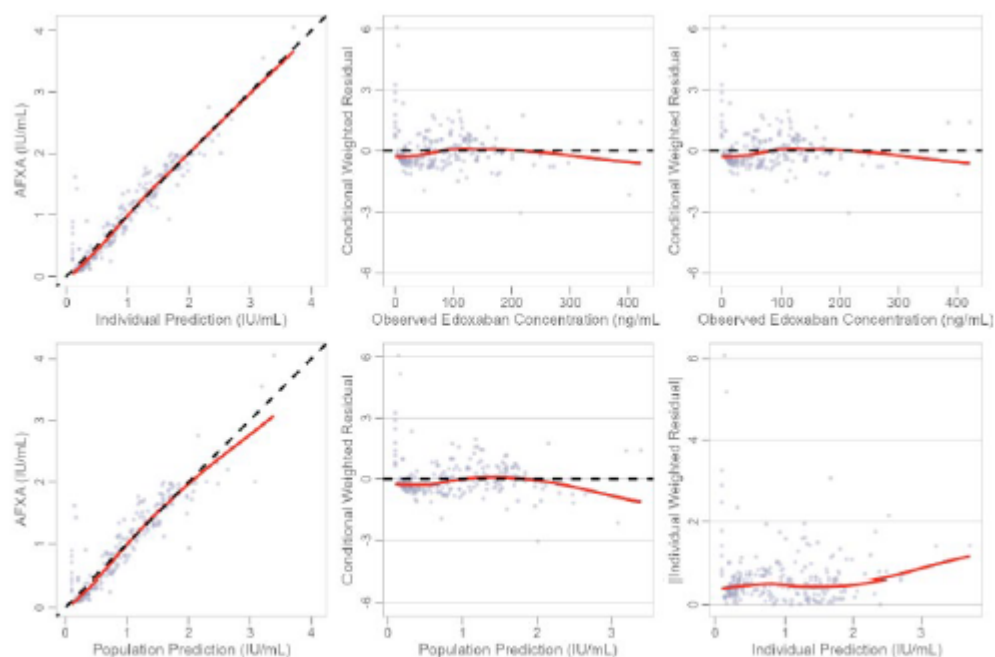
Table 24 Parameter Estimates for the AFXA Final Model with Bootstrap Estimates of 95 % CI

Parameter	Estimate	RSE%	Shrinkage	95% CI
Typical Values				
Baseline Anti-Factor Xa Activity (IU/mL)	0.100 Fixed	n/a		0.100 – 0.100
Maximum effect of Edoxaban (IU/mL)	9.44	37.6		5.02 – 28.6
Edoxaban concentration at half max (ng/mL)	819	43.8		376 – 2777
Weight on EC50	0.151	17.5		0.103 – 0.213
Between Subject Variability				
On EMAX	9.89	37.4	54.1%	0.0986 – 18.4
Residual Error				
Additive Error (IU/mL)	0.243	14.4		0.157 – 0.300

Source: Edoxaban-PKPD-final-models-summary-29oct2022

Abbreviations: AFXA = anti-activated Factor X; CI = confidence interval; CV = coefficient of variation; RSE = relative standard error

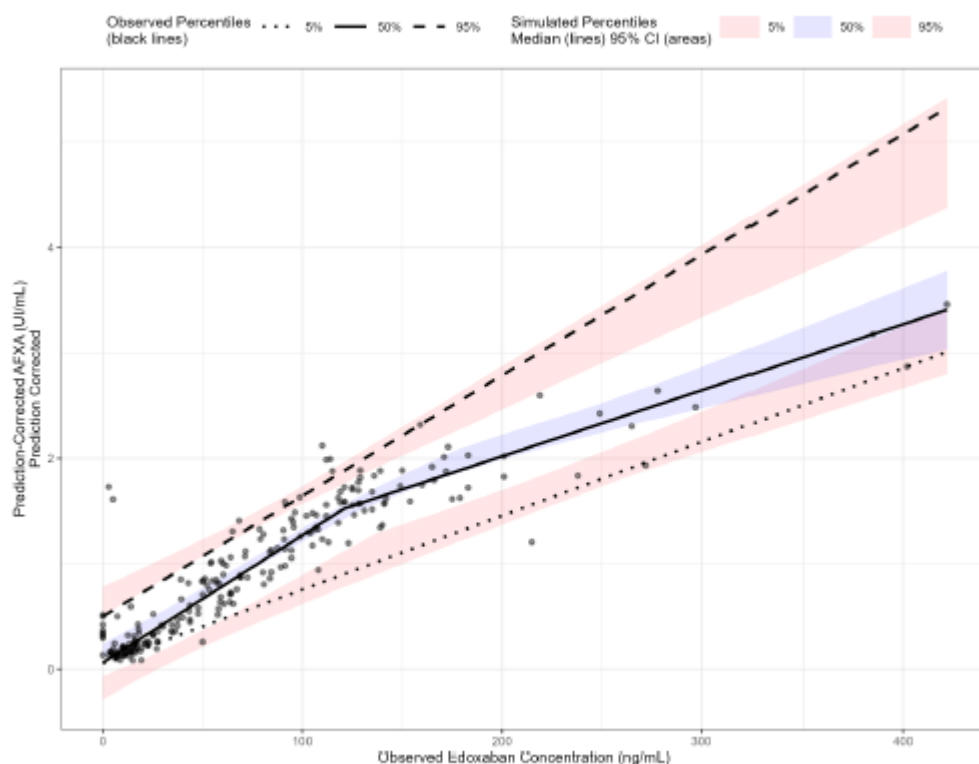
Figure 21 Goodness-of-Fit Plots for the AFXA Final Model



Source: Edoxaban-PKPD-final-model-summary-29oct2022.html

Abbreviation: AFXA = anti-activated Factor X

Figure 22 Prediction-Corrected Visual Predictive Check of AFXA Observations vs. Edoxaban Concentration



Source: [Edoxaban-PKPD-final-model-summary-26oct2022.html](#)
 Abbreviations: AFXA = anit-activated Factor X; CI = confidence interval

APTT model

Base structural model

APTT data were best fit with a linear model with IIV on the intercept (E0). The residual model for APTT is a proportional error model.

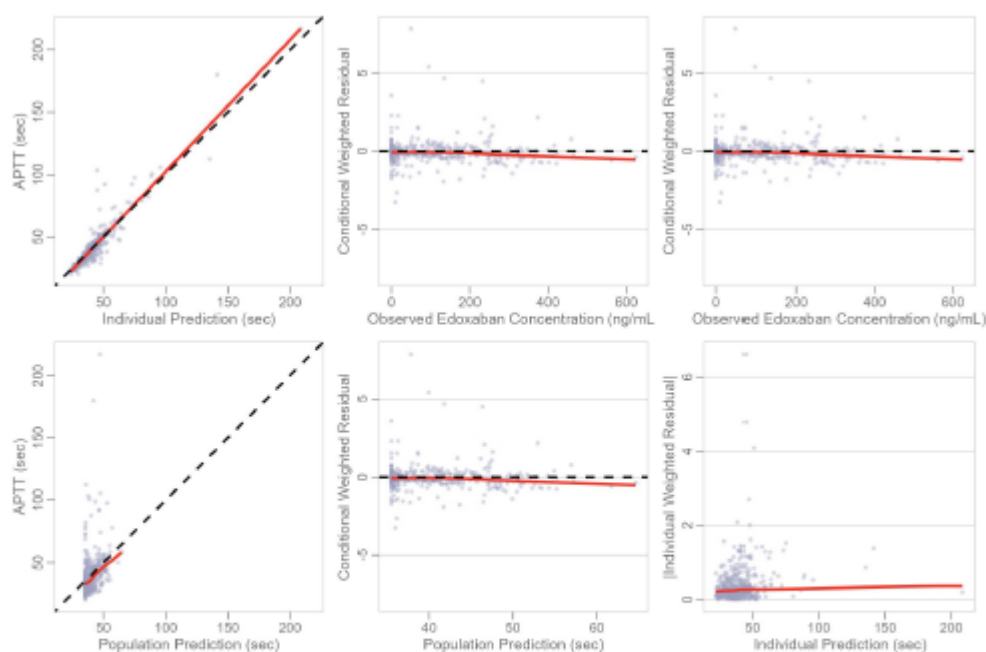
Parameter estimates for the APTT base model are presented in Table 19. Parameter estimates for the APTT Base Model. Goodness-of-fit plots for this model are shown in Figure 19.

Table 19 Parameter Estimates for the APTT Base Model

Parameter	Estimate	RSE%	Shrinkage
Typical Values			
Baseline Activated Partial Thromboplastin Time (sec)	35.5	2.30	
Slope of effect of Edoxaban (sec*mL/ng)	0.0467	10.3	
Between Subject Variability			
On Baseline	30.7	13.7	13.9%
Residual Error			
Proportional Error (CV%)	19.7	15.3	

Source: [Edoxaban-PKPD-base-model-summary-11oct2022.html](#)
 Abbreviations: APTT = activated partial thromboplastin time; CV = coefficient of variation;
 RSE = relative standard error

Figure 19 Goodness-of-Fit Plots for the APTT Base Model



Source: [Edoxaban-PKPD-base-model-summary-11oct2022.html](https://www.ema.europa.eu/en/documents/assessment-report/edoxaban-pkpd-base-model-summary-11oct2022_en.pdf)

Abbreviation: APTT = activated partial thromboplastin time

Covariate selection

A univariate search with $p < 0.05$ revealed that PMA on E0 and eGFR on slope are significant covariate effects. After forward addition ($p < 0.05$) and backward elimination ($p < 0.01$), RACE was found to have significant impact on E0. After further refinement, Asian race effect on E0 was found to be significant.

Final Model

APTT data was best fit with a linear model with IIV on the intercept (E0). Asian race effect on E0 was included in the final APTT model. The covariate effect of race on E0 is generally minimal (22%) and is not expected to be clinically relevant.

Table 25 Parameter Estimates for the APTT Final Model with Bootstrap Estimates of 95 % CI

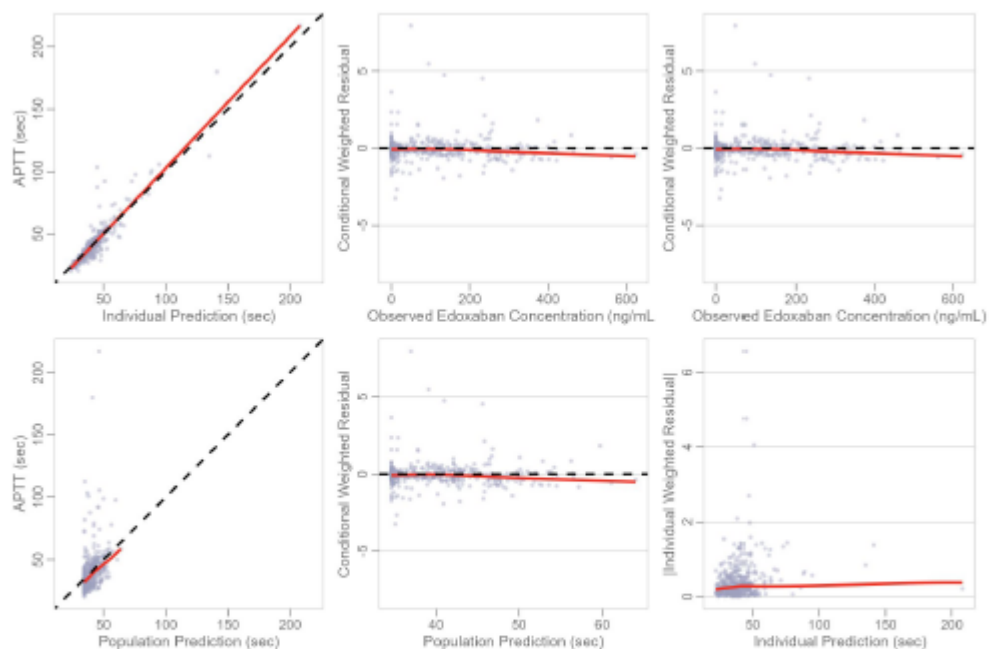
Parameter	Estimate	RSE%	Shrinkage	95% CI
Typical Values				
Baseline Activated Partial Thromboplastin Time (sec)	34.6	2.53		32.9 – 36.3
Slope of effect of Edoxaban (sec*mL/ng)	0.0471	10.2		0.0377 – 0.0566
Asian race on E0	0.217	47.5		0.0149 – 0.418
Between Subject Variability				
On Baseline	29.7	15.1	14.8%	18.7 – 38.0
Residual Error				
Proportional Error (CV%)	19.9	15.3		14.0 – 25.9

Source: [Edoxaban-PKPD-final-models-summary-18oct2022](https://www.ema.europa.eu/en/documents/assessment-report/edoxaban-pkpd-final-models-summary-18oct2022_en.pdf)

Abbreviations: APTT = activated partial thromboplastin time; CI = confidence interval;

CV = coefficient of variation; RSE = relative standard error

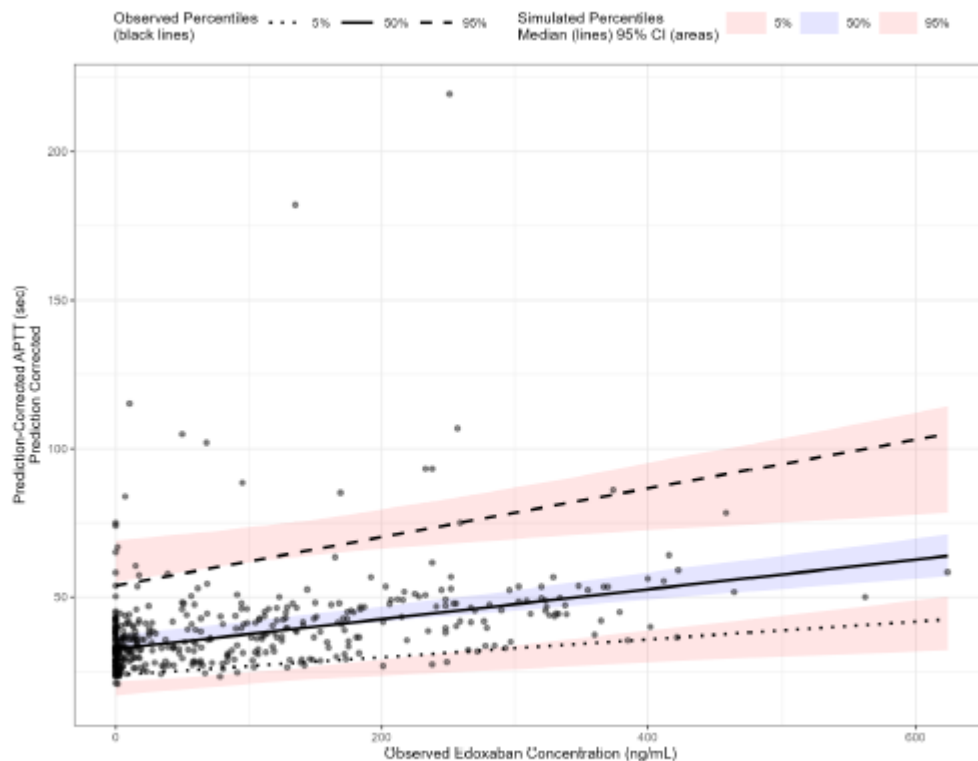
Figure 23 Goodness-of-Fit Plots for the APTT Final Model



Source: [Edoxaban-PKPD-final-model-summary-18oct2022.html](https://www.ema.europa.eu/en/documents/assessment-report/edoxaban-pkpd-final-model-summary-18oct2022_en.pdf)

Abbreviation: APTT = activated partial thromboplastin time

Figure 24 Prediction-Corrected Visual Predictive Check of APTT Observations vs. Edoxaban Concentration



Source: [Edoxaban-PKPD-final-model-summary-18oct2022.html](https://www.ema.europa.eu/en/documents/assessment-report/edoxaban-pkpd-final-model-summary-18oct2022_en.pdf)

Abbreviations: APTT = activated partial thromboplastin time; CI = confidence interval

PT Model

Base structural model

PT data were best fit with a linear model with IIV on the intercept (E0). The residual model for PT is a proportional error model.

Parameter estimates for the PT base model are presented in Table 20. Goodness-of-fit plots for this model are shown in Figure 20.

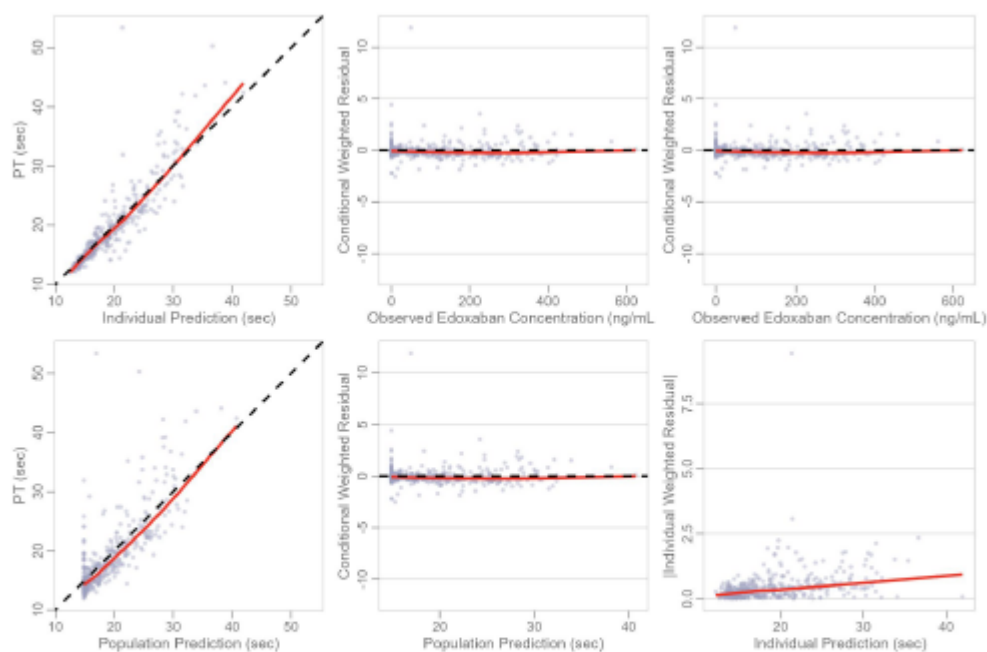
Table 20 Parameter Estimates for the PT Base Model

Parameter	Estimate	RSE%	Shrinkage
Typical Values			
Baseline Prothrombin Time (sec)	14.9	1.47	
Slope of effect of Edoxaban (sec*mL/ng)	0.0415	3.92	
Between Subject Variability			
On Baseline	14.5	20.3	29.8%
Residual Error			
Proportional Error (CV%)	15.9	28.1	

Source: [Edoxaban-PKPD-base-model-summary-11oct2022.html](#)

Abbreviations: CV = coefficient of variation; PT = prothrombin time; RSE = relative standard error

Figure 20 Goodness-of-Fit Plots for the PT Base Model



Source: [Edoxaban-PKPD-base-model-summary-11oct2022.html](#)

Abbreviation: PT = prothrombin time

Covariate selection

A univariate search with $p < 0.05$ revealed that Sex and Race on E0 and eGFR on slope are significant covariate effects. After forward addition ($p < 0.05$) and backward elimination ($p < 0.01$), Race and Sex was found to have significant impact on E0. Further refinement, resulted in Black race effect remaining, along with the sex effect.

Final Model

PT data was best fit with a linear model with IIV on the intercept (E0). Black race effect on E0 and sex effect on E0 were included in the final PT model. The covariate effects of race and sex on E0 are generally minimal (10-14%) and are not expected to be clinically relevant.

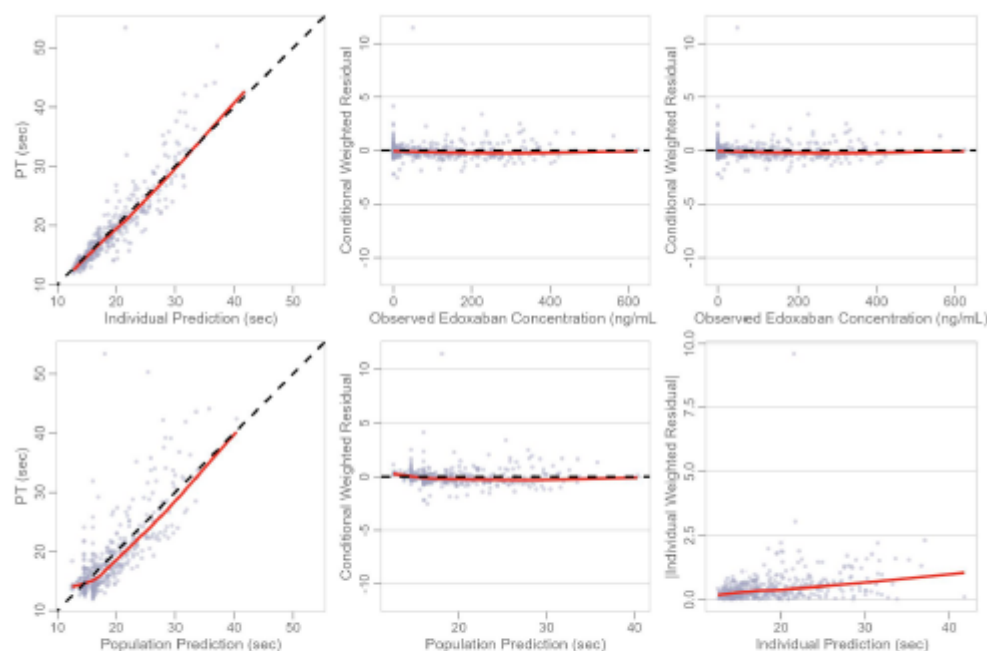
Table 26 Parameter Estimates for the PT Final Model with Bootstrap Estimates of 95 % CI

Parameter	Estimate	RSE%	Shrinkage	95% CI
Typical Values				
Baseline Prothrombin Time (sec)	14.5	2.22		13.9 – 15.2
Slope of effect of Edoxaban (sec*mL/ng)	0.0414	3.83		0.0383 – 0.0445
Sex on E0	0.101	64.2		-0.0260 – 0.227
Black race on E0	-0.139	28.0		-0.215 – -0.0626
Between Subject Variability				
On Baseline	14.6	19.7	28.6%	6.91 – 19.5
Residual Error				
Proportional Error (CV%)	15.4	26.6		7.37 – 23.4

Source: Edoxaban-PKPD-final-models-summary-18oct2022

Abbreviations: CI = confidence interval; CV = coefficient of variation; PT = prothrombin time;
RSE = relative standard error

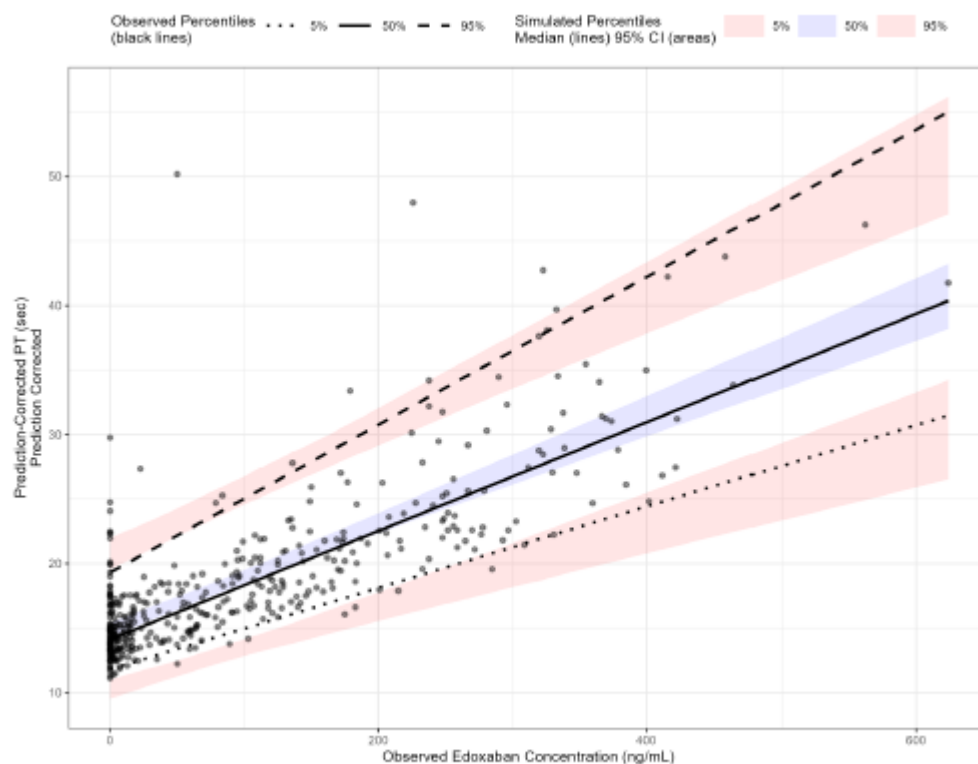
Figure 25 Goodness-of-Fit Plots of the PT Final Model



Source: Edoxaban-PKPD-final-model-summary-18oct2022.html

Abbreviation: PT = prothrombin time

Figure 26 Prediction-Corrected Visual Predictive Check of PT Observations vs. Edoxaban Concentration



Source: [Edoxaban-PKPD-final-model-summary-18oct2022.html](https://www.ema.europa.eu/en/documents/assessment-report/edoxaban-pkpd-final-model-summary-18oct2022_en.pdf)
 Abbreviations: CI = confidence interval, PT = prothrombin time

6.5. Discussion

The pharmacology of edoxaban has been extensively described in adults. The current submission aims to characterise the PK and PD of edoxaban in paediatric patients.

The Phase I single-dose DU176b-A-U157 study included 5 paediatric age cohorts (12 to <18 years, 6 to <12 years, 2 to <6 years, 6 months to <2 years and 0 months to <6 months) and 2 different doses in each age cohort. The main objective was to select the dosing regimen in pediatric patients that achieves exposures comparable to approved adult doses (30 and 60 mg). Two different formulations were used, tablets and suspensions in subjects older and younger, respectively, than 12 years of age.

A previous Population PK analysis was developed using adult data in order to propose dose regimens for each paediatric dose cohort in the Phase 3 studies. The previous Population PK model incorporated a 2-compartment model with theoretical allometric body weight exponents, 0.75 for clearance and 1 for volume. The model also incorporates a post-menstrual age (PMA) effect on CL/F. Pediatric dose for specific age cohort was selected if the median estimated exposure at the pediatric dose was within the 0.5 to 1.5-fold of the median exposure in adult VTE subjects at 60 and 30 mg QD dose, respectively.

The population PK analysis was based on a pooled dataset from the 3 paediatric studies, which includes data of paediatric patients who were under risk of thromboembolic events and needed anticoagulant treatment (Phase 1 single-dose study DU176b-A-U157), paediatric patients with confirmed VTE (Phase 3 Study DU176b-D-U312) and paediatric subjects with cardiac diseases at risk of thromboembolic events (Phase 3 Study DU176b-C-U313). The dataset includes 208 subjects from 4 days through 18 years of age. The Applicant updated the population PK model by keeping the same structural definition of the PK model (two compartment model with linear absorption and disposition,

fixed allometric effects on CL/Q and V1/V2) together with PMA and eGFR effects on clearance. During the covariate analysis, a formulation effect on Ka was incorporated. The PK analysis of edoxaban data included 208 subjects with 589 measurable PK observations.

When comparing the population PK model of edoxaban in adult and pediatric patients, despite similar structural definition was assumed among both populations, large differences were detected on ka (3.36 vs 0.365), V2/F (209 vs 44), V3/F (93.2 vs 262) and Q/F (5.9 vs 15.7) that suggest that differences in the PK properties of edoxaban exist on absorption and distribution that were not explained by allometric effects.

The Applicant has partially provided the explanation of these differences, although no clear justification regarding additional factors to allometry has been given.

Regarding the differences in CL/F, eGFR was included to estimate renal function in the paediatric Pop PK model, on the other hand, CrCl was used in the adult model. The CL/F parameters were calculated for a subject of 70 kg and CrCl and eGFR of 110ml/min/1.73m². Despite the differences in the covariate selected for renal function between both populations, adolescents patients of 70 kg show higher CL/F value compared to adults of 70 kg. Such relationship is age, body-weight and renal function dependent, so additional evidence should be provided in case dose recommendations in younger pediatric patients.

Concerning the Vc/F, the sparse PK sampling in the paediatric studies makes it difficult to properly characterize the C_{max} in this population, and makes it difficult to properly calculate the Vc/F. In the paediatric population, Vc/F is 4-fold lower than the Vc/F in the adult population, which may bias the Vp/F. For that reason Q/F is higher in the paediatric population due to the high value of Vp/F. In general, the lack of adequate experimental characterization of the alpha- and beta-disposition phases may compromise the estimation of Vp/F and Q/F.

The differences in the Ka are explained by the different formulation used as well as the differences in physiological characteristics, although a 10-fold difference is observed.

Additional efforts would be required to fully understand whether the hypothesis is plausible. As a consequence, paediatric doses for each paediatric subgroup should be based on age, weight and renal function in order to investigate if those patients achieve edoxaban exposures that are comparable to adult

Based on the GOF and pcVPC plots, a moderately adequate description of the data is observed. According to the DV vs PRED plot, a relevant dispersion is observed in the high concentration range, perhaps due to poor characterization of the absorption mechanisms due to lack of experimental values. On the other hand, DV vs IPRED plot shows an under-prediction of inter-individual variability, since data points are not aligned around the identity line. The overall performance of the final population PK model seems moderately adequate based on the stratified analysis of the pcVPC across the different age cohorts. No relevant deviations were observed across the different age cohorts.

Then, a simulation-based analysis was conducted in order to predict the overall exposure (AUC) across the different age cohorts using the final population PK model with the dosing regimens selected. Although the AUC results are within the 0.5-1.5 range of the adult population, the results show that the proposed dosing regimens in pediatric patients would lead to an under-exposure in pediatric patients compared to adult patients. Moreover, Figure 7 does not allow to fully understand whether pediatric patients within the same age cohort but different body weight would achieve similar exposure than the adult population. Moreover, a simulation-based analysis was conducted (Table 11) in order to explore different dosing regimens by age and eGFR cohorts, but no comparison with the adult exposure was provided. For that reason, the Applicant was asked to provide the simulated exposure

for each age, eGFR and body weight cohort with the proposed dosing regimens, including the median (50th percentile) and extreme percentiles (5th and 95th) of the paediatric (simulated) and adult patients (observed) in order to clarify whether similar exposure would be achieved. The paediatric doses tested in the studies lead to an under-exposure in paediatric patients compared to adult patients, especially in adolescent patients with high body weight and paediatric patients across different age and eGFR values. Due to the absence of an exposure-safety analysis in pediatric patients, dose selection should be established based on achieving similar exposure range compared to the adult patients. In that sense, additional simulation-based analyses would be needed in order to justify the dose selection regimen in paediatric patients able to achieve similar exposure compared to the adult patients.

A PK/PD analysis was conducted using several PD endpoints: anti-FXa activity, prothrombin time (PT) and activated partial thromboplastin time (aPTT), which have been measured in the 3 paediatric studies. The PK/PD relationship of edoxaban was compared for the 5 paediatric cohort and adult VTE patients. The use of direct PK/PD relationships suggest that there is no time delay between the PK observations in plasma and the PD outcome, which is expected based on the mechanism of action of edoxaban. Overall, a similar PK/PD relationship across the different age cohorts for each PD endpoint is observed, and it suggests that no PK/PD differences due to age effect are expected. Three PK/PD models have been developed (for each PD endpoint) with an adequate description of the observed data based on the GOF and pcVPC. The AFXA model incorporates an Emax model with baseline and weight effect on EC50. Adequate final parameter estimates and low RSE was estimated. The PK/PD relationship for APTT and PT endpoints incorporates a linear PD model with baseline and covariate effects on baseline parameters (APTT and PT) with good description of the data. Linear models for APTT and PT should be considered with caution and no extrapolation analysis out of the PK range evaluated should be performed. Based on the PK/PD relationships that have been established across the three PD endpoints, showing that a moderate-to-high PD response of anti-FXa activity, prothrombin time and activated partial thromboplastin time is expected in the exposure range of 150-300 ng/mL of edoxaban. This is not supported by the previous adult VTE program or the exposure-response analysis for safety, where higher bleeding events were predicted as Cave increases. Therefore, the selection of the exposure range of 60 mg QD of edoxaban for pediatric patients is endorsed, despite the efficacy could be compromised.

7. Clinical Efficacy aspects

7.1. *Methods – analysis of data submitted*

Study U312

Title: "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)"
Overview of Design

This was an event-driven Phase 3, prospective, randomised, multicentre, open-label, blinded-endpoint-evaluation, parallel-group study to compare the efficacy and safety of edoxaban with SOC anticoagulant therapy, and to evaluate the PK and PD of edoxaban in paediatric subjects from birth to <18 years of age with confirmed VTE.

The study was designed to demonstrate the noninferiority of edoxaban to SOC, including LMWH, VKA, or synthetic pentasaccharide (SP)-FXa inhibitors, in the treatment and secondary prevention of VTE in paediatric subjects.

The study included 2 periods: the Main Treatment Period with, and the Extension Period without, multiple-dose PK/PD assessment.

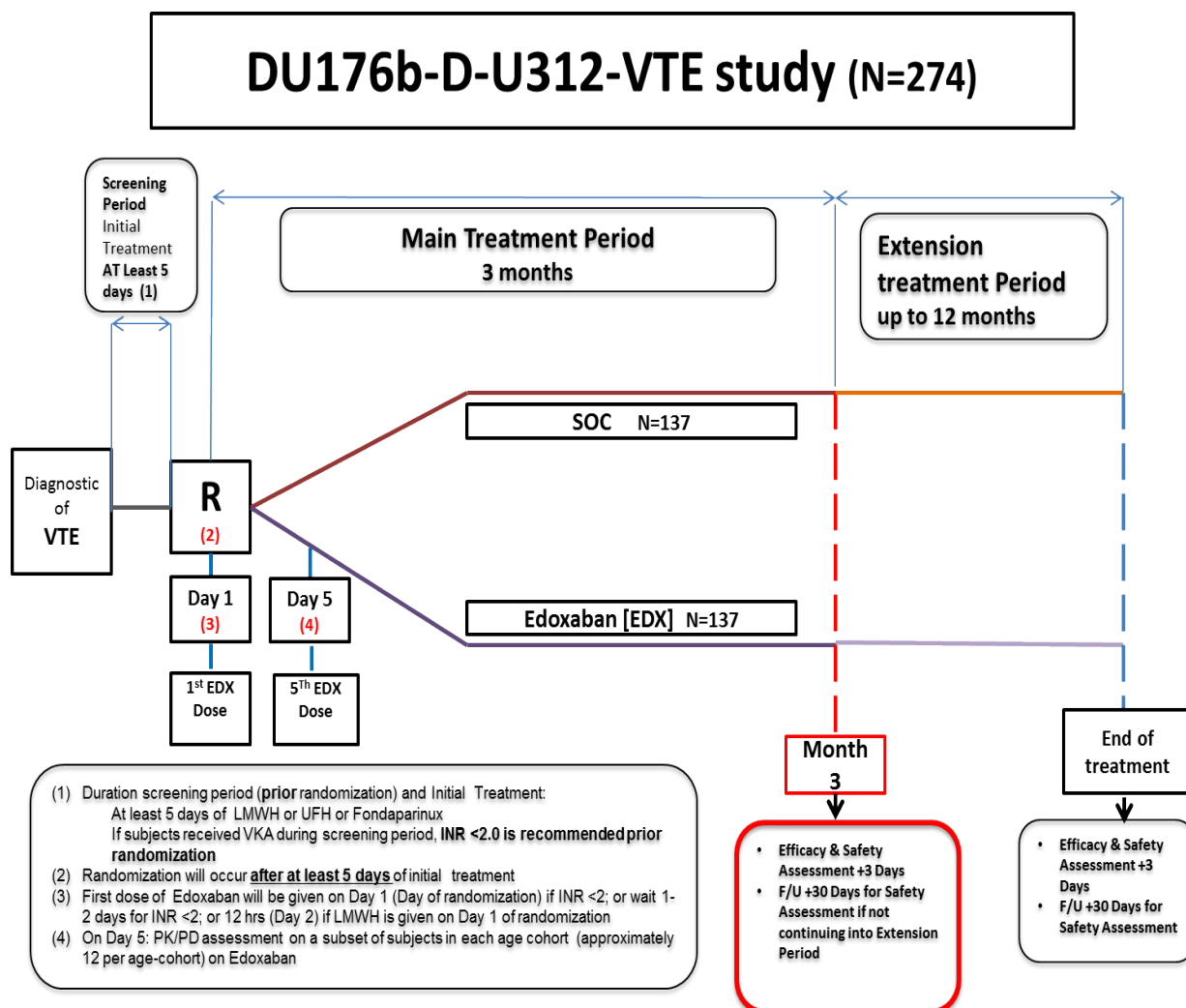
- The Main Treatment Period was defined as the time from randomisation until the end of Month 3 of treatment. The Main Treatment Period for subjects <6 months old (Cohort 5) was defined as the time from randomisation until the end of anticoagulant therapy for at least 6 to 12 weeks.
- The Extension Period 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 required anticoagulant treatment after discontinuation of the study drug at any time were transitioned to therapy as determined by the investigator.

Approximately 274 subjects were planned to be included in this randomised study (137 subjects in each treatment group), which was conducted at clinical sites located worldwide. Randomisation was stratified by age cohorts and by region (North America, European Union, Middle East, North Africa, and the rest of the world). After subjects were assessed for eligibility and underwent bridging treatment for at least 5 days of heparin (LMWH, SP-FXa inhibitors, or unfractionated heparin [UFH; with overlapping VKAs if needed]) prior to randomisation, the subjects were randomised in a 1:1 ratio to receive either edoxaban (subjects received selected dose of edoxaban) or SOC anticoagulant according to study site's SOC treatment (LMWH alone or followed with VKA, SP-FXa inhibitors alone or followed with VKA, or VKA).

The subjects were recruited into 1 of the 5 age cohorts, which were similar to those of Study U157, but the distribution of subjects across age cohorts was different (ie, more subjects were enrolled in the older age cohorts). Sequential enrolment of age cohorts was used for randomisation. The order of enrolment was from the oldest age cohort to the youngest age cohort.

An overview of the study design is provided in Figure E01.

Figure E01. Study U312 Overall Study Design



EDX = edoxaban; F/U = Follow-up; INR = international normalised ratio; LMWH = low molecular weight heparin; PD = pharmacodynamic; PK = pharmacokinetic; R = randomisation; SOC = standard of care; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Study U312. Subject Population

To be enrolled, subjects had to be aged between birth (defined as 38 weeks gestational age) and <18 years of age, with documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 90 days (or at least 6 to 12 weeks subjects for <6 months old [Cohort 5]). Subjects must have received at least 5 days of heparin therapy prior to randomisation to treat the newly identified index VTE. In addition, prior to being randomised to edoxaban or SOC, subjects initially treated with VKA were recommended to have an international normalised ratio ≤ 2.5 .

Key exclusion criteria included the following: active bleeding or high risk of bleeding, contraindicating treatment with LMWH, SP-FXa inhibitors, VKAs, or direct oral anticoagulants; current or previous treatment with thrombolytic agents, thrombectomy, or insertion of a caval filter for the newly identified index VTE; severe hepatic impairment or hepatic disease associated with coagulopathy; estimated glomerular filtration rate <30% of normal for age and size; stage 2 hypertension; thrombocytopenia; life expectancy <3 months; a history of thrombosis; and subjects diagnosed with antiphospholipid syndrome who were triple positive.

Rifampin was prohibited during the study, subjects on concomitant use of rifampin were excluded, and antiplatelet therapy was contraindicated in both arms except for low-dose aspirin, defined as 1 to 5 mg/kg/day, with a maximum of 100 mg/day.

Study U312. Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the composite endpoint of incidence of symptomatic recurrent venous thromboembolic disease, death as a 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).

All efficacy endpoints described below were adjudicated in a blinded manner by the Clinical Events Committee (CEC).

Radiologic examination

- Utilising the same diagnostic technique at Baseline and Follow-up to determine the thrombotic burden.

Diagnosis of new / recurrent PE required 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 computed tomography (CT) scan
- A mismatched defect on a nuclear ventilation/perfusion scan compared with the prior imaging
- A nondiagnostic lung scan accompanied by documentation of new DVT by (Doppler) ultrasonography or venography.

Diagnosis of symptomatic recurrent VTE required the confirmation by appropriate diagnostic imaging (see imaging criteria of recurrent VTE) and at least 1 of the symptoms of VTE.

- Imaging criteria of recurrent VTE
- Abnormal compression ultrasonography where compression had been normal or, if noncompressible during screening, an increase in diameter of the thrombus during full compression
- An extension of the echogenic intraluminal thrombus or absence of flow in the central venous system on Doppler ultrasonography
- An extension of an intraluminal filling defect, a new intraluminal filling defect, or an extension of nonvisualisation of veins in the presence of a sudden cut-off on venography
- An extension of an intraluminal filling defect or a new intraluminal filling defect on CT angiogram

Diagnosis of fatal VTE was based on 1 or more of the following:

- Objective diagnostic testing
- Autopsy
- Death that cannot be attributed to a documented cause and for which VTE cannot be ruled out

Thrombotic burden was assessed by comparison of the diagnostic method used at Baseline and at Month 3 $\pm$ 5 days (for Cohort 5, at 6 to 12 weeks $\pm$ 5 days) in the absence of symptomatic recurrent VTE. Hence, the same imaging technique that was used at the enrolment of the subject into the study was required to be used at the end of the observational period $\pm$ 3 days. A thrombotic burden endpoint was registered if there was no regression of the thrombus size or extension of the thrombus at Month 3 Visit $\pm$ 3 days (for Cohort 5, at 6 to 12 weeks $\pm$ 3 days) after randomisation.

Additionally, thrombotic burden was assessed at Month 12 $\pm$ 5 days/Discontinuation Visit for those subjects who participated in the Extension Period.

Secondary Efficacy Endpoints

The secondary efficacy endpoints included the following:

- A composite endpoint of symptomatic recurrent venous thromboembolic disease, death as a result of VTE, and no change or extension of thrombotic burden from randomisation to the date of the last dose of study drug plus 30 days
- The individual components of the primary efficacy endpoint during the first 3-month treatment period are as follows:
 - Symptomatic recurrent VTE
 - Death as a result of VTE
 - No change or extension of thrombotic burden.
- All-cause mortality from randomisation to the date of the last dose of study drug plus 30 days

- Deep vein thrombosis, catheter-related thrombosis, sinovenous thrombosis, and PE events within and after the first 3-month treatment period (For Cohort 5, the intended duration of treatment was 6 to 12 weeks.)

Clinical Outcome Endpoint

The clinical outcome endpoint is defined as follows:

A composite combination of major and clinically relevant nonmajor (CRNM) bleedings, symptomatic recurrent VTEs, and death as a result of VTE that occurred from the first to the last dose plus 30 days. Clinically relevant nonmajor bleeding was defined as an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least 1 of the following:

- A hospital admission for bleeding
- A physician-guided medical or surgical treatment for bleeding or
- A change in antithrombotic therapy (including interruption or discontinuation of study drug)

Study U312. Efficacy Analyses

Analysis Sets

As detailed in the statistical analysis plan (SAP), the efficacy analyses were conducted on the following analysis sets:

- The Randomised Analysis Set that included all enrolled subjects who signed the informed consent form and were randomised.
- The modified Intent-to-Treat (mITT) Analysis Set that included all randomised subjects who received at least 1 dose of randomised study drug.
- The Per Protocol (PP) Analysis Set that included all subjects in the mITT Analysis Set who were sufficiently compliant with the protocol. Criteria of sufficiently compliant were detailed in SAP.

Methods

The primary efficacy analysis was based on the mITT Analysis Set using the randomised group even if a subject inadvertently received the incorrect study drug. In this analysis, the time to the first event of the composite primary efficacy outcome was analysed using a Cox proportional hazards regression model including treatment group and age cohorts as covariates.

The time to first event was defined as the time (days) from the date of randomisation to the date of the first event experienced by a subject during the first 3-month period. Subjects who did not have a primary efficacy outcome during the 3 months plus 3 days period were censored at 3 months plus 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 an image taken in the first 3-month period were censored at the date of randomisation.

The edoxaban-to-comparator hazard ratio (HR) and 95% confidence interval (CI) of HR were computed based on this Cox proportional hazard regression model. Edoxaban was considered noninferior to comparator if the upper limit of the 95% CI was <1.5 .

If noninferiority of edoxaban was established, edoxaban was tested for superiority to comparator. Edoxaban was considered superior to comparator if the upper limit of the 95% CI from above analysis was <1.0 . Two-sided *P* values for superiority were also reported from the same model. To control study-wise type I error, fixed-sequence testing procedure was used for testing noninferiority and superiority for the primary efficacy analysis.

The following secondary efficacy analyses were conducted:

- A composite endpoint, including symptomatic recurrent venous thromboembolic disease, death as a result of VTE, and no change or extension of thrombotic burden from randomisation to the date of the last dose of study drug plus 30 days, was calculated with the same Cox proportional hazards regression model used for the primary efficacy analysis. The time to first event was defined as the time (days) from the date of randomisation to the first event experienced by a subject. Subjects who did not have a primary efficacy outcome during the study period were censored at the last day the subject had a complete assessment for study outcomes or the last dose of study drug plus 30 days, whichever came first. These efficacy analyses were based on the mITT and PP Analysis Sets. The incidence of this composite endpoint was also summarised by treatment arm for the mITT and PP Analysis Sets.
- Incidence of all-cause mortality from randomisation to the date of the last dose of study drug plus 30 days was also summarised by treatment arm for the mITT Analysis Set.

- 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 occurred during the first 3-month treatment period was summarised by treatment arm for the MITT and PP Analysis Sets.
- The occurrence of DVT, catheter-related thrombosis, sinovenous thrombosis, and PE during the first 3-month treatment period, and after the 3-month treatment period was summarised by treatment arm for the MITT Analysis Set.

The incidence of primary efficacy endpoint was summarised for the subgroups defined on the basis of the following categorised variables:

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

Study U313

Title: "An Open-Label, Randomized, Parallel-Group, Multi-Center, Observational Trial to Evaluate the Safety and Efficacy of Edoxaban Tosylate in Children From 38 Weeks Gestational Age to Less than 18 Years of Age with Cardiac Diseases at Risk of Thromboembolic Events"

Study U313. Overview of Design

This was a Phase 3, open-label, randomised, parallel-group, multicentre, observational study to evaluate and to compare the safety and efficacy of edoxaban against SOC anticoagulants in subjects at risk of TEs.

This study was designed to compare the safety and efficacy of edoxaban with SOC anticoagulants in paediatric subjects with cardiac conditions at risk of TEs who require anticoagulation and to evaluate the PK and PD of edoxaban in this population.

The study included 2 periods:

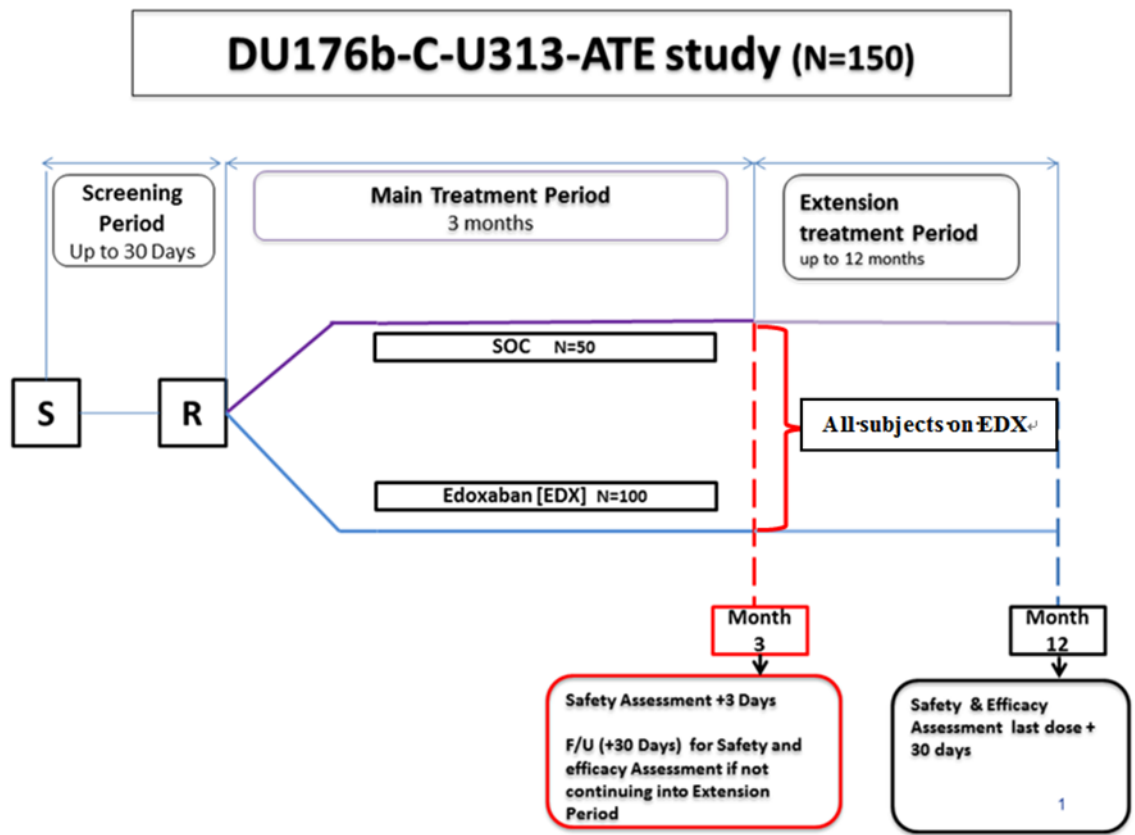
- The Main Treatment Period was defined as the time from randomisation until the end of Month 3 of treatment.
- The Extension Period was discretionary for the subject based on the investigator's judgment of risk burden and included treatment from the end of the Main Treatment Period (Month 3) up through the end of Month 12. All subjects who entered the Extension Period were given edoxaban for the duration of the Extension Period (Protocol Version 3.0). Subjects who enrolled in the protocol earlier than Version 3.0 and continued to the Extension Period with SOC anticoagulants were given edoxaban once the site approved Protocol Version 3.0.
- Subjects who required anticoagulant treatment after discontinuation of the study drug at any time were transitioned to a therapy as determined by the investigator.

Approximately 150 subjects were planned be included in this randomised study (100 subjects in the edoxaban group and 50 subjects in the SOC group), which was conducted at clinical sites located in North America, European Union, Middle East, and North Africa. After subjects were assessed for eligibility, they were randomised to receive either edoxaban (subjects received selected dose of edoxaban) or SOC anticoagulant according to study site's SOC treatment (UFH, LMWH alone or followed with VKA, or VKA).

Subjects from birth to <18 years of age were recruited into 1 of the 5 age cohorts. Sequential enrolment of age cohorts was used for randomisation. The order of enrolment was from the oldest age cohort to the youngest age cohort.

The overall study design is shown in Figure E0.

Figure E02. Study U313 Overall Study Design



ATE = arterial thromboembolism; EDX = edoxaban; F/U = Follow-up; R = randomisation; S = Screening; SOC = standard of care

Study U313. Subject Population

To be enrolled, subjects had to be aged between birth (defined as 38 weeks gestational age) and <18 years of age with cardiac diseases who were at risk for thromboembolic complications and required at least 3 months antithrombotic anticoagulant prophylaxis. Either children with cardiac disease who had a history of cardiac shunt occlusion/thrombosis, with shunt still in place (secondary prevention), or children with cardiac disease who required (including those already taking and those not yet taking) anticoagulation for the primary prevention of TE. Subjects had to have a history of a TE that met all of the following criteria:

- The TE was old, organised, and/or resolved per the discretion of the investigator.
- The subject was asymptomatic.
- The subject continued to require at least 3 months of anticoagulation treatment.
- There was no intracardiac thrombus or thrombi on the screening echocardiogram.

Key exclusion criteria included the following: a history of symptomatic venous or arterial TE, asymptomatic venous or arterial TE found by routine imaging; asymptomatic intracardiac thrombosis confirmed by an echocardiogram during study Screening Period, mechanical heart valves, active

bleeding or high risk of bleeding contraindicating treatment with anticoagulant, contraindication to the use of heparin (UFH or LMWH) and/or VKA, severe hepatic impairment or hepatic disease associated with coagulopathy, estimated glomerular filtration rate <30% of normal for age and size, stage 2 hypertension, thrombocytopenia, Fontan procedure with a history of or signs/symptoms suggestive of protein-losing enteropathy, life expectancy <3 months, a history of thrombosis wherein subjects diagnosed with antiphospholipid syndrome were triple positive.

Rifampin was prohibited during the study, subjects on concomitant use of rifampin were excluded, and antiplatelet therapy was contraindicated in both arms except for low-dose aspirin, defined as 1 to 5 mg/kg/day, with a maximum of 100 mg/day.

Study U313. Efficacy Endpoints

Primary Efficacy Endpoint
Not applicable.

Secondary Efficacy Endpoints

The secondary efficacy endpoints were as follows:

- The combination of symptomatic TE in the systemic arterial or venous pathways, including DVT, PE, stroke, intracardiac thrombus, systemic embolic event (SEE), and myocardial infarction (MI), and asymptomatic intracardiac thrombus identified by cardiac imaging that occurred from randomisation to the Month 3 Visit
- Deaths as a result of TE that occurred from randomisation to the Month 3 Visit
- All-cause mortality from randomisation to the Month 3 Visit
- The combination of symptomatic TE in the systemic arterial or venous pathways including DVT, PE, stroke, intracardiac thrombus, SEE, and MI, and asymptomatic intracardiac thrombus identified by cardiac imaging that occurred from the day after the Month 3 Visit to the date of the last dose of study drug plus 30 days for subjects who participated in the Extension Period
- Deaths as a result of TE that occurred from the day after the Month 3 Visit to the date of the last dose of study drug plus 30 days for subjects who participated in the Extension Period
- All-cause mortality from the day after the Month 3 Visit to the date of the last dose of study drug plus 30 days for subjects who participated in the Extension Period

Study U313. Efficacy Analyses

Analysis Sets: The efficacy analyses were conducted on the mITT Analysis Set.

- The Intent-to-Treat Analysis Set that included all subjects who signed the informed consent form and were randomised.
- The mITT Analysis Set that included all subjects in the ITT Analysis Set who received at least 1 dose of randomised study drug.

Methods: The following secondary efficacy endpoints were summarised using incidence and annualised event rate by treatment group for the Main Treatment Period and in the edoxaban group for the Extension Period plus 30 days for subjects who participated in the Extension Period, as well the rate difference between edoxaban and the comparator with the corresponding 95% CI for the Main Treatment Period. The incidence of each component was summarised by treatment group.

This analysis was based on CEC adjudication-confirmed events, which are as follows:

- The combination of symptomatic TE in the systemic arterial or venous pathways, including DVT, PE, stroke, SEE, intracardiac thrombus, and MI, and asymptomatic intracardiac thrombus identified by cardiac imaging
- Deaths as a result of TE
- All-cause mortality

The exploratory endpoints combination of symptomatic TE and asymptomatic intracardiac thrombus, death as a result of TE, and all-cause mortality were analysed on the basis of CEC adjudicated results for periods and subjects below:

- Events from randomisation to the date of last dose of study drug plus 30 days for subjects who did not participate in the Extension Period
- Events from the day after the Month 3 Visit to the date of the last dose of study drug for subjects who participated in the Extension Period

- Events that occurred from randomisation to the Month 3 Visit or to the date of the last dose of study drug plus 3 days if study drug was discontinued in the Main Treatment Period, whichever was earlier.

Subgroup analysis based on CEC-adjudicated results was conducted for the combination of symptomatic TE in the systemic arterial or venous pathways, including DVT, PE, stroke, SEE, intracardiac thrombus, and MI, and asymptomatic intracardiac thrombus identified by cardiac imaging by treatment group for the Main Treatment Period and in the edoxaban group only for the Extension Period. Predefined subgroups are as follows:

- Sex
- Region
- Underlying disease (Kawasaki, Fontan, Heart Failure, and other)
- Concomitant aspirin usage (yes, no)

Dose Recommendation in Studies U312 and U313

The dose recommendations for Studies U312 and U313 (Table E01) were based on the PK and safety data from Study U157 and on population PK (PopPK) and were reviewed on an ongoing basis by an Independent Data Monitoring Committee. Edoxaban doses were selected to achieve exposures comparable to adult doses of 60 mg (recommended dose) and 30 mg (dose reduction based on clinical factors, including renal function, low body weight, and concomitant use of P-glycoprotein [P-gp] inhibitors), referred to as a high-dose and a low-dose regimen (for details, refer to Module 2.7.2 Section 4.7).

The PK results from Studies U312 and U313 indicate that the doses administered in paediatric subjects were comparable across the 5 age cohorts from birth to <18 years and were aligned with those in adult VTE subjects administered with edoxaban at 60 mg once daily (QD; Module 2.7.2 Section 4.5). Likewise, PD data (prothrombin time [PT], activated partial thromboplastin time [aPTT], and anti-FXa) for the doses in paediatric subjects were consistent with those in adult subjects with VTE administered with edoxaban at 60 mg QD (Module 2.7.2 Section 4.6.2).

Table E01. Edoxaban Dose Recommended by Age Cohort in Studies U312 and U313

Age at Date of Consent	Body Weight	Dose (Tablet) ^a	Dose (Suspension) ^a	Dose Reduction ^a
12 to <18 years	≥60 kg	60 mg	NA	45 mg
	≥30 and <60 kg	45 mg	NA	30 mg
	<5th percentile for age	30 mg	NA	NA
6 to <12 years	<60 kg; dosed based on mg/kg	NA	1.2 mg/kg, maximum dose of 45 mg	0.8 mg/kg, maximum dose of 45 mg
2 to <6 years	Dosed based on mg/kg	NA	1.4 mg/kg, maximum dose of 45 mg	0.7 mg/kg, maximum dose of 24 mg
6 months to <2 years	Dosed based on mg/kg	NA	1.5 mg/kg, maximum dose of 45 mg	0.75 mg/kg, maximum dose of 24 mg
>28 days to <6 months	Dosed based on mg/kg	NA	0.8 mg/kg, maximum dose of 12 mg	0.4 mg/kg, maximum dose of 6 mg
Birth (38 weeks of gestation) to ≤28 days	Dosed based on mg/kg	NA	0.4 mg/kg, maximum dose of 6 mg	0.4 mg/kg, maximum dose of 6 mg

NA = not applicable

^a Subjects were instructed to take edoxaban (tablets or granules) orally once a day, at the same time every day, with or without food. Tablets were to be swallowed with a glass of water.

Measurement of treatment compliance

The total duration of study participation for any individual subject was a maximum of 13 months.

In both studies, edoxaban compliance was assessed by calculating the percentage of time the subject was receiving edoxaban during the treatment period. In the SOC groups, warfarin and VKA compliance were measured and assessed by summarising INR and time in therapeutic range levels (in Study U313 only). Enoxaparin, UFH, and LMWH compliance was measured and assessed by summarising the anti-FXa levels (no subjects received fondaparinux).

Results

Study Populations

Study U312

A total of 290 subjects were randomised into the study: 147 in the edoxaban group and 143 in the SOC group (Table 3.1). The mITT Analysis Set comprised 286 randomised subjects. Four randomised subjects were excluded from the mITT Analysis Set as the subjects did not receive the study drug.

Table E02. Data Sets Analyzed for Main Treatment Period – Study U312 (Randomised Analysis Set)

Analysis Set	Edoxaban (N = 147) n (%)	SOC (N = 143) n (%)	Total (N = 290) n (%)
Randomised	147 (100.0)	143 (100.0)	290 (100.0)
mITT ^a	145 (98.6)	141 (98.6)	286 (98.6)
Safety ^b	145 (98.6)	141 (98.6)	286 (98.6)
PK ^c	68 (46.3)	0	68 (23.4)
PD ^d	74 (50.3)	0	74 (25.5)
Per Protocol ^e	129 (87.8)	110 (76.9)	239 (82.4)

CSR = clinical study report; mITT = modified Intent-to-Treat; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SOC = standard of care

^a The mITT Analysis Set is defined as all subjects in the Randomised Analysis Set who received at least 1 dose of the study drug.

^b The Safety Analysis Set is defined as all subjects in the Randomised Analysis Set who received at least 1 dose of the study drug.

^c The PK Analysis Set is defined as all subjects in the Safety Analysis Set who had at least 1 PK sample with measurable concentration of edoxaban.

^d The PD Analysis Set is defined as all edoxaban subjects in the Safety Analysis Set who had at least 1 measurable PD sample.

^e The Per Protocol Analysis Set is defined as all subjects in the mITT Analysis Set who were sufficiently compliant with the protocol.

Source: Module 5.3.5.1 DU176b-D-U312 CSR Table 14.1.1.4

Study U313

A total of 168 subjects were randomised into the study: 110 in the edoxaban group and 58 in the SOC group (Table E03). The mITT Analysis Set comprised 167 randomised subjects. One randomised subject was excluded from the mITT Analysis Set as the subject did not receive the study drug.

Table E03. Data Sets Analyzed for Main Treatment Period – Study U313 (All Randomised Subjects)

Analysis Set	Edoxaban (N = 110) n (%)	SOC (N = 58) n (%)	Total (N = 168) n (%)
ITT	110 (100.0)	58 (100.0)	168 (100.0)
mITT	109 (99.1)	58 (100.0)	167 (99.4)
Safety	109 (99.1)	58 (100.0)	167 (99.4)
Pharmacokinetics	73 (66.4)	0	73 (43.5)
Pharmacodynamics	77 (70.0)	0	77 (45.8)

CSR = clinical study report; ITT = intent-to-treat; mITT = modified intent-to-treat; SOC = standard of care

Note: The percentages are based on the number of all randomised subjects.

Source: Module 5.3.5.1 DU176b-C-U313 CSR Table 14.1.1.2.

Subject Disposition and Exposure

Study U312

Of the 286 subjects in the mITT Analysis Set, a total of 141 (49.3%) subjects completed the 3-month Main Treatment Period, 30-day Follow-up, and the Extension Period: 77 (53.1%) subjects in the edoxaban group and 64 (45.4%) subjects in the SOC group (Table E04). A total of 107 (37.4%) subjects completed the 3-month Main Treatment 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.

A total of 16 (5.6%) subjects prematurely discontinued the study prior to Month 3: 6 (4.1%) subjects in the edoxaban group and 10 (7.1%) subjects in the SOC group. The discontinuations in the edoxaban group prior to Month 3 were because of physician decision (2 subjects), “other” reasons (2 subjects), death (1 subject), and AEs (1 subject). The discontinuations in the SOC group prior to Month 3 were because of withdrawal of consent (4 subjects), death (2 subjects), physician decision (1 subject), AEs (1 subject), lost to follow-up (1 subject), and “other” reasons (1 subject).

A total of 23 (8.0%) subjects discontinued prematurely during the Extension Period: 11 (7.6%) subjects in the edoxaban group and 12 (8.5%) subjects in the SOC group. The discontinuations in the edoxaban group in the Extension Period were because of AEs (6 subjects), “other” reasons (3 subjects), physician decision (1 subject), and death (1 subject). The discontinuations in the SOC group in the Extension Period were because of physician decision (6 subjects), withdrawal of consent (2 subjects), “other” reasons (2 subjects), death (1 subject), and AEs (1 subject).

Table E04. Subject Disposition – Study U312 (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 Treatment 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 Treatment 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)
Physician decision	1 (0.7)	6 (4.3)	7 (2.4)
Other	3 (2.1)	2 (1.4)	5 (1.7)
Withdrawal by subject	0	2 (1.4)	2 (0.7)
Death	1 (0.7)	1 (0.7)	2 (0.7)

CRF = case report form; CSR = clinical study report; 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.” The 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 the 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 randomised are not counted in the Total header.

Source: Module 5.3.5.1 DU176b-D-U312 CSR Table 14.1.1.2

The median (range) duration of treatment was 147.0 (1 to 400) days in the edoxaban group and 110.0 (1 to 412) days in the SOC group (Table E05).

Study drug interruptions during the Main Treatment Period were required in 16.6% (24/145), 20.6% (29/141), 14.7% (17/116), 0% (0/5), and 31.7% (13/41) of subjects treated with edoxaban, SOC,

LMWH, SP-FXa inhibitor, and VKA, respectively (Module 5.3.5.1 DU176b-D-U312 clinical study report [CSR] [Table 14.2.2.3](#)).

Table E05. Study Drug Exposure – Study U312 (Safety Analysis Set)

	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 (on-treatment 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

CSR = clinical study report; FXa = activated Factor X; SD = standard deviation; SOC = standard of care;

SP = synthetic pentasaccharide; VKA = vitamin K antagonist

Note: Study treatment duration is calculated as the number of days from the date of the first dose of study drug taken to the date of the last dose of study drug taken, inclusively, with interruptions included in the interval of time (date of last dose of study drug – date of first dose of study drug + 1).

Note: Study duration is calculated as the number of days from the date of randomisation to the 30-day Follow-up Visit or to the date of the last visit if no 30-day Follow-up Visit occurred.

Note: On-treatment days are counted as the number of days the subjects actually took study drug, with interruptions not included in the interval of time.

Source: Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.2.2.1](#)

Study U313

Of the 168 subjects randomised, a total of 147 (87.5%) subjects completed the Main Treatment Period and the Extension Period: 98 (89.1%) subjects in the edoxaban group and 49 (84.5%) subjects in the SOC group (Table E06). A total of 15 (8.9%) subjects completed the Main Treatment Period but did not participate in the Extension Period: 9 (8.2%) subjects in the edoxaban group and 6 (10.3%) subjects in the SOC group.

A total of 6 (3.6%) subjects prematurely discontinued the study prior to Month 3: 3 (2.7%) subjects in the edoxaban group and 3 (5.2%) subjects in the SOC group. The discontinuations in the edoxaban group prior to Month 3 were because of withdrawal of consent (2 subjects) and AEs (1 subject). The discontinuations in the SOC group prior to Month 3 were because of withdrawal of consent (2 subjects) and physician decision (1 subject).

Of the 144 subjects who received edoxaban in the Extension Period, 3 (1.8%) subjects discontinued prematurely during the Extension Period: 1 subject (0.9%) who had been randomised to the edoxaban group in the Main Treatment Period and 2 (3.4%) subjects who had been randomised to the SOC group in the Main Treatment Period. The discontinuations were because of AEs (2 subjects) and physician decision (1 subject).

Table E06. Subject Disposition – Study U313 (mITT Analysis Set)

	Edoxaban (N = 110) n (%)	SOC (N = 58) n (%)	Total (N = 168) n (%)
Completed 3-Month Main Treatment Period	107 (97.3)	55 (94.8)	162 (96.4)
Completed the Main Treatment Period and did not participate in the Extension Period	9 (8.2)	6 (10.3)	15 (8.9)
With 30-day Follow-up	9 (8.2)	6 (10.3)	15 (8.9)
Without 30-day Follow-up	0	0	0
Completed 3-Month Main Treatment Period and the Extension Period	98 (89.1)	49 (84.5)	147 (87.5)
With 30-day Follow-up	98 (89.1)	47 (81.0)	145 (86.3)
Without 30-day Follow-up	0	0	0
Premature discontinued study from Main Treatment Period	3 (2.7)	3 (5.2)	6 (3.6)
Withdrawal by subject	2 (1.8)	2 (3.4)	4 (2.4)
AE	1 (0.9)	0 (0.0)	1 (0.6)
Subject discontinued at PI discretion	0	1 (1.7)	1 (0.6)
Premature discontinued study from Extension Period	1 (0.9)	2 (3.4)	3 (1.8)
AE	0	2 (3.4)	2 (1.2)
Subject discontinued at PI discretion	1 (0.9)	0	1 (0.6)

AE = adverse event; CSR = clinical study report; mITT = modified Intent-to-Treat; PI = principal investigator; SOC = standard of care

Note: Percentages are based on the number of all randomised subjects.

Note: If a subject had a Month 3 Visit or a visit afterwards for subject participation in the Extension Period, the subject was considered to have completed the study. The 30-day Follow-up Visit was not a criterion.

Source: Module 5.3.5.1 DU176b-C-U313 CSR Table 14.1.1.1.

For the Main Treatment Period, the median (range) duration of treatment was 92.0 (30 to 121) days in the edoxaban group, 89.5 (10 to 101) days for subjects treated with UFH/LMWH, and 91.0 (27 to 158) days for subjects treated with VKA (Table E07).

Study drug interruptions during the Main Treatment Period were required in 3.7% (4/109), 16.7% (2/12), and 16.0% (8/50) of subjects treated with edoxaban, UFH/LMWH, and VKA, respectively (Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.2.3).

Table E07. Study Drug Exposure in the Main Treatment Period – Study U313 (Safety Analysis Set)

Parameter	Statistic	Edoxaban (N = 109)	UFH/LMWH (N = 12)	VKA (N = 50)
Study treatment duration (days)	Mean ($\pm$ SD)	90.4 ($\pm$ 11.08)	74.7 ($\pm$ 32.59)	87.9 ($\pm$ 19.84)
	Median	92.0	89.5	91.0
	Minimum, maximum	30, 121	10, 101	27, 158
Study duration up to Month 3 (days)	Mean ($\pm$ SD)	92.2 ($\pm$ 10.01)	89.5 ($\pm$ 23.75)	90.9 ($\pm$ 18.09)
	Median	93.0	91.0	92.0
	Minimum, maximum	30, 121	40, 145	3, 161
On-treatment days	Mean ($\pm$ SD)	89.8 ($\pm$ 10.72)	68.8 ($\pm$ 37.19)	86.1 ($\pm$ 20.12)
	Median	91.0	89.5	91.0
	Minimum, maximum	30, 115	10, 98	27, 158

CSR = clinical study report; LMWH = low-molecular weight heparin; SD = standard deviation;

UFH = unfractionated heparin; VKA = vitamin K antagonist

Note: Study treatment duration is calculated as the number of days from the date of the first dose of study drug taken to the date of the last dose of study drug taken, inclusively in Main Treatment Period, with interruptions included in the interval of time (date of last dose of study drug – date of first dose of study drug + 1).

Note: Study duration is calculated as the number of days from the date of the randomisation to the Month 3 Visit or to the date of last visit if subject was discontinued from study prior to the Month 3 Visit.

Note: On-treatment days were counted as the number of days the subjects actually took study drug, with interruptions not included in the interval of time.

Source: Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.2.1.

The median duration of exposure to edoxaban in the Extension Period was 273 days (range: 17 to 552 days) and median study duration was 308.0 days (range: 54 to 583 days; Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.2.2).

Study U312. Completion rates and treatment compliance.

In study U312, completion rates were slightly higher in the edoxaban group than in the SOC group.

- In Study U312, 77/145 (53.1%) subjects in the edoxaban group and 64/141 (45.4%) subjects in the SOC group completed the 3-month Main Treatment Period, 30-day Follow-up, and the Extension Period.

In Study U312, compliance with edoxaban was also higher than with SOC.

- In the edoxaban group, 91.0% of subjects (132/145) had 80% to 120% treatment compliance during the first 3-month period (Main Treatment Period) of Study U312 (Module 5.3.5.1 Study U312 CSR [Table 14.1.4.1](#)).
- In the SOC group, 38 subjects received warfarin during the Main Treatment Period. A total of 42.87% of subjects were within the INR therapeutic range of 2.0 to 3.0, and approximately 44% of subjects were within the INR range between 1.5 and 2.0 (Module 5.3.5.1 Study U312 CSR [Table 14.1.4.3](#)).
- In the SOC group, 52 subjects received enoxaparin. The mean percent time for enoxaparin was 24.15% and 59.37% for the anti-FXa levels of <0.5 and 0.5 to 1.0, respectively (Module 5.3.5.1 Study U312 CSR [Table 14.1.4.4](#)). Compliance with enoxaparin was considered to be low due to use of injectables and the inconvenience caused to the subject and their family members.

Study U313. Completion rates and treatment compliance.

In Study U313, completion rates were slightly higher in the edoxaban group than in the SOC group.

- 145 (86.3%) subjects completed the 3-month Main Treatment Period and the Extension Period: 98 (89.1%) subjects who had been randomised to edoxaban in the Main Treatment Period and 47 (81.0%) subjects who had been randomised to SOC in the Main Treatment Period.

In Study U313, compliance with edoxaban was also higher than with SOC:

- In the edoxaban group, 93.6% of subjects (102/109) had 80% to 120% treatment compliance during the first 3-month period (Main Treatment Period; Module 5.3.5.1 Study U313 CSR [Table 14.1.4.1](#)).
- In the SOC group, 47 subjects received VKA during the Main Treatment Period. A total of 45% of subjects were within the INR therapeutic range of 2.0 to 3.0, followed by approximately 31% of subjects with INR range between 1.5 and 2.0. The overall TTR percentage was 16.41%, 30.84%, and 44.99% for the INR categories of <1.5, <2.0, and 2.0 to 3.0, respectively (Module 5.3.5.1 Study U313 CSR [Table 14.1.4.5](#)).
- In the SOC group, 3 subjects received treatment with UFH/LMWH during the Main Treatment Period. The median percent time was 0.0% and 100.00% for the anti-FXa levels of <0.5 and 0.5 to 1.0, respectively ([Table 14.1.4.6](#)).

Study U312. Demographic and Baseline Characteristics

Demographics and baseline characteristics were generally similar between the 2 treatment groups (Table E08).

Approximately half of the overall subjects were male (52.4%). The majority of subjects treated were White (177 [61.9%] subjects), 50 (17.5%) subjects were Asian, 18 (6.3%) subjects were Black or African American, 1 (0.3%) subject was American Indian or Alaska Native, and 1 (0.3%) subject was Native Hawaiian or Other Pacific Islander.

The mean weight was 45.35 kg (range: 2.6 to 183.0 kg), and the mean BMI was 20.4 kg/m² (range: 11 to 56 kg/m²).

Median age was 13.24 years (range 0.05 to 17.95); 167 (58.4%) subjects were in the 12 to <18 years cohort, 44 (15.4%) subjects were in the 6 to <12 years cohort, 31 (10.8%) subjects were in the 2 to <6 years cohort, 28 (9.8%) subjects were in the 6 months to <2 years cohort, and 16 (5.6%) subjects were in the 0 to <6 months cohort.

The most common type of index event among all subjects was DVT (246 [86.0%] subjects), and it was confirmed in 203 (71.0%) subjects.

Table E08. Demographic and Baseline Characteristics – Study U312 (mITT Analysis Set)
Edoxaban

	Edoxaban (N = 145)	SOC (N = 141)	Total (N = 286)
Age (years)			
Mean ($\pm$ SD)	10.935 ($\pm$ 5.9701)	11.072 ($\pm$ 6.0752)	11.002 ($\pm$ 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 ($\pm$ SD)	44.99 ($\pm$ 28.099)	45.72 ($\pm$ 31.369)	45.35 ($\pm$ 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/m²)			
Mean ($\pm$ SD)	20.3 ($\pm$ 6.04)	20.6 ($\pm$ 7.31)	20.4 ($\pm$ 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)

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

Note: Percentages are based on the total number of subjects randomised to the particular group

Source: Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.1.2.1](#)

Study U313. Demographic and Baseline Characteristics

Demographics and baseline characteristics were generally similar between the 2 treatment groups (Table E09). Approximately two-thirds of subjects were male (109 [65.3%] subjects). The majority of subjects were White (118 [70.7%]), 9 (5.4%) subjects were Asian, 7 (4.2%) subjects were Black or African American, and 3 (1.8%) subjects were Native Hawaiian/Pacific Islander. The mean weight was 28.59 kg (range: 4.5 to 90.0 kg), and the mean BMI was 17.211 kg/m² (range: 11.39 to 34.22 kg/m²). Median age was 7.430 years (range: 0.12 to 17.80 years); 57 (34.1%) subjects were in the 6 to <12 years cohort, 50 (29.9%) subjects were in the 2 to <6 years cohort, 44 (26.3%) subjects were in the 12 to <18 years cohort, 12 (7.2%) subjects were in the 6 months to <2 years cohort, and 4 (2.4%) subjects were in the 0 to <6 months cohort. The percentage of subjects who were 0 to <6 months of age was 0.9% (1/109) in the edoxaban group and 5.2% (3/58) in the SOC group. The percentage of subjects who were 6 to <12 years of age was 36.7% (40/109) in the edoxaban group and 29.3% (17/58) in the SOC group.

Overall, the most frequently reported underlying cardiac disorder at Baseline in the mITT Analysis Set was Fontan surgery (73 [43.7%] subjects), followed by Kawasaki disease (37 [22.2%] subjects), and Other (50 [29.9%] subjects, including postsurgical procedures other than Fontan surgery). Approximately half of the subjects had a history of aspirin consumption (86 [51.5%] subjects). The majority of subjects (145 [86.8%] subjects) were enrolled in the study as receiving primary anticoagulant prophylaxis.

Table E09. Demographic and Baseline Characteristics – Study U313 (mITT Analysis Set)

Characteristic	Edoxaban (N = 109)	SOC (N = 58)	Overall (N = 167)
Age^a (years)			
Mean (± SD)	8.215 (± 4.8808)	7.797 (± 5.1842)	8.070 (± 4.9767)
Median	7.920	7.100	7.430
Minimum, maximum	0.49, 17.80	0.12, 17.73	0.12, 17.80
Age cohort (n, %)			
0 to <6 months	1 (0.9)	3 (5.2)	4 (2.4)
6 months to <2 years	7 (6.4)	5 (8.6)	12 (7.2)
2 to <6 years	33 (30.3)	17 (29.3)	50 (29.9)
6 to <12 years	40 (36.7)	17 (29.3)	57 (34.1)
12 to <18 years	28 (25.7)	16 (27.6)	44 (26.3)
Gender (n, %)			
Male	72 (66.1)	37 (63.8)	109 (65.3)
0 to <6 months	1 (0.9)	2 (3.4)	3 (1.8)
6 months to <2 years	7 (6.4)	4 (6.9)	11 (6.6)
2 to <6 years	23 (21.1)	11 (19.0)	34 (20.4)
6 to <12 years	25 (22.9)	12 (20.7)	37 (22.2)
12 to <18 years	16 (14.7)	8 (13.8)	24 (14.4)
Female	37 (33.9)	21 (36.2)	58 (34.7)
0 to <6 months	0	1 (1.7)	1 (0.6)
6 months to <2 years	0	1 (1.7)	1 (0.6)
2 to <6 years	10 (9.2)	6 (10.3)	16 (9.6)
6 to <12 years	15 (13.8)	5 (8.6)	20 (12.0)
12 to <18 years	12 (11.0)	8 (13.8)	20 (12.0)
Race (n, %)			
Asian	6 (5.5)	3 (5.2)	9 (5.4)
Black or African American	4 (3.7)	3 (5.2)	7 (4.2)
American Indian or Alaska Native	0	0	0
Native Hawaiian/Pacific Islander	2 (1.8)	1 (1.7)	3 (1.8)
White	79 (72.5)	39 (67.2)	118 (70.7)
Other	10 (9.2)	7 (12.1)	17 (10.2)

Baseline Weight (kg)			
Mean ($\pm$ SD)	29.22 ($\pm$ 19.328)	27.39 ($\pm$ 17.142)	28.59 ($\pm$ 18.567)
Median	22.50	23.00	22.60
Minimum, maximum	6.2, 90.0	4.5, 80.4	4.5, 90.0
Baseline BMI^b (kg/m²)			
Mean ($\pm$ SD)	17.232 ($\pm$ 4.0024)	17.170 ($\pm$ 3.8171)	17.211 ($\pm$ 3.9276)
Median	15.970	16.455	16.330
Minimum, maximum	11.57, 34.22	11.39, 31.41	11.39, 34.22
Type of underlying cardiac disease (n, %)			
Kawasaki disease	24 (22.0)	13 (22.4)	37 (22.2)
Fontan surgery	48 (44.0)	25 (43.1)	73 (43.7)
Concomitant use of low-/standard-dose aspirin	11 (10.1)	6 (10.3)	17 (10.2)
No use of low-/standard-dose aspirin	37 (33.9)	19 (32.8)	56 (33.5)
Heart failure	4 (3.7)	3 (5.2)	7 (4.2)
Concomitant use of low-/standard-dose aspirin	1 (0.9)	1 (1.7)	2 (1.2)
No use of low-/standard-dose aspirin	3 (2.8)	2 (3.4)	5 (3.0)
Other	33 (30.3)	17 (29.3)	50 (29.9)
Concomitant use of low-/standard-dose aspirin	20 (18.3)	10 (17.2)	30 (18.0)
No use of low-/standard-dose aspirin	13 (11.9)	7 (12.1)	20 (12.0)
History of aspirin consumption (n, %)			
Yes	56 (51.4)	30 (51.7)	86 (51.5)
No	53 (48.6)	28 (48.3)	81 (48.5)
Indication for anticoagulation (n, %)			
Primary TE prevention	96 (88.1)	49 (84.5)	145 (86.8)
Secondary TE prevention	13 (11.9)	9 (15.5)	22 (13.2)

BMI = body mass index; CSR = clinical study report; mITT = modified intent-to-treat; SD = standard deviation;

SOC = standard of care; TE = thromboembolic event

Source: Module 5.3.5.1 DU176b-C-U313 CSR Table 14.1.2.1.

Study U312. Analysis of 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; defined in Section 1.3.1.3.1) during the Main Treatment Period is presented in Table E10 for the mITT Analysis Set. The Kaplan-Meier estimate for this analysis is presented in Figure E03. 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 with 2 (1.4%) subjects in the SOC group.

Table E10. Adjudicated Composite Primary Efficacy Endpoint in the Main Treatment Period – Study U312 (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 for 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 HR	(0.594, 1.719)	
2-sided p-value	0.9694	

CI = confidence interval; CSR = clinical study report; DVT = deep vein thrombosis; HR = hazard ratio; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

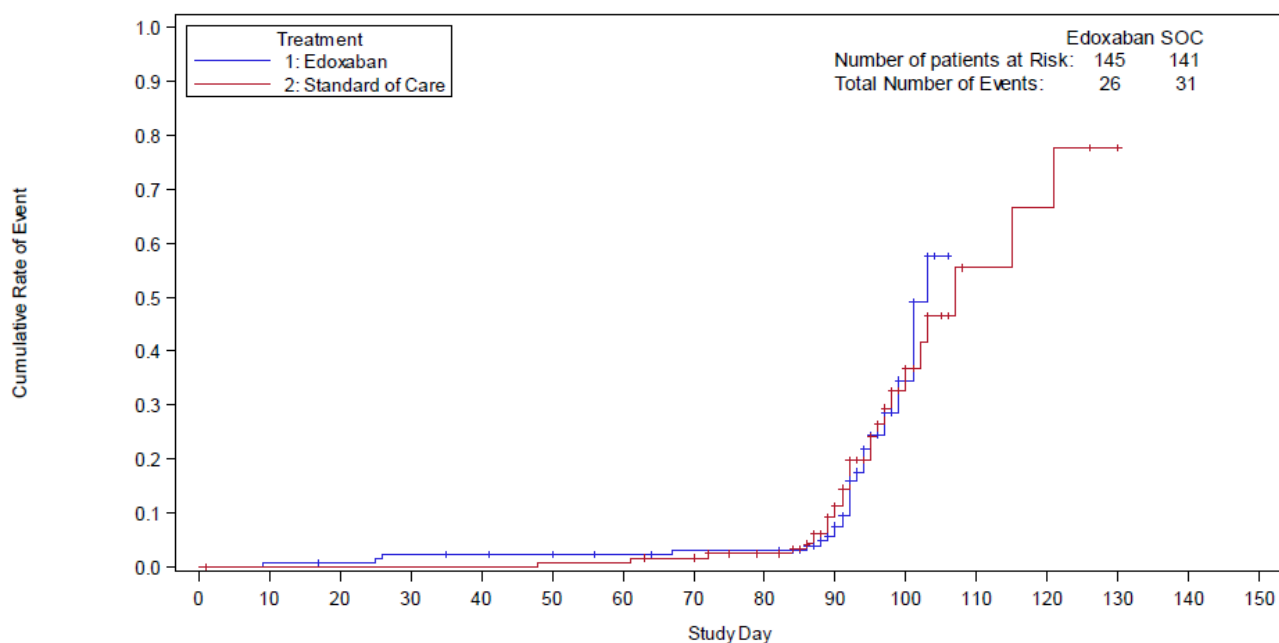
^a Edoxaban-to-SOC HR based on Cox proportional hazards regression model including treatment and age group as covariates. Edoxaban is considered non-inferior to SOC if the upper limit of the 95% CI is <1.5. If non-inferiority is established, edoxaban is considered superior to SOC if the upper limit of the 95% CI is <1.0.

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 randomisation to Month 3 Visit + 3 days.

Source: Module 5.3.5.1 DU176b-D-U312 CSR Table 14.2.1.1

Figure E03. Kaplan-Meier Cumulative Event Rate Estimates for the Primary Efficacy Endpoint in the Main Treatment Period – Study U312 (mITT Analysis Set)



Number of Patients

1: Edoxaban	145	132	130	128	127	126	124	122	122	100	9	0	
2: Standard of Care	140	122	122	122	122	121	121	119	113	87	16	4	3

Source Data: ADTTE.

Note: Main Treatment Period is defined as from randomization to Month 3 visit + 3 days. Composite Primary Efficacy Endpoint consisting of incidence of symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden during the first 3-month period.

Note: Subject 77030008 has an event reported for main treatment period (V5 from imaging data). However, the date of event is 19Jun2021 which is 5 days before randomization on 24Jun2021. This subject is not counted in the footnote: Number of Patients.

Five subjects had nonfatal DVT (4 subjects in the edoxaban group [2.8%]) or PE (1 subject in the SOC group [0.7%]). None of these events were considered related to study drug.

There was 1 unexplained death in each group (0.7%) for which VTE could not be ruled out. Neither was considered to be related to study drug.

In the summary of clinical pharmacology is stated that the PopPK model estimated edoxaban mean AUC_{0-24h,ss} in 3 patients with VTE (2060 ng*h/mL) was higher than that in patients without VTE (1310 ng*h/mL). Among the 3 patients with VTE, only subject had edoxaban exposure (1207 ng*h/mL) slightly lower than the mean exposure in patients without VTE (Table E11). The data indicate that the three VTE events were not associated with a low PK exposure of edoxaban.

Table E11. Summary of Steady-State Edoxaban PK Exposures of 3 Paediatric Patients with VTE

Subject ID	Study	Event	Day of Onset	Treatment Period	C _{max} (ng/mL)	C _{trough} (ng/mL)	AUC (ng*h/mL)
Case 1	312	DVT	67	Main	188.51	9.42	1179
Case 2	312	DVT	4	Main	392.24	25.30	2442
Case 3	312	Unexplained Death	26	Main	384.62	32.17	2581

AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; C_{trough} = minimum plasma concentration; DVT = deep vein thrombosis; ID = identification; PK = pharmacokinetic(s); VTE = venous thromboembolism.

There was no change or extension of thrombotic burden based on imaging in 21 (14.5%) subjects in the edoxaban group and 29 (20.6%) subjects in the SOC group. The HR for the edoxaban group versus the SOC group for the Main Treatment Period 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 for the Main Treatment Period.

There were no subjects who had multiple VTEs during the Main Treatment Period in the mITT Analysis Set (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.2.1.5](#)).

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 (Table E12). The HR for noninferiority was 0.94 (95% CI: 0.495 to 1.800). The upper bound of the 95% CI was 1.800, which was above the prespecified noninferiority margin of 1.5.

Table E12. Adjudicated Composite Primary Efficacy Endpoint in the Main Treatment Period – Study U312 (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 HR ^b	(0.495, 1.800)	
2-sided p-value ^b	0.8608	

CI = confidence interval; CSR = clinical study report; DVT = deep vein thrombosis; HR = hazard ratio; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

^a Edoxaban-to-SOC HR. Edoxaban is considered non-inferior to SOC if the upper limit of the 95% CI is <1.5. If non-inferiority is established, edoxaban is considered superior to SOC if the upper limit of the 95% CI is <1.0.

^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 randomisation to Month 3 Visit + 3 days.

Note: Percentages are based on the total number of subjects randomised to the particular group.

Source: Module 5.3.5.1 DU176b-D-U312 CSR Table 14.2.1.2

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 E13.

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

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 HR for the edoxaban group versus the SOC group in this analysis was 0.86 (95% CI: 0.548 to 1.342).

Table E13. Adjudicated Composite Primary Efficacy Endpoint in the Main Treatment Period Plus Extension Period and On-treatment – Study U312 (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 HR ^b	(0.548, 1.342)	
2-sided p-value ^b	0.5021	

CI = confidence interval; CSR = clinical study report; DVT = deep vein thrombosis; HR = hazard ratio; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

^a Edoxaban-to-SOC HR. Edoxaban is considered non-inferior to SOC if the upper limit of the 95% CI is < 1.5. If non-inferiority is established, edoxaban is considered superior to SOC if the upper limit of the 95% CI is < 1.0.

^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 randomisation 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: Module 5.3.5.1 DU176b-D-U312 CSR Table 14.2.1.3

Study U312. Analyses of Key Secondary Efficacy Endpoints. 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 E14.

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. 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 versus the SOC group in this analysis was 0.71 (95% CI: 0.469 to 1.074). The upper bound of the 95% CI (1.074) was below the prespecified noninferiority margin of 1.5.

The same analysis was conducted for the Overall Treatment Period in the mITT (Module 5.3.5.1 DU176b-D-U312 CSR Table 14.2.1.9) and PP (Module 5.3.5.1 DU176b-D-U312 CSR Table 14.2.1.10) Analysis Sets. The results from the mITT Analysis Set were identical to those in Table 3.12 and the results from the PP Analysis Set (HR: 0.67; 95% CI: 0.419 to 1.084) were very similar to those from the mITT Analysis Set.

Table E14. Analysis of Adjudicated Key Secondary Efficacy Endpoints in the Main Treatment Period Plus Extension Period and 30-day Follow-up – Study U312 (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 HR ^b	(0.469, 1.074)	
2-sided p-value ^b	0.1045	

CI = confidence interval; CSR = clinical study report; DVT = deep vein thrombosis; HR = hazard ratio; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

^a Edoxaban-to-SOC HR. Edoxaban is considered non-inferior to SOC if the upper limit of the 95% CI is <1.5. If non-inferiority is established, edoxaban is considered superior to SOC if the upper limit of the 95% CI is <1.0.

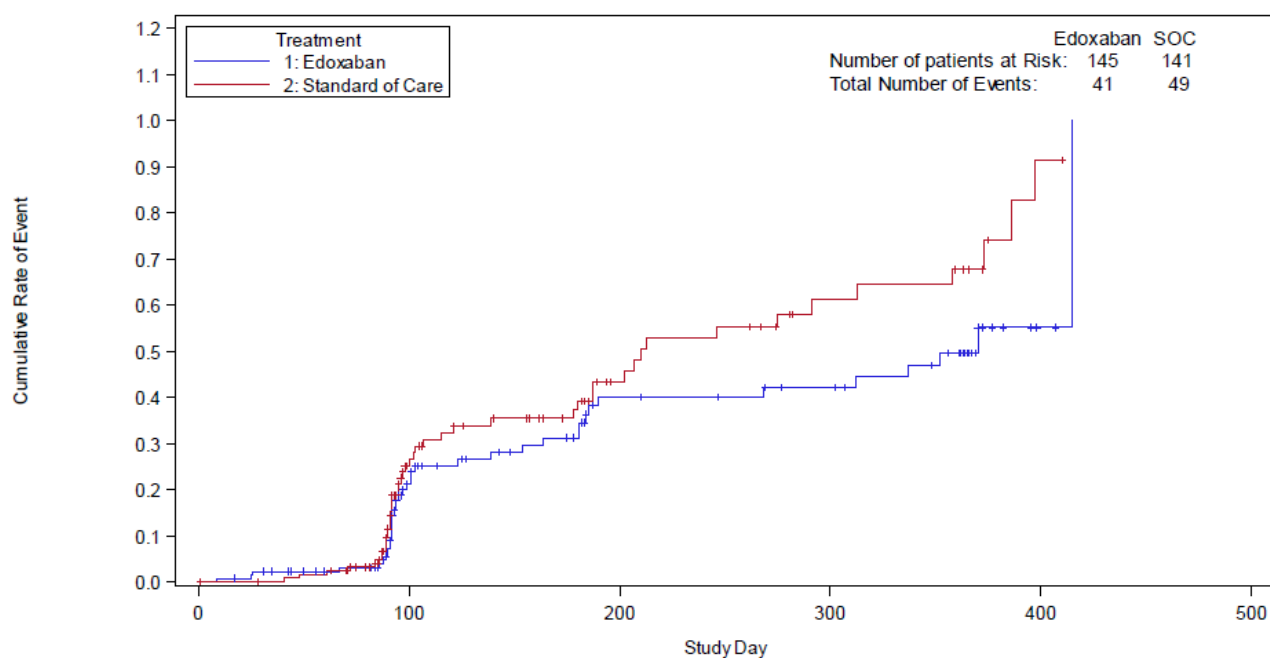
^b Based on Cox proportional hazards regression model including treatment and age group as covariates

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 randomisation 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.

Source: Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.2.1.11](#)

Figure 14.2.1.3 Kaplan-Meier Plot for Time to First Event of the Secondary Composite Efficacy Endpoint, Overall Treatment Period, Modified ITT Analysis Set



Number of Patients

1: Edoxaban	145	61	31	26	2	0
2: Standard of Care	140	53	24	12	1	0

Source Data: ADTTE.

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

Note: Subject 77030008 has an event reported for Overall treatment period (V5 from imaging data). However, the date of event is 19Jun2021 which is 5 days before randomization on 24Jun2021. This subject is not counted in the footnote: Number of Patients.

Study U312. All-cause Mortality

The incidence of adjudicated all-cause mortality during the Overall Treatment Period is summarised in Table E15. 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. The VTE events with fatal outcome were endocarditis in the edoxaban group and pneumococcal sepsis in the SOC group (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.2.1.25](#)).

Refer to Section [3.2.1.2.1](#) for additional details. Full details of the deaths are provided in the narratives in Module 5.3.5.1 DU176b-D-U312 CSR, Section [14.3.3](#).

Table E15. Incidence of Adjudicated All-cause Mortality in the Overall Treatment Period – Study U312 (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 for 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 randomisation to the date of the last dose of study drug + 30 days.

Source: DU176b-D-U312 CSR Table 14.2.1.12

Study U312. Incidence of Each Component in Composite Primary Endpoint

The incidence of each component in the composite primary endpoint is summarised for the mITT Analysis Set during the Main Treatment Period in Table E16.

Table E16. Incidence of Adjudication-confirmed Individual Component of Primary Efficacy Endpoints in the Main Treatment Period – Study U312 (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 for 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 randomisation to Month 3 Visit + 3 days.

Source: DU176b-D-U312 CSR Table 14.2.1.13

Incidence of DVT, Catheter-related Thrombosis, Sinovenous Thrombosis, and PE

A summary of the incidence of DVT, catheter-related thrombosis, sinovenous thrombosis, and PE by treatment period is provided in Table E17. During the Overall Treatment Period, 5 (3.4%) subjects in the edoxaban group had a DVT compared with no subjects in the SOC group. One (0.7%) subject in the edoxaban group had catheter-related thrombosis and a sinovenous thrombosis. One (0.7%) subject in each group had a PE.

Table E17. Incidence of Adjudication-confirmed DVT, Catheter-related Thrombosis, Sinovenous Thrombosis, and PE in the Main Treatment Period, Extension Period, and Overall Treatment Period – Study U312 (mITT Analysis Set)

	Edoxaban (N = 145) n (%)	SOC (N = 141) n (%)
During Main Treatment Period		
Subjects with DVT only	4 (2.8)	0
Subjects with catheter-related thrombosis	1 (0.7)	0
Subjects with cerebral sinovenous DVT thrombosis	0	0
Subjects with PE with or without DVT	0	1 (0.7)
During Extension Treatment Period		
Subjects with DVT	1 (0.7)	0
Subjects with catheter-related thrombosis	0	0
Subjects with sinovenous thrombosis	1 (0.7)	0
Subjects with PE with or without DVT	1 (0.7)	0
During Overall Treatment Period		
Subjects with DVT	5 (3.4)	0
Subjects with catheter-related thrombosis	1 (0.7)	0
Subjects with sinovenous thrombosis	1 (0.7)	0
Subjects with PE with or without DVT	1 (0.7)	1 (0.7)

DVT = deep vein thrombosis; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SOC = standard of care

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

Source: DU176b-D-U312 CSR [Table 14.2.1.15](#)

Clinical Benefit Analysis

A summary of net clinical outcome, defined as the composite of symptomatic recurrent VTE events, death as a result of VTE, and major and CRNM bleeding that occurred during the Overall Treatment Period, was analysed by using the proportional hazard model similar to that in the primary efficacy analysis for the mITT Analysis Set (Table E18).

A total of 16 (11.0%) subjects in the edoxaban group and 7 (5.0%) subjects in the SOC group had an event. Major and CRNM bleeding was experienced by 10 (6.9%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group.

Table E18. Analysis of Adjudication-confirmed Net Clinical Outcome in the Overall Treatment Period – Study U312 (mITT Analysis Set)

	Edoxaban (N = 145)	SOC (N = 141)
Subjects with net clinical outcome ^a (n, %)	16 (11.0)	7 (5.0)
Subjects with symptomatic recurrent VTE (n, %)	6 (4.1)	1 (0.7)
Subjects with death as a result of VTE (n, %)	1 (0.7)	1 (0.7)
Subjects with major bleeding (n, %)	2 (1.4)	0
Subjects with CRNM bleeding (n, %)	9 (6.2)	5 (3.5)
Subjects with major and CRNM bleeding (n, %)	10 (6.9)	5 (3.5)
Net clinical outcome		
n (%)	16 (11.0)	7 (5.0)
Time to first event		
Hazard ratio ^b	2.16	
95% CI for HR ^c	(0.884, 5.255)	
p-value ^c	0.0912	

CI = confidence interval; CRNM = clinically relevant nonmajor; CSR = clinical study report; HR = hazard ratio;

mITT = Modified Intent-to-Treat; SOC = standard of care; VTE = venous thromboembolism

^a Symptomatic recurrent VTE events, death as a result of VTE, and major and CRNM bleeding

^b Edoxaban-to-SOC HR

^c Based on Cox proportional hazards regression model including treatment and age group as covariates

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

Source: DU176bDU312 CSR Table 14.2.1.16

Study U312. Exploratory Endpoint Quality of Life

A paediatric quality of life questionnaire was issued at randomisation and at the end of the Main Treatment Period to assess categories of physical, emotional, social, and school functional behaviors.

The Psychosocial Health Summary score is the calculated mean of the Emotional, School, and Social Functioning subscales of the Paediatric Quality of Life Inventory. The Physical Summary score is computed from the physical functioning score. The Total Summary score is the computed mean of the Emotional, Social and School Functioning, and Physical scales.

The Physical Health summary score increased (improved) for all age groups in the edoxaban group and for the 12 to <18 years of age group in the SOC group (Table 3.19). The Psychosocial Health Summary score increased (improved) for the 6 to <12 years and 2 to <6 years of age groups in the edoxaban group and for the 2 to <6 years of age group in the SOC group. The Total Summary score (decreased) for all age groups in the SOC group.

Study U313. Adjudication-confirmed Secondary Efficacy Endpoints: Main Treatment Period

During the Main Treatment Period, 1 (1.7%) subject in the SOC group experienced 2 TE events (annualised rate of 0.07; Table E19).

Table E19. Analysis of Adjudication-confirmed Secondary Efficacy Endpoints in the Main Treatment Period – Study U313 (mITT Analysis Set)

Endpoint	Statistics	Edoxaban (N = 109)	SOC (N = 58)
TE, subjects with events	n (%)	0	1 (1.7)
	Annualised rate	0	0.07
	Rate difference (95% CI)	-0.07 (-0.22, 0.07)	
DVT	n (%)	0	1 (1.7)
PE	n (%)	0	1 (1.7)
Stroke	n (%)	0	0
SEE	n (%)	0	0
Intracardiac thrombus	n (%)	0	0
MI	n (%)	0	0
Asymptomatic intracardiac thrombus identified by cardiac imaging	n (%)	0	0
Death as a result of TE	n (%)	0	0
Death as a result of TE	n (%)	0	0
	Annualised rate	0	0
	Rate difference (95% CI)	0 (0, 0)	
All-cause mortality	n (%)		
	Annualised rate	0	0
	Rate difference (95% CI)	0 (0, 0)	

CI = confidence interval; CSR = clinical study report; DVT = deep vein thrombosis; MI = myocardial infarction; mITT = modified intent-to-treat; PE = pulmonary embolism; SEE = systemic embolic event; SOC = standard of care; TE = thromboembolic event.

Note: TEs included DVT, PE, stroke, SEE, intracardiac thrombus, MI, asymptomatic intracardiac thrombus identified by cardiac imaging, and death as a result of TE.

Note: Annualised rate = number of subjects with event/total time at risk (years). Total time at risk is the sum, across subjects, of the number of "at risk" years. For each subject, the "at risk" years = (the event or censoring – date of randomisation + 1)/365.25. If a subject has multiple events, the time of the first event is used.

Note: 95% CI for rate difference was calculated by using Wald's method.⁷

Source: Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.1.1.

Adjudication-confirmed Secondary Efficacy Endpoints: Extension Period (mITT Analysis Set)

During the Extension Period, 4 (2.8%) subjects experienced an adjudication-confirmed TE event as shown in Table E20. Of the 4 subjects with an endpoint event, 2 subjects experienced an adjudication-confirmed stroke, and 2 subjects experienced an MI.

Table E20. Analysis of Adjudication-confirmed Secondary Efficacy Endpoints - Extension Period – Study U313 (mITT Analysis Set)

Endpoint	Statistics	Edoxaban (N = 144)
TE, subjects with events	n (%)	4 (2.8)
	Annualised rate	0.05
DVT	n (%)	0
PE	n (%)	0
Stroke	n (%)	2 (1.4)
SEE	n (%)	0
Intracardiac thrombus	n (%)	0
MI	n (%)	2 (1.4)
Asymptomatic intracardiac thrombus identified by cardiac imaging	n (%)	0
Death as a result of TE	n (%)	0
Death as a result of TE	n (%)	0
	Annualised rate	0
All-cause mortality	n (%)	2 (1.4)
	Annualised rate	0.03

CSR = clinical study report; DVT = deep vein thrombosis; MI = myocardial infarction; mITT = modified intent-to-treat; PE = pulmonary embolism; SEE = systemic embolic event; TE = thromboembolic event.

Note: TEs included DVT, PE, stroke, SEE, intracardiac thrombus, MI, asymptomatic intracardiac thrombus identified by cardiac imaging, and death as a result of TE.

Note: Annualised rate = number of subjects with event/total time at risk (years). Total time at risk is the sum, across subjects, of the number of "at risk" years. For each subject, the "at risk" years = (the event or censoring – date of randomisation + 1)/365.25. If a subject has multiple events, the time of the first event is used.

Note: Extension Period is defined as from the day after the Month 3 Visit to the date of the last dose of study drug.

Source: Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.1.4.

During the Extension Period plus 30-day Follow-up (all patients received edoxaban during extension), 5 (3.5%) subjects of a total of 144 participants experienced a TE event. Of the 5 subjects, 2 subjects experienced a stroke, 2 subjects experienced an MI, and 1 subject experienced an intracardiac thrombus (Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.1.2). The 2 events of MI are poorly documented and were considered to be related to study drug by the investigators.

During the Overall Treatment Period plus 30-day Follow-up for subjects who did not participate in the Extension Period (n=141), no subjects experienced a TE event (Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.1.3).

Comparison of Results of Subpopulations

Study U312 Subgroup Analyses of the Primary Efficacy Endpoint

Due to the low number of subjects with events, it was not possible to draw any conclusions (Module 5.3.5.1 DU176b-C-U312 CSR Table 14.2.1.7).

Table 14.2.1.7 Subgroup Analysis of Adjudication Confirmed Primary Efficacy Endpoints
– Main Treatment Period
– Modified ITT Analysis Set

Variable			Edoxaban (N=145)	SOC (N=141)
Age Cohort	0 - < 6 months	n (%)	0	1 (0.7)
		Hazard ratio ^{1,2} (95% CI)	NA	
	6 months - < 2 years	n (%)	3 (2.1)	5 (3.5)
		Hazard ratio ^{1,2} (95% CI)	0.44 (0.089, 2.143)	
	2 - < 6 years	n (%)	5 (3.4)	5 (3.5)
		Hazard ratio ^{1,2} (95% CI)	2.75 (0.774, 9.800)	
	6 - < 12 years	n (%)	4 (2.8)	5 (3.5)
		Hazard ratio ^{1,2} (95% CI)	1.07 (0.217, 5.226)	
	12 - < 18 years	n (%)	14 (9.7)	15 (10.6)
		Hazard ratio ^{1,2} (95% CI)	0.92 (0.444, 1.922)	

Table 14.2.1.7 Subgroup Analysis of Adjudication Confirmed Primary Efficacy Endpoints
- Main Treatment Period
- Modified ITT Analysis Set

Variable			Edoxaban (N=145)	SOC (N=141)
Region - IXRS	US/Canada	n (%)	4 (2.8)	3 (2.1)
		Hazard ratio ^{1,2} (95% CI)	3.15 (0.508, 19.493)	
	Europe	n (%)	13 (9.0)	15 (10.6)
		Hazard ratio ^{1,2} (95% CI)	1.02 (0.489, 2.108)	
	Asia/Pacific	n (%)	6 (4.1)	9 (6.4)
		Hazard ratio ^{1,2} (95% CI)	0.83 (0.296, 2.322)	
	Rest of the World	n (%)	3 (2.1)	4 (2.8)
		Hazard ratio ^{1,2} (95% CI)	0.86 (0.168, 4.376)	
Sex	Male	n (%)	16 (11.0)	17 (12.1)
		Hazard ratio ^{1,2} (95% CI)	0.98 (0.482, 2.013)	
	Female	n (%)	10 (6.9)	14 (9.9)
		Hazard ratio ^{1,2} (95% CI)	1.02 (0.425, 2.428)	

Table 14.2.1.7 Subgroup Analysis of Adjudication Confirmed Primary Efficacy Endpoints
- Main Treatment Period
- Modified ITT Analysis Set

Variable			Edoxaban (N=145)	SOC (N=141)
Race	Asian	n (%)	5 (3.4)	9 (6.4)
		Hazard ratio ^{1,2} (95% CI)	0.86 (0.263, 2.821)	
	Black or African American	n (%)	1 (0.7)	0
		Hazard ratio ^{1,2} (95% CI)	NA	
	American Indian or Alaska Native	n (%)	0	0
		Hazard ratio ^{1,2} (95% CI)	NA	
	Native Hawaiian or Other Pacific Islander	n (%)	0	0
		Hazard ratio ^{1,2} (95% CI)	NA	
	White	n (%)	14 (9.7)	17 (12.1)
		Hazard ratio ^{1,2} (95% CI)	0.89 (0.437, 1.819)	
	Other	n (%)	2 (1.4)	2 (1.4)
		Hazard ratio ^{1,2} (95% CI)	1.67 (0.241, 11.523)	
	Not Applicable	n (%)	1 (0.7)	0
		Hazard ratio ^{1,2} (95% CI)	NA	

Table 14.2.1.7 Subgroup Analysis of Adjudication Confirmed Primary Efficacy Endpoints
- Main Treatment Period
- Modified ITT Analysis Set

Variable			Edoxaban (N=145)	SOC (N=141)
Index VTE type (PE vs DVT)	PE	n (%)	8 (5.5)	3 (2.1)
		Hazard ratio ^{1,2} (95% CI)	2.24 (0.630, 7.988)	
	DVT	n (%)	18 (12.4)	27 (19.1)
		Hazard ratio ^{1,2} (95% CI)	0.82 (0.448, 1.509)	
	PE with DVT	n (%)	0	1 (0.7)
		Hazard ratio ^{1,2} (95% CI)	NA	
Index DVT Characteristics (Catheter vs. not)	Catheter-related	n (%)	5 (3.4)	7 (5.0)
		Hazard ratio ^{1,2} (95% CI)	0.64 (0.205, 1.988)	
	Not Catheter-related	n (%)	13 (9.0)	21 (14.9)
		Hazard ratio ^{1,2} (95% CI)	0.78 (0.385, 1.587)	

Table 14.2.1.7 Subgroup Analysis of Adjudication Confirmed Primary Efficacy Endpoints
- Main Treatment Period
- Modified ITT Analysis Set

Variable			Edoxaban (N=145)	SOC (N=141)
Recurrent VTE supported by a new identified thrombus by imaging (Yes vs no)	Yes	n (%)	4 (2.8)	0
		Hazard ratio ^{1,2} (95% CI)	NA	
	No	n (%)	22 (15.2)	31 (22.0)
		Hazard ratio ^{1,2} (95% CI)	1.00 (0.619, 1.618)	

Study U313 Subgroup Analysis of Adjudicated Confirmed Secondary Efficacy Endpoints

Due to the low number of subjects with events, it was not possible to draw any conclusions for the Main Treatment Period (Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.1.5) or the Extension Period (Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.1.6).

7.2. Discussion

This variation application intends to update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with available paediatric data based on final results from study U312 (Hokusai VTE PEDIATRICS; n = 290). This is a phase 3, open-label, randomised, multicentre, 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 paediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE). The Package also includes the study U313 (ENNOBLE-ATE; n=168) as supportive for efficacy that included paediatric subjects with cardiac diseases at risk of TE complications who requires primary or secondary anticoagulant prophylaxis.

In the pivotal study (Hokusai VTE PEDIATRICS), a Phase 3, open-label, randomised, multi-centre, controlled study to evaluate the PK and PD of edoxaban and compare the efficacy and safety of edoxaban with standard of care (SOC) anticoagulant therapy in paediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE), a total of 290 subjects were randomised into the study: 147 in the edoxaban group and 143 in the SOC group, of which 286 subjects took at least one dose of study medication (MITT: edoxaban 145 subjects vs. SOC 141 subjects). The primary efficacy endpoint (the composite endpoint of symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden during the first 3-month period) occurred in 26 of 145 patients (17.9) in the edoxaban group and 31 of 141 patients (22%) of the SOC group (HR: 1.01; 95%CI: 0.59 to 1.72). The upper bound of the 95% CI (1.72) exceeded the predefined non-inferiority margin of 1.5, hence the non-inferiority of edoxaban versus SOC was not confirmed. Nevertheless, looking at the key secondary endpoint (same as the primary endpoint but assessed during the main treatment period plus extension period and 30-day follow up), the HR for the edoxaban group versus the SOC group in this analysis would have met the noninferiority criteria for edoxaban vs. SOC. in the MITT (HR: 0.71; 95%CI: 0.47 to 1.07), and also in the PP Analysis Set (HR: 0.67; 95% CI: 0.42 to 1.08). The study was powered to achieve 68 primary endpoints, whereas 57 were achieved. Therefore, the failure to achieve non-inferiority seems related to insufficient number of primary events and not to a lack of efficacy of edoxaban in children. Additionally, the HR of ≥ 1.0 was mainly driven by the specified “time-to-event” analysis, as edoxaban recurrent primary events tended toward early occurrence vs. SOC recurrent primary events.

The analysis of the secondary efficacy endpoints revealed that during treatment periods that extended beyond 3 months (for both on-treatment and overall study populations), the HR for edoxaban vs. SOC was numerically favourable (HRs: 0.86 [95% CI: 0.548, 1.342] and 0.71 [95% CI: 0.469, 1.074], respectively), concluding that edoxaban, when indicated and given for >3 months, may provide an alternative treatment option over SOC therapy, especially considering the inconvenience of long-term injectable therapy (UFH, heparin) or continued need for therapeutic monitoring VKA (warfarin). Regarding recurrent symptomatic VTE in study U312, it is reassuring that all four non-fatal events reported in the edoxaban arm were recurrent DVTs. Three cases corresponded to adolescents who had concomitant cancer treated with chemotherapy, and only 1 recurrent DVT was reported in a younger children. No relationship was found between edoxaban levels and the development of symptomatic VTE. In fact, most patients with VTE had edoxaban levels above the median, suggesting that the recurrence was related more likely to underlying disease and risk factors. There were two patients that developed symptomatic recurrent DVT while on edoxaban (subjects iliac DVT, CVC DVT) that are not mentioned in the table 4.8 of the Summary of Clinical Pharmacology in relationship with

edoxaban levels. The MAH clarified that there were noPK data available for these two patients (see assessment of Q13 in the RSI). In study U312, 21 of 26 primary recurrent VTE events in the edoxaban group and 29 of the 31 recurrent VTE events in the SOC group corresponded to “no change or extension of thrombotic burden”. The MAH clarified that one subject of 21 children (4.8%) with “no change or extension of thrombotic burden” in the edoxaban group started additional anticoagulation before the primary efficacy outcome assessment. In the SOC group, 3 of 29 children (10.3%) with “no change or extension of thrombotic burden” started additional anticoagulation before the primary efficacy outcome assessment and 1 additional subject in the SOC started additional anticoagulation on the same day as the primary efficacy outcome assessment. On the other hand, Among the 26 subjects with primary efficacy events in the edoxaban group, PK samples were collected from 14 subjects (2 subjects with symptomatic recurrent VTE, 1 death where VTE could not be ruled out and 11 subjects with no change or extension of thrombotic burden). The median and average exposures of edoxaban of the 14 subjects were slightly higher than that of subjects enrolled in Study U312 and comparable to that of subjects enrolled in Study U313. No relationship between edoxaban levels and primary efficacy events was observed (see assessment of Q14 in the RSI).

The dossier also includes data from study U313 (ENNOBLE-ATE; n=168) as supportive for efficacy. In paediatric subjects with cardiac diseases at risk of TE complications who requires primary or secondary anticoagulant prophylaxis, no TE were reported in 109 patients on edoxaban during the 3 month main observation period, while one of 58 patients in the SOC group (1.7%) experienced a DVT followed by PE. During the Extension Period, 4 subjects in the edoxaban group experienced a TE event. Of the 4 subjects with an event, 2 subjects experienced a stroke, and 2 subjects experienced an MI. Although Study U313 was neither designed nor powered to test superiority or noninferiority of edoxaban in comparison to SOC anticoagulants, it supports the conclusion that edoxaban may be an appropriate alternative to SOC (VKA or UFH/LMWH) in paediatric subjects with cardiac diseases at risk of TE complications who require primary or secondary anticoagulant prophylaxis. Overall, the results of both studies continue to support the findings to date that edoxaban is effective in children ages 0 to <18 years.

There is an unmet clinical need in paediatric thrombosis for having alternatives to parenteral anticoagulants (mainly LMWH) and VKA (requiring regular monitoring and subject to a broad number of drug-drug and drug-food interactions that need regular anticoagulant monitoring). In studies Hokusai VTE PEDIATRICS and ENNOBLE-ATE, edoxaban has shown to improve treatment compliance compared with SOC, without the need for parenteral administration or regular control its anticoagulant effect, and also positive trends were found on a exploratory endpoint of QoL. Edoxaban could be a useful addition to rivaroxaban and dabigatran for oral anticoagulation for treating thrombosis in children.

The applicant does not propose a paediatric indication or posology for edoxaban arguing that study DU176b-D-U312 did not meet the primary objective of showing non-inferiority of edoxaban versus SOC on a primary endpoint including symptomatic VTE. This approach was not endorsed initially by the CHMP. The pivotal study did not apparently show a lack of efficacy of edoxaban, while EMA rules allow extrapolation of the efficacy of a medicinal product from adults to children (EMA/199678/2016). In addition, paediatric addendum on VTE prophylaxis and treatment does not require a formal hypothesis of non-inferiority or superiority at the time of designing paediatric phase III trials in children with acute VTE (EMA/CHMP/763438/2017). The number of children recruited is expected to be low and comparative trials in the treatment of VTE versus standard of care will normally not be focussing on formal hypothesis testing of non-inferiority or superiority due to lack of statistical power, but rather on descriptive analyses [EMA/CHMP/763438/2017]. The sponsors are advised to consider analysis methods that capitalise on all available data, for example using statistical modelling (see *CHMP Guideline on clinical trials in small populations: CHMP/EWP/83561/2005*).

In the response to CHMP RSI, the applicant provided and discussed some key pitfalls of the paediatric development of edoxaban in children (see assessment of the answer to Q10 of the RSI). Regarding dose and posology, similar exposure as obtained in adults was not achieved using the proposed dose regimen of edoxaban tablets in subjects 12 to <18 years of age (rather, it could lead to an approximately 20% to 30% underexposure). This was translated into a higher annualized rate of recurrent symptomatic VTE with edoxaban vs. SOC in the meta-analysis provided in response to the list of questions (15.6% vs. 6.4% in the study U312 in children), while in the adult study U305, the trend was the opposite in favour of edoxaban (3.5% vs. 3.9%). In addition, in sensitivity analyses, using the endpoint of symptomatic recurrent VTE as defined in the EINSTEIN-Jr study, edoxaban would have been declared inferior to SOC with statistical significance (HR: 2.34; 95% CI: 0.453 to 12.054) (see also assessment of Q11 of the RSI). Therefore, a potential lack of efficacy of edoxaban due to underexposure in children at the doses tested in study U312 is a real possibility. In addition, it is unknown whether the tablet and granule formulations are bioequivalent in patients younger than 12 years. There are inadequate PK/PD, efficacy, or safety data to support the use of the edoxaban 30 mg or 15 mg tablets in patients younger than 12 years of age. As a result, establishing a paediatric posology is challenging and subject to significant uncertainty with the data available, and an extrapolation exercise of the efficacy from adults is fraught with risk ((see assessment to the MAH answer to Q10 of the RSI). Finally, there are several treatment options for paediatric VTE (i.e.: rivaroxaban, dabigatran, heparins and VKAs (see assessment to the MAH answer to Q10 of the RSI). Given the treatment options available for paediatric patients and the uncertainty that edoxaban offers at least an equivalent benefit to SOC in this patient population, the MAH does not consider that a recommendation for formulation development is warranted.

It is unfortunate that the paediatric PIP has failed in achieving the goal of establishing an appropriate effective and safe dose that provides a similar edoxaban exposure as in adults. Given the uncertainties about the benefit-risk profile of edoxaban in the paediatric population and the difficulties in establishing an appropriate paediatric dose, the Rapporteur finally shares the MAH proposal of not recommending the use of edoxaban in children.

The U312 study population was poorly characterized for essential clinical data, like age ranges (e.g.: 12 to < 18 years; 6 to < 12 years; 2 to < 6 years; and < 2 years), type of index VTE (e.g.: DVT related to central venous catheter, cerebral venous sinus, lower limbs, PE) and type of risk factors (persistent, transient or both, cancer yes/no, CVC yes/no) in the initial submission. The applicant provided these data after the CHMP request (see assessment of Q15 in the RSI). As stated in the paediatric addendum of the EMA VTE guideline, the presence of cancer and chemotherapy with asparaginase are major prothrombotic risk factors that could result in different VTE rates and/or treatment effects. The applicant clarified how many patients were recruited into the U312 study with cancer and/or asparaginase chemotherapy by treatment group and provided subgroup analyses of efficacy and safety depending on the presence/absence of a history of neoplasms at baseline. Due to the low number of events, no conclusions can be made (see assessment of the response to Q15 in the RSI).. The index VTE events in study U312 were also poorly characterized in the documentation. The description of VTE location is rather scarce (VTE is only differentiated into DVT or PE). The MAH was invited to describe locations of index DVTs (i.e.: lower limbs, upper limbs, catheter-associated DVT, cerebral venous thrombosis, etc) and to provide subgroup analyses of recurrent VTE according to location of index DVT/PE (see assessment of the MAH answer to Q12 of the RSI). There were 46 cases where VTE was not confirmed but most cases were included in the efficacy analyses. These patients should have been excluded from the mITT and PP populations and the main analysis, and only included in sensitivity analyses. The MAH provided efficacy analyses including only confirmed cases of VTE (240: 129 in the edoxaban group and 111 in the SOC group) (see assessment of the MAH answer to Q12a in the RSI). The MAH indicated that the imbalance in the number of unconfirmed cases of the

index VTE (30 in the SOC group and 16 in the edoxaban group is likely due to chance (see assessment of the MAH answer to Q12b in the RSI). The MAH also provided, after the CHMP request, a description of VTE location (see assessment of the MAH answer to Q12c). The type of index event was DVT with or without PE in 125 (86.2%) of 145 children of the edoxaban group and 121 (85.8%) of 141 children in the SOC group, while the remaining cases, 20 (13.8%) in the edoxaban group and 20 (14.2%) in the SOC group were PE without DVT. DVTs were most frequently localized in the lower extremities (50 and 44 cases in the edoxaban and SOC groups, respectively), upper extremities (22 vs 24), and cerebral venous sinus (27 vs. 21). The number of catheter-related thrombosis as index VTE event was low in the edoxaban and SOC groups (8 vs. 9).

The company also provided subgroup analyses of recurrent VTE according to location of index DVT/PE, but due to the low number of subjects with events, it is not possible to draw any conclusions. (see assessment of the MAH answer to Q12d).

The MAH also clarified that discrepancies found in the net clinical benefit analysis (Table 3.16 of the summary of clinical efficacy), which disfavoured edoxaban in study U312, and the analysis of VTE events, major bleeding and CRNM bleeding events described in other sections, which were numerically in favour of edoxaban versus SOC were due to different time-points for assessment (see assessment of the MAH answer to Q16 in the RSI).

In study U313 the results seemed worse for patients who switched from SOC to edoxaban (i.e.: SOC-edoxaban arm) than for those who continued with edoxaban since the start of the study (i.e.: edoxaban-edoxaban arm). The MAH provided brief narratives of the 5 subjects developing TE events during the extension period +30 days follow-up in study U313. All reported events were unrelated to the study medication but were attributed to progression of the underlying medical condition. Therefore, it is considered unlikely that switching from SOC treatment to edoxaban in the extension period was the fundamental cause of the increased reporting in TE events (see assessment of the MAH answer to Q17 in the RSI).

8. Clinical Safety aspects

8.1. *Methods – analysis of data submitted*

Safety data are available from the two Phase 3 studies and the supporting Phase 1 study conducted in paediatric subjects. Results from Studies U312, U313, and U157 have been presented in the Clinical Overview Addendum. Safety data were not pooled across these studies because of the differences in the study designs and subject populations.

For all studies, safety analyses were conducted in the Safety Analysis Set (SAS; ie, all subjects who received at least 1 dose of study drug). Safety data were analysed with descriptive statistics, except when otherwise specified. For details on the statistical analyses, please refer to the SAP of the individual studies (Module 5.3.5.1 DU176b-D-U312 CSR [Appendix 16.1.9](#); Module 5.3.5.1 DU176b-C-U313 CSR [Appendix 16.1.9](#); Module 5.3.4.2 DU176b-A-U157 CSR [Appendix 16.1.9](#)).

Definition, Adjudication, and Analysis of Bleeding in Studies U312 and U313:

In Studies U312 and U313, all investigator-reported bleeding events and potential safety endpoints were adjudicated by an independent CEC blinded to the treatment group and categorised as major bleeding, CRNM, and minor bleeding (nuisance bleeding). Bleeding definitions were based on presentations/discussions at the Perinatal and Paediatric Haemostasis Subcommittee meetings during the 56th-58th Scientific and Standardization Committee Meeting of the International Society on Thrombosis and Haemostasis (Schulman S, et al. J Thromb Haemost. 2005;3:692–4). Minimal criteria defining a significant bleeding were according to the International Society on Thrombosis and

Haemostasis (Rodeghiero F, et al. J Thromb Haemost. 2010; 8:2063–5). Bleeding events were summarised and analysed according to the following categories: major and CRNM bleeding events combined, major bleeding event, and all bleeding events (major, CRNM, and minor bleeding combined).

In Study U312, the analysis of the composite endpoint of major and CRNM bleeding events was based on an “on-treatment” approach. An event was considered as an “on-treatment” event if it occurred while on study drug or within 3 days of study drug interruption or discontinuation. The time to “on-treatment” major or CRNM bleeding was compared between treatment groups by using a Cox proportional hazards regression model including treatment and age groups as covariates; the edoxaban-to-comparator HR was computed with 95% CIs based on this model. Similar analyses were conducted for each bleeding category occurring from the date of randomisation to the date of the last dose of study drug plus 30 days (ie, Overall Treatment Period). The incidence of bleeding events was also summarised by treatment group for On-treatment Period up to 3 months plus 3 days (ie, Main Treatment Period and On-treatment), On-treatment up to the date of last dose of study drug plus 3 days (ie, Main Treatment Period plus Extension Period and On-treatment), and from the date of randomisation to the date of the last dose of study drug plus 30 days (ie, Overall Treatment Period). Further details on the statistical analyses of bleeding events, including sensitivity analyses and subgroup analyses, can be found in the SAP (Module 5.3.5.1 DU176b-D-U312 CSR [Appendix 16.1.9](#)).

In Study U313, the time to major or CRNM bleeding occurring during the Main Treatment Period was compared between the treatment groups using a Cox proportional hazards regression model with treatment group, concomitant usage of aspirin at Baseline, and underlying disease (Kawasaki disease, Fontan surgery, heart failure, or other) as covariates. Hazard ratios between the edoxaban and the SOC groups were calculated with the corresponding 95% CIs. Incidence, annualised event rate, and rate difference between edoxaban and SOC groups with corresponding 95% CIs were calculated for the Main Treatment Period for the bleeding event category. In addition, incidence and annualised event rate were calculated occurring from the day after the Month 3 Visit to the date of last dose of study drug plus 30 days, from the day after the Month 3 Visit to the date of last dose of study drug, and for events occurring in the Extension Period plus 3 days. Further details on the statistical analyses of bleeding events, including exploratory and subgroup analyses, can be found in the SAP (Module 5.3.5.1 DU176b-C-U313 CSR [Appendix 16.1.9](#)).

8.2. Results

Study U312. Extent of Exposure

The SAS included 286 subjects overall: 145 subjects in the edoxaban group and 141 subjects in the SOC group.

The median duration of treatment was 147.0 (range: 1 to 400) days in the edoxaban group. In the SOC group, median duration of treatment was 95.5 (range: 1 to 412) days for subjects treated with LMWH, 87.0 (range: 3 to 162) days for subjects treated with SP-FXa inhibitor, and 112.0 (range: 2 to 368) days for subjects treated with VKA (Table S01). Study drug interruptions were required in 24 (16.6%), 17 (14.7%), 0 (0%), and 13 (31.7%) of subjects treated with edoxaban, LMWH, SP-FXa inhibitor, and VKA, respectively (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.2.2.3](#)).

The amount (mg) of edoxaban taken per subject is presented in Module 5.3.5.1 DU176b-D-U312 CSR [Listing 16.2.5.1](#).

Table S01. Study Drug Exposure – Study U312 (Safety Analysis Set)

	Edoxaban (N = 145)	LMWH (N = 116)	SP-FXa Inhibitor (N = 5)	VKA (N = 41)
Study Treatment Duration (days) ^a				
Mean (±SD)	187.6 (±120.95)	133.6 (±106.34)	84.6 (±56.44)	160.1 (±109.04)
Median (min, max)	147.0 (1, 400)	95.5 (1, 412)	87.0 (3, 162)	112.0 (2, 368)
Study Duration (days) ^b				
Mean (±SD)	223.5 (±119.32)	194.6 (±109.47)	151.6 (±53.17)	213.2 (±117.98)
Median (min, max)	176.0 (25, 477)	149.5 (0, 543)	120.0 (104, 210)	206.0 (7, 562)
Treatment Exposure (days) ^c				
Mean (±SD)	186.1 (±120.14)	132.9 (±106.13)	84.6 (±56.44)	156.6 (±108.92)
Median (min, max)	147.0 (1, 394)	94.5 (1, 412)	87.0 (3, 162)	102.0 (2, 368)

FXa = activated Factor X; LMWH = low molecular weight heparin; max = maximum; min = minimum; SD = standard deviation; SP = synthetic pentasaccharide; VKA = vitamin K antagonist

^a Study treatment duration is calculated as the number of days from the date of the first dose of study drug taken to the date of the last dose of study drug taken, inclusively, with interruptions included in the interval of time (date of last dose of study drug – date of first dose of study drug + 1).

^b Study duration is calculated as the number of days from the date of the randomisation to the 30-day Follow-up Visit or to the date of last visit if no 30-day Follow-up Visit occurred.

^c On-treatment days are counted as the number of days the subjects actually took the study drug, with interruptions not included in the interval of time.

Source: Module 2.7.4 [Table 1.5](#)

Study U313. Extent of Exposure

The SAS included 167 subjects overall: 109 subjects in the edoxaban group and 58 subjects in the SOC group.

The median duration of treatment during the Main Treatment Period was 92.0 (range: 30 to 121) days for the subjects in the edoxaban group. In the SOC group, the median duration of treatment during the Main Treatment Period was 89.5 (range: 10 to 101) days for subjects treated with UFH/LMWH and 91.0 (range: 27 to 158) days for subjects treated with VKA (Table S02). Study drug interruptions during the Main Treatment Period were required in 3.7% (4/109), 16.7% (2/12), and 16.0% (8/50) of subjects treated with edoxaban, UFH/LMWH, and VKA, respectively (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.2.2.3](#)).

The median duration of exposure to edoxaban in the Extension Period was 273.0 (range: 17 to 552) days (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.2.2.2](#)).

The amount (mg) of edoxaban taken per subject is presented in Module 5.3.5.1 DU176b-C-U313 CSR [Listing 16.2.5.1](#).

Table S02. Study Drug Exposure, Main Treatment Period – Study U313 (Safety Analysis Set)

	Edoxaban (N = 109)	UFH/LMWH (N = 12)	VKA (N = 50)
Study Treatment Duration (days) ^a			
Mean (±SD)	90.4 (±11.08)	74.7 (±32.59)	87.9 (±19.84)
Median (min, max)	92.0 (30, 121)	89.5 (10, 101)	91.0 (27, 158)

	Edoxaban (N = 109)	UFH / LMWH (N = 12)	VKA (N = 50)
Study Duration up to Month 3 (days) ^b			
Mean (±SD)	92.2 (±10.01)	89.5 (±23.75)	90.9 (±18.09)
Median (min, max)	93.0 (30, 121)	91.0 (40, 145)	92.0 (3, 161)
On-treatment Days ^c			
Mean (±SD)	89.8 (±10.72)	68.8 (±37.19)	86.1 (±20.12)
Median (min, max)	91.0 (30, 115)	89.5 (10, 98)	91.0 (27, 158)

LMWH = low molecular weight heparin; max = maximum; min = minimum; SD = standard deviation; UFH = unfractionated heparin; VKA = vitamin K antagonist

^a Study treatment duration is calculated as the number of days from the date of the first dose of study drug taken to the date of the last dose of study drug taken, inclusively in Main Treatment Period, with interruptions included in the interval of time (date of last dose of study drug – date of first dose of study drug + 1).

^b Study duration is calculated as the number of days from the date of the randomisation to the Month 3 Visit or to the date of last visit if discontinued from the study prior to the Month 3 Visit.

^c On-treatment days are counted as the number of days the subjects actually took the study drug, with interruptions not included in the interval of time.

Source: Module 2.7.4 [Table 1.6](#)

Study U157. Extent of exposure

A total of 66 subjects were enrolled in the study. All subjects received 1 dose of the study drug under the supervision of clinical study personnel and completed the study. The amount (mg) of edoxaban taken per subject is presented in Module 5.3.4.2 DU176b-A-U157 CSR [Listing 16.2.5.1](#).

Safety Endpoints: Bleeding

Study U312

Safety endpoints were as follows:

- A combination of major and CRNM bleedings occurring during treatment or within 3 days of completing or interrupting or stopping study during the first 3 month treatment period (ie, Main Treatment Period). For subjects in Cohort 5, (ie, <6 months old), the primary safety endpoint was a combination of major and CRNM bleedings occurring during treatment or within 3 days of completing or interrupting or stopping study within 6 to 12 weeks period plus 3 days.
- All bleedings from the first to the last dose of study drug plus 30 days (ie, Overall Treatment Period).
- A combination of major and CRNM bleedings from the first to the last dose of study drug plus 30 days (ie, Overall Treatment Period).

Adjudicated Major and Clinically Relevant Nonmajor Bleeding Events

During the Main Treatment Period and On-treatment, 3 (2.1%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudication-confirmed major/CRNM bleeding event (HR: 0.60, 95% CI: 0.139, 2.597; Module 5.3.5.1 DU176b-D-U312 CSR Table 10.2 (Table S03).

Table S03. Summary of Characteristics of Adjudication-confirmed Major and CRNM Bleeding Events by Location – Main Treatment Period and On-treatment (Safety Analysis Set)

	Edoxaban (N = 145) n (%)	SOC (N = 141) n (%)
Major/CRNM bleeding characteristic	3 (2.1)	5 (3.5)
Clinically overt	3 (2.1)	5 (3.5)
Fall in hemoglobin ≥ 2 g/dL	1 (0.7)	0
Requiring surgery in an operating room or suite	1 (0.7)	3 (2.1)
Location		
Critical sites	0	0
Noncritical sites		
Upper gastrointestinal tract	0	1 (0.7)
Lower gastrointestinal tract	0	1 (0.7)
Vaginal	1 (0.7)	0
Epistaxis	1 (0.7)	2 (1.4)
Other	1 (0.7)	1 (0.7)

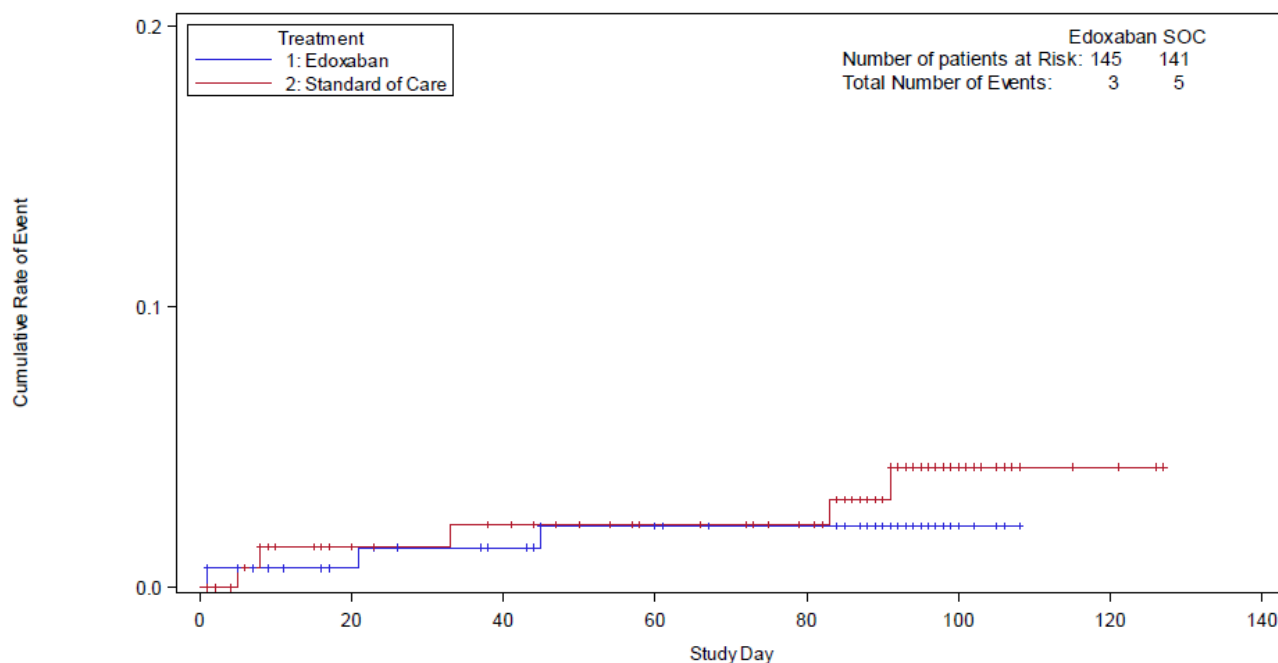
CRNM = clinically relevant nonmajor; SOC = standard of care

Note: Main Treatment Period is defined as from the date of the first dose of study drug to Month 3 Visit + 3 days, or to the date of the last dose of study drug + 3 days if study treatment is discontinued prior to Month 3 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: Table 14.3.1.19

Figure S01. Kaplan-Meier Plot for Time to First Event of Major and CRNM Bleeding Event, Main Treatment Period and On-Treatment, Safety Analysis Set



Number of Patients

1: Edoxaban	145	136	130	125	121	9	0
2: Standard of Care	141	128	124	117	110	16	3

Source Data: ADTTE.

Note: Main Treatment Period is defined as from the date of the first dose of study drug to Month 3 visit + 3 days, or to the date of the last dose of study drug + 3 days if study treatment is discontinued prior to Month 3 visit.

On-Treatment is defined as on study drug, within 3 days of study drug interruption, discontinuation and last dose of study drug.

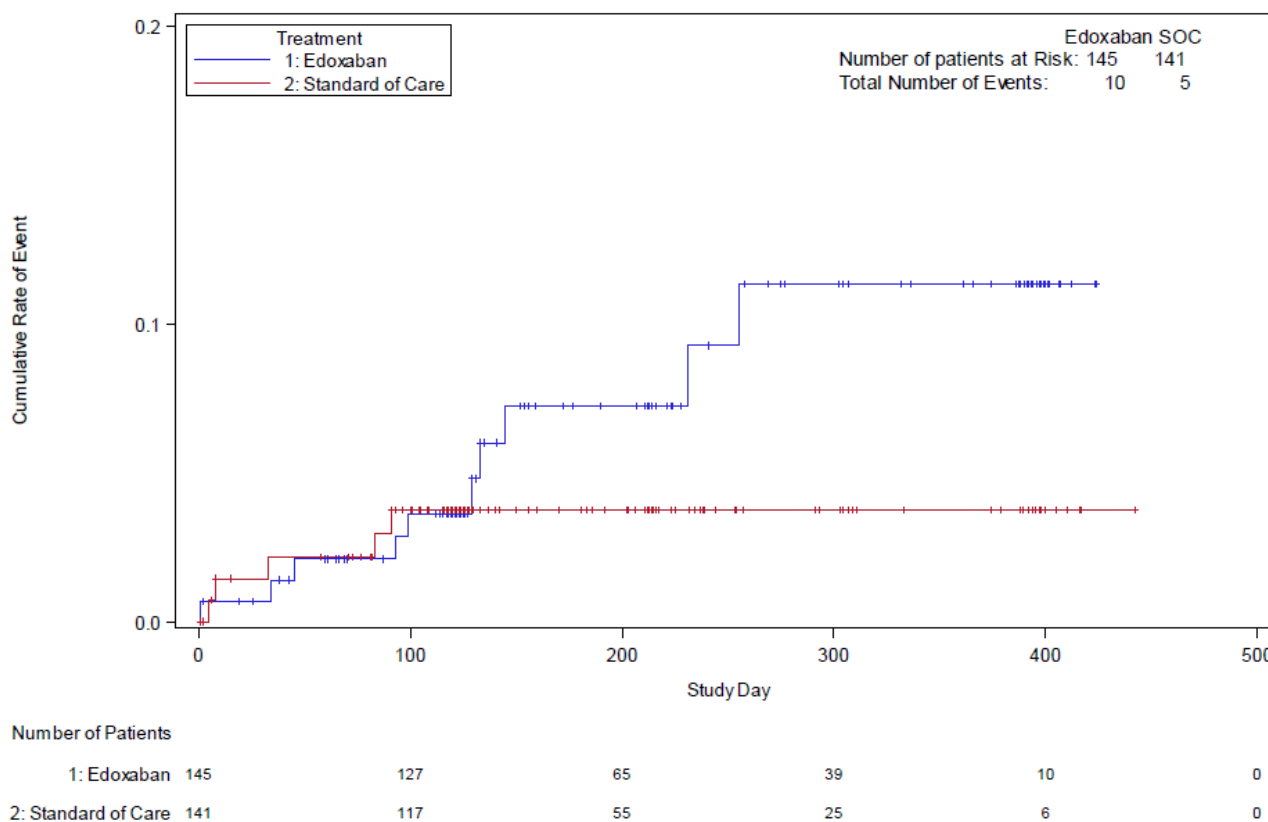
During the Main Treatment Period and On-treatment, all major/CRNM bleeding events were localised in noncritical sites (upper and lower gastrointestinal tract bleeding, vaginal bleeding, epistaxis, and other bleeding; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.19](#)). All subjects experienced clinically overt bleeding events; in addition, 1 (0.7%) subject in the edoxaban group had a decrease in haemoglobin level of ≥ 2 g/dL, and 1 (0.7%) subject in the edoxaban group and 3 (2.1%) subjects in the SOC group had bleeding events that required surgery in an operating room or suite.

During the Main Treatment Period plus Extension Period and On-treatment, 8 (5.5%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudication-confirmed major/CRNM bleeding event (HR: 1.48, 95% CI: 0.484, 4.503; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.7](#)).

During the Main Treatment Period plus Extension Period and On-treatment, 1 bleeding event occurred in a critical site (pulmonary haemorrhage in 1 subject in the edoxaban group), while all other bleeding events were localised in noncritical sites (upper and lower gastrointestinal tract bleeding, vaginal bleeding, epistaxis, and other bleeding; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.25](#)). All subjects experienced clinically overt bleeding events; in addition, 1 (0.7%) subject in the edoxaban group had a decrease in haemoglobin level of ≥ 2 g/dL, 1 (0.7%) subject in the edoxaban group required transfusion(s), and 4 (2.8%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group required surgery in an operating room or suite.

During the Overall Treatment Period, 10 (6.9%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudication-confirmed major/CRNM bleeding event (HR: 1.85, 95% CI: 0.637, 5.370; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.14](#)).

Figure S02. Kaplan-Meier Plot for Time to First Event of Major and CRNM Bleeding Event, Overall Treatment Period, Safety Analysis Set



Source Data: ADTTE.

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

Adjudicated Major Bleeding Events

During the Main Treatment Period and On-treatment, 1 (0.7%) subject in the edoxaban group experienced a major bleeding event (ie, a clinically overt event of epistaxis with a decrease in haemoglobin level of ≥ 2 g/dL; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.3](#) and [Table 14.3.1.21](#)). During the Main Treatment Period and On-treatment, there were no major bleeding events in the SOC group.

During the Main Treatment Period plus Extension Period and On-treatment, 2 (1.4%) subjects in the edoxaban group and no subjects in the SOC group experienced an adjudication-confirmed major bleeding event (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.9](#)). The 2 major bleeding events were the event of epistaxis described above and a clinically overt event of pulmonary haemorrhage (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.27](#)). The same number of major bleeding events were observed during the Overall Treatment Period (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.16](#) and [Table 14.3.1.36](#)).

Adjudicated Clinically Relevant Nonmajor Bleeding Events

During the Main Treatment Period, 3 (2.1%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced an adjudication-confirmed CRNM bleeding event (HR: 0.59, 95% CI: 0.140, 2.527; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.2](#)).

During the Main Treatment Period plus Extension Period and On-treatment, 7 (4.8%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced an adjudication-confirmed CRNM bleeding event. All CRNM bleeding events occurred at noncritical sites (ie, upper and lower gastrointestinal tract bleeding, vaginal bleeding, epistaxis, and other bleeding) and were clinically overt (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.29](#)). In addition, 1 (0.7%) subject in the edoxaban group required transfusion(s), and 4 (2.8%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group required surgery in an operating room or suite.

Adjudicated All Bleeding Events

During the Main Treatment Period and On-treatment, 21 (14.5%) subjects in the edoxaban group and 24 (17.0%) subjects in the SOC group experienced at least 1 adjudication-confirmed bleeding event (HR: 0.87, 95% CI: 0.479, 1.569; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.5](#)). All bleeding events were clinically overt and occurred in noncritical sites (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.23](#)).

During the Main Treatment Period plus Extension Period and On-treatment, 25 (17.2%) subjects in the edoxaban group and 24 (17.0%) subjects in the SOC group experienced an adjudication-confirmed bleeding event (HR: 1.00, 95% CI: 0.570, 1.755; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.11](#)). All events but one (ie, pulmonary haemorrhage) were located in noncritical sites, and all events but one were clinically overt (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.31](#)).

During the Overall Treatment Period, 26 (17.9%) subjects in the edoxaban group and 24 (17.0%) subjects in the SOC group experienced an adjudication-confirmed bleeding event (HR: 1.04, 95% CI: 0.596, 1.806; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.18](#)). All events but one (ie, pulmonary haemorrhage) were located in noncritical sites, and all events but one were clinically overt (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.1.38](#)).

Study U313

The safety endpoints were as follows:

Primary: A combination of major bleeding events and CRNM bleeding events, occurring during the Main Treatment Period from the date of first dose of study drug to the Month 3 Visit or to the date of last dose of study drug plus 3 days if study drug was discontinued, whichever was earlier.

Secondary:

- All bleeding events occurring during the Main Treatment Period from the date of first dose of study drug to the Month 3 Visit or to the date of last dose of study drug plus 3 days if study drug was discontinued, whichever was earlier
- A combination of major and CRNM bleedings from the day after Month 3 Visit to the date of the last dose of study drug plus 30 days for subjects who participated in the Extension Period
- All bleeding events from the day after the Month 3 Visit to the date of last dose of study drug plus 30 days for subjects who participated in the Extension Period

Adjudicated Bleeding Events – Main Treatment Period

There was 1/109 (0.9%) subject in the edoxaban group and 1/58 (1.7%) subject in the SOC group who experienced a CRNM bleeding event during the Main Treatment Period (annualised rate: 0.04, edoxaban group; 0.07, SOC group). The proportion of subjects with all bleeding event was similar in the edoxaban and SOC groups: 3.7% and 3.4%, respectively (Table S04).

Table S04. Summary of Adjudicated Bleeding Events, Main Treatment Period – **Study U313** (Safety Analysis Set)

Adjudicated Bleeding Events	Statistics	Edoxaban (N = 109)	SOC (N = 58)
Major/CRNM bleeding events	n (%)	1 (0.9)	1 (1.7)
	Annualised rate	0.04	0.07
	Rate difference (95% CI)	-0.03 (-0.18, 0.12)	
Major bleeding events	n (%)	0	0
	Annualised rate	-	-
	Rate difference (95% CI)	-	
All bleeding events (Major/CRNM/Minor)	n (%)	4 (3.7)	2 (3.4)
	Annualised rate	0.15	0.14
	Rate difference (95% CI)	0 (-0.24, 0.25)	

CI = confidence interval; CRNM = clinically relevant nonmajor; SOC = standard of care

Note: Annualised rate = number of subjects with events/total time at risk (years). Total time at risk is the sum, across subjects, of the number of 'at risk' years. For each subject, the "at risk" years = (the event or censoring – date of randomization + 1)/365.25. If a subject has multiple events, the time of the first event is used.

Note: The 95% CI for rate difference is calculated by using Wald's method. [Error! Reference source not found.](#)

Source: Module 2.7.4 [Table 2.1](#).

The CRNM bleeding events were as follows: epistaxis in 1 subject in the edoxaban group and lower gastrointestinal tract bleeding (haematochezia) in 1 subject in the SOC group.

Minor bleeding events were reported in 3 subjects in the edoxaban group: 1 subject had 1 event of epistaxis, 1 subject had 3 events of epistaxis, and 1 subject had 1 event of vaginal bleed (metrorrhagia). In addition, 1 subject in the SOC group had a minor event of epistaxis (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.1.5](#) and [Table 14.3.2.55](#)).

One of the subjects who did not enter the Extension Period experienced a CRNM bleeding event of epistaxis during the Main Treatment Period plus 30 days (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.1.8](#)).

One subject in the edoxaban group and 1 subject in the SOC group had a CRNM bleeding event that required a change in antithrombotic therapy (including interruption or discontinuation of study drug; Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.1.9](#)). The remaining 3 (2.8%) subjects in the edoxaban group and 1 (1.7%) subject in the SOC group had clinically overt bleeding events (non-CRNM).

For the aforementioned subjects who did not enter the Extension Period with a CRNM bleeding event of epistaxis during the Main Treatment Period plus 30-day Follow-up, a change in antithrombotic therapy (including interruption or discontinuation of study drug) was required (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.1.12](#)).

Adjudicated Bleeding Events – Extension Period

During the Extension Period plus 3 days, 4 (2.8%) subjects experienced a major, CRNM, or minor bleeding event (ie, 3 minor events and 1 major event; Table S05). No further events were reported in the Extension Period plus 30-day Follow-up (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.1.4](#)).

Notably, post-database lock, upon query by the Steering Committee chair, 1 adjudicated TE (fatal haemorrhagic stroke [in Subject], which occurred 25 days after the last edoxaban dose) was subsequently defined by the CEC chair as consistent with the protocol definition of a major bleeding event. When this additional event was considered in the major bleeding category, the total number (rate) of major bleeding events in the Extension Period plus 3 days and 30-day Follow-up was 2 (1.4%) subjects.

Table S05. Summary of Adjudicated Bleeding Events, Extension Period Plus 3 Days – **Study U313** (Safety Analysis Set)

Adjudicated Bleeding Events	Statistics	Edoxaban (N = 144)
Major/CRNM bleeding events	n (%)	1 (0.7)
	Annualised rate	0.01
Major bleeding events	n (%)	1 (0.7)
	Annualised rate	0.01
All bleeding events (major/CRNM/minor)	n (%)	4 (2.8)
	Annualised rate	0.06

CRNM = clinically relevant nonmajor; SOC = standard of care

Note: Annualised rate = number of subjects with events/total time at risk (years). Total time at risk is the sum across subjects of the number of “at risk” years. For each subject, the “at risk” years = (the event or censoring – date of randomization + 1)/365.25. If a subject has multiple events, the time of the first event is used.

Note: Percentages are based on the number of subjects in the Safety Analysis Set with at least 1 dose of edoxaban in Extension Period without any SOC treatment.

Note: Extension Period is defined as from the day after the Month 3 Visit to the date of the last dose of study drug.

Source: Module 2.7.4 [Table 2.2](#)

Four (2.8%) subjects experienced a total of 6 major, CRNM, or minor bleeding events, including cutaneous/soft tissue (haematoma <2.5 cm²), epistaxis, lower gastrointestinal tract (haematochezia), oral/pharyngeal (aphthous ulcer), other (haematoma), and vaginal bleeding (menorrhagia) (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.1.6](#), [Table 14.3.1.7](#), [Table 14.3.2.56](#), and [Table 14.3.2.57](#)).

Of the 4 subjects with bleeding events, 1 (0.7%) subject required a change in antithrombotic therapy (including interruption or discontinuation of study drug), 3 (2.1%) subjects had clinically overt bleeding events (non-CRNM), and 1 (0.7%) subject had a decrease in haemoglobin level of ≥ 2 g/dL or leading to transfusion of the equivalent of ≥ 2 units of whole blood or red blood cells (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.1.10](#) and [Table 14.3.1.11](#)).

Analysis of Adverse Events

In all studies, AEs were coded according to the Medical Dictionary for Regulatory Activities version 23.0 and according to study-specific rules detailed in Module 2.7.4 [Table 1.3](#). Treatment-emergent AEs (TEAEs) were defined as events that started on or after the initial dose of study drug or started prior to but then worsened after the initial dose of study drug. For details regarding the assessment of seriousness, intensity, and relationship to study drug, refer to Module 2.7.4 Section [1.1.1.2](#).

Of note, liver function is an area of special interest. In Studies U312 and U313, critical liver laboratory assessments included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), and alkaline phosphatase. Particular attention was paid to subjects with ALT or AST $\geq 3 \times$ upper limit of normal (ULN) and TBL ≥ 2 ULN simultaneously without evidence of cholestasis (alkaline phosphatase $\geq 2 \times$ ULN was considered evidence of possible cholestasis) and without alternative aetiology for hepatocellular damage. Hepatic events were adjudicated in a blinded manner by the CEC.

Overview of Treatment-emergent Adverse Events

Study U312

Overall, 622 and 386 TEAEs were reported in 103 (71.0%) subjects in the edoxaban group and 95 (67.4%) subjects in the SOC group, respectively (Table S06). The proportion of subjects with TEAEs leading to premature discontinuation of study drug was higher in the edoxaban group than in the SOC group: 5.5% vs. 2.1%. Other differences in frequency between treatment groups were $\leq 2.8\%$. Notably, there were 2 deaths in each treatment group.

An overview of the TEAEs reported during the Overall Treatment Period is presented in Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.17](#).

Table S06. Summary of Treatment-emergent Adverse Events, Main Treatment Period Plus Extension Period and On-treatment – Study U312 (Safety Analysis Set)

	Edoxaban (N = 145) n (%)	SOC (N = 141) n (%)
Total number of TEAEs	622	386
Number of subjects with at least 1 TEAE	103 (71.0)	95 (67.4)
Number of subjects with at least 1 study drug-related TEAE	24 (16.6)	20 (14.2)
Number of subjects with at least 1 serious TEAE	38 (26.2)	33 (23.4)
Number of subjects with at least 1 study drug-related serious TEAE	3 (2.1)	3 (2.1)
Number of subjects with at least 1 severe TEAE	14 (9.7)	15 (10.6)
Number of subjects with at least 1 study drug-related severe TEAE	2 (1.4)	1 (0.7)
Number of subjects with at least 1 TEAE leading to premature discontinuation of study drug	8 (5.5)	3 (2.1)
Number of subjects with at least 1 study drug-related TEAE leading to premature discontinuation of study drug	2 (1.4)	1 (0.7)
Number of subjects who died	2 (1.4)	2 (1.4)

AE = adverse event; SOC = standard of care; TEAE = treatment-emergent adverse event

Note: TEAEs with missing causality are counted as related.

Note: If severity is missing for an AE starting prior to the date of the first dose of study drug, then a severity of “mild” will be assigned. If severity is missing for an AE starting on or after the date of the first dose of study drug, then a severity of “severe” will be assigned.

Source: Module 2.7.4 [Table 3.1](#)

Study U313

Overall, 128 and 53 TEAEs were reported in 51 (46.8%) subjects in the edoxaban group and 24 (41.4%) subjects in the SOC group, respectively (Table S07). The proportion of subjects with study drug-related TEAE was higher in the edoxaban group than in the SOC group (6.4% vs. 1.7%), and TEAEs leading to premature discontinuation of the study drug were reported only in the edoxaban group (in 3 [2.8%] subjects vs. none). Other differences in frequency between treatment groups were ≤1.6%.

Notably, there were no serious TEAEs or severe TEAEs considered as study drug related. In addition, there were no deaths.

Table S07. Summary of Treatment-emergent Adverse Events, Main Treatment Period – Study U313 (Safety Analysis Set)

	Edoxaban (N = 109) n (%)	SOC (N = 58) n (%)
Total number of TEAEs	128	53
Number of subjects with at least 1 TEAE	51 (46.8)	24 (41.4)
Number of subjects with at least 1 drug-related TEAE	7 (6.4)	1 (1.7)
Number of subjects with at least 1 serious TEAE	5 (4.6)	3 (5.2)
Number of subjects with at least 1 drug-related serious TEAE	0	0
Number of subjects with at least 1 severe TEAE	2 (1.8)	2 (3.4)

	Edoxaban (N = 109) n (%)	SOC (N = 58) n (%)
Number of subjects with at least 1 drug-related severe TEAE	0	0
Number of subjects with at least 1 TEAE leading to premature discontinuation of study drug	3 (2.8)	0
Number of subjects with at least 1 drug-related TEAE leading to premature discontinuation of study drug	1 (0.9)	0
Number of subjects who died	0	0

SOC = standard of care; TEAE = treatment-emergent adverse event

Note: All bleeding events and thromboembolic events are included.

Source: Module 2.7.4 [Table 3.2](#).

Overall, 216 and 225 TEAEs were reported in 69 (47.9%) subjects during the Extension Period plus 3 days and 70 (48.6%) subjects during the Extension Period plus 30-day Follow-up, respectively (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.2](#) and [Table 14.3.2.3](#)).

The number (%) of subjects with the following types of events was the same in the Extension Period plus 3 days and the Extension Period plus 30-day Follow-up:

- Study drug-related TEAEs: 9 (6.3%) subjects
- Serious TEAEs and study drug-related serious TEAEs: 19 (13.2%) subjects and 3 (2.1%) subjects, respectively
- Severe TEAEs and corresponding study drug-related events: 11 (7.6%) subjects and 3 (2.1%) subjects, respectively
- TEAEs leading to premature discontinuation of study drug and corresponding study drug-related events: 5 (3.5%) subjects and 2 (1.4%) subjects, respectively

A total of 2 deaths were reported during the Extension Period plus 3 days/plus 30-day Follow-up.

Study U157

Overall, 15 (22.7%) subjects (4 subjects in Cohorts 1a/1b, 6 subjects in Cohorts 2a/2b, 1 subject in Cohorts 3a/3b, 4 subjects in Cohorts 4a/4b, and no subjects in Cohorts 5a/5b) experienced TEAEs during the study (Module 2.7.4 [Table 3.3](#)). Given the small number of subjects in each group, the number of TEAEs in the low and high dose groups in each cohort was comparable. Overall, 5 (7.6%) subjects (1 subject in Cohorts 1a/1b, 2 subjects in Cohorts 2a/2b, 1 subject in Cohorts 3a/3b, 1 subject in Cohorts 4a/4b, and no subjects in Cohorts 5a/5b) experienced study drug-related TEAEs.

There were no serious TEAEs, severe TEAEs, TEAEs leading to discontinuation of study drug, or deaths.

Common Treatment-emergent Adverse Events

Study U312

During the Main Treatment Period plus Extension Period and On-treatment, the most frequently reported TEAEs (ie, in $\geq 4\%$ of subjects in either group) in the edoxaban group were headache (14.5%); vomiting (11%); pyrexia and epistaxis (8.3% each); upper respiratory tract infection (6.2%); nasopharyngitis, diarrhoea, pain in extremity, and febrile neutropenia (5.5% each); nausea, dizziness, and cough (4.8% each); and abdominal pain, rash, and thrombocytopenia (4.1% each).

During the Main Treatment Period plus Extension Period and On-treatment, the most frequently reported TEAEs (ie, in $\geq 4\%$ of subjects in either group) in the SOC group were headache (9.9%);

epistaxis (7.1%); vomiting and pyrexia (6.4% each); upper respiratory tract infection, diarrhoea, and abdominal pain (5% each); and nausea, oropharyngeal pain, pain in extremity, febrile neutropenia, and thrombocytopenia (4.3% each).

The TEAEs of nasopharyngitis, vomiting, headache, dizziness, musculoskeletal chest pain, and rash occurred more frequently in the edoxaban group (5.5% vs. 2.1%, 11% vs. 6.4%, 14.5% vs. 9.9%, 4.8% vs. 1.4%, 2.8% vs. 0%, and 4.1% vs. 0.7%, respectively). The TEAEs of ecchymosis and drug hypersensitivity occurred more frequently in the SOC group (each 2.8% vs. 0%). The incidences of all other reported TEAEs differed between the groups by $\leq 2.2\%$ (refer to Module 2.7.4 [Table 3.4](#)).

A summary of TEAEs by System Organ Class and Preferred Term reported during the Overall Treatment Period is presented in Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.19](#).

Study U313

During the Main Treatment Period, the most frequently reported TEAEs (ie, in $\geq 4\%$ of subjects in either group) were nasopharyngitis (edoxaban group: 3.7% and SOC group: 5.2%), headache (edoxaban group: 4.6% and SOC group: 3.4%), and pyrexia (edoxaban group: 4.6% and SOC group: 1.7%; Module 2.7.4 [Table 3.5](#)). The TEAEs of pyrexia and bronchitis occurred more frequently in the edoxaban group. The TEAEs of laryngitis, catheterisation cardiac, and iron deficiency occurred more frequently in the SOC group. The incidence of all other reported TEAEs differed between the groups by $\leq 2\%$.

During the Extension Period plus 3 days and Extension Period plus 30-day Follow-up, the most frequently reported TEAEs (ie, in $\geq 4\%$ of subjects) were the following (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.17](#) and [Table 14.3.2.18](#)):

- Pyrexia, in 13 (9.0%) subjects in the Extension Period plus 3 days and 14 (9.7%) subjects in the Extension Period plus 30-day Follow-up
- Cough and headache, each in 9 (6.3%) subjects in both periods
- Upper respiratory tract infection, in 7 (4.9%) subjects in both periods
- Epistaxis and vomiting, each in 6 (4.2%) subjects in both periods

Study U157

Treatment-emergent AEs reported in >1 subject overall were the following (Module 5.3.4.2 DU176b-A-U157 CSR [Table 14.3.1.3](#)):

- Cough, in 2 (28.6%) subjects in the low dose group of Cohort 4 (4a)
- Rash, in 1 (16.7%) subject in the high dose group of Cohort 2 (2b) and 1 (16.7%) subject in the high dose group of Cohort 4 (4b)
- Fatigue, in 1 (12.5%) subject in the low dose group of Cohort 1 (1a) and 1 (14.3%) subject in the high dose group of Cohort 1 (1b)

Relationship of Treatment-emergent Adverse Events to Study Drug

Study U312

During the Main Treatment Period plus Extension Period and On-treatment, TEAEs considered as related to the study drug were reported in 24 (16.6%) subjects in the edoxaban group and 20 (14.2%) subjects in the SOC group (Module 2.7.4 [Table 3.6](#)). The most frequently reported study drug related TEAEs (ie, in $\geq 2\%$ of subjects) were the following:

- Edoxaban group – epistaxis (in 5 [3.4%] subjects) and headache (in 3 [2.1%] subjects)

- SOC group – epistaxis (in 4 [2.8%] subjects) and metrorrhagia (in 3 [2.1%] subjects)

Study drug-related TEAEs reported during the Overall Treatment Period are presented in Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.32](#).

Study U313

During the Main Treatment Period, TEAEs considered as related to the study drug were reported in 7 (6.4%) subjects in the edoxaban group and 1 (1.7%) subject in the SOC group. The only study drug-related TEAE that occurred in ≥ 2 subjects was epistaxis, which occurred in 2 (1.8%) subjects in the edoxaban group (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.13](#)).

During the Extension Period plus 3 days, TEAEs considered as related to the study drug were reported in 9 (6.3%) subjects (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.14](#)). No further study drug-related TEAEs were reported during the Extension Period plus 30-day Follow-up (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.15](#)). The only study drug-related TEAEs that occurred in ≥ 2 subjects were epistaxis and headache, each in 2 (1.4%) subjects.

Study U157

Overall, 5 (7.6%) subjects experienced TEAEs considered as related to the study drug (Module 5.3.4.2 DU176b-A-U157 CSR [Table 14.3.1.5](#)). Study drug-related TEAEs were reported at most in 1 subject/cohort as follows:

- Activated partial thromboplastin time prolonged, in 1 (16.7%) subject in the high dose group of Cohort 2 (2b)
- Prothrombin time prolonged, in 1 (14.3%) subject in the high dose group of Cohort 1 (1b)
- Haematochezia, in 1 (14.3%) subject in the low dose group of Cohort 2 (2a)
- Psychomotor hyperactivity, in 1 (14.3%) subject in the low dose group of Cohort 3 (3a)
- Rash, in 1 (16.7%) subject in the high dose group of Cohort 4 (4b)

Intensity of Treatment-emergent Adverse Events

Study U312

During the Main Treatment Period plus Extension Period and On-treatment, severe TEAEs were reported in 14 (9.7%) subjects in the edoxaban group and 15 (10.6%) subjects in the SOC group (Module 2.7.4 [Table 3.7](#)). Severe TEAEs reported in ≥ 2 subjects were as follows:

- Edoxaban group – thrombocytopenia (in 3 [2.1%] subjects) and anaemia and neutropenia (each in 2 [1.4%] subjects)
- SOC group – anaemia, febrile neutropenia, and vomiting (each in 2 [1.4%] subjects)

The majority of severe TEAEs was not considered as related to the study drug (Module 5.3.5.1 DU176b-D-U312 CSR [Listing 16.2.7.1](#)); exceptions were as follows:

- One event of pulmonary haemorrhage reported in 1 subject in the edoxaban group, which led to study drug interruption and resolved by the end of the study
- One event of alanine aminotransferase increased and 1 event of aspartate aminotransferase increased, both reported in 1 subject in the SOC group, which led to study drug withdrawal and resolved by the end of the study

Study drug-related TEAEs reported during the Overall Treatment Period are presented in Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.30](#).

Notably, the following severe TEAEs led to death (see Section 0):

- Edoxaban group – cardiogenic shock and endocarditis in 1 subject; seizure and respiratory failure in 1 subject
- SOC group – adrenal insufficiency in 1 subject; pneumococcal sepsis in 1 subject; and cardiopulmonary failure, systemic inflammatory response syndrome, acute respiratory distress syndrome, and noncardiogenic pulmonary oedema in 1 subject

Study U313

During the Main Treatment Period, severe TEAEs were reported in 2 (1.8%) subjects in the edoxaban group and 2 (3.4%) subjects in the SOC group (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.10](#) and [Listing 16.2.7.1](#)). Specifically:

- Edoxaban group – brain natriuretic peptide increased and cardiac failure in 1 subject, and headache in 1 subject
- SOC group – hyponatraemia and cardiac failure in 1 subject, and PE in 1 subject

None of the severe TEAEs were considered to be related to the study drug.

During the Extension Period plus 3 days, severe TEAEs were reported in 11 (7.6%) subjects (Module 2.7.4 [Table 3.8](#)). No further severe TEAEs were reported during the Extension Period plus 30-day Follow-up (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.12](#)).

All severe TEAEs by Preferred Term were reported at most in 1 subject.

The majority of severe TEAEs were considered to be unrelated to the study drug, with the exception of the events of myocardial ischaemia, MI, and traumatic liver injury (Module 5.3.5.1 DU176b-C-U313 CSR [Listing 16.2.7.1](#)). Notably, 2 severe TEAEs led to death: cardiac disorder (ie, progression of underlying cardiac disease) and cerebral haematoma (ie, stroke; see Section 0).

Study U157

There were no severe TEAEs reported during the study. The majority of TEAEs were of mild intensity, in 12 (18.2%) subjects overall (Module 5.3.4.2 DU176b-A-U157 CSR [Table 14.3.1.4](#)). Moderate TEAEs were reported in 3 (4.5%) subjects overall.

Deaths

Study U312

During the Overall Treatment Period, TEAEs leading to death were reported in 3 subjects in the edoxaban group and 3 subjects in the SOC group (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.25](#) and [Listing 16.2.7.4](#)):

- Edoxaban group – cardiogenic shock and endocarditis in 1 subject; seizure and respiratory failure in 1 subject; and pleural effusion in 1 subject
- SOC group – adrenal insufficiency in 1 subject; pneumococcal sepsis in 1 subject; and cardiopulmonary failure, systemic inflammatory response syndrome, acute respiratory distress syndrome, and noncardiogenic pulmonary oedema, in 1 subject

None of the above events were considered as related to the study drug.

Study U313

There were 2 deaths that were reported during the Extension Period plus 3 days (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.38](#)) and were due to progression of underlying cardiac disease (Preferred Term: cardiac disorder) and stroke (Preferred Term: cerebral haematoma, which was a CEC adjudication-confirmed event of fatal haemorrhagic stroke [Module 5.3.5.1 DU176b-C-U313 CSR [Listing 16.2.6.7](#)]). Both events were severe and considered to be unrelated to the study drug.

Study U157

No deaths were reported during the study.

Other Serious Adverse Events

Study U312

During the Overall Treatment Period, serious TEAEs were reported in 44 (30.3%) subjects in the edoxaban group and 37 (26.2%) subjects in the SOC group (Module 2.7.4 [Table 3.9](#)). Serious TEAEs that occurred in ≥ 2 subjects were as follows:

- Edoxaban group – febrile neutropenia (in 6 [4.1%] subjects); pneumonia (in 4 [2.8%] subjects); urinary tract infection (in 3 [2.1%] subjects); and thrombocytopenia, headache, intracranial pressure increased, cerebral venous sinus thrombosis, vomiting, suicidal ideation, and PE (each in 2 [1.4%] subjects)
- SOC group – febrile neutropenia (in 6 [4.3%] subjects); thrombocytopenia and headache (each in 3 [2.1%] subjects); and gastroenteritis, cellulitis, rhinovirus infection, dehydration, and vomiting (each in 2 [1.4%] subjects)

During the Overall Treatment Period, serious TEAEs considered as related to the study drug were reported in 3 (2.1%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group. The study drug-related serious TEAEs that occurred in the edoxaban group were pulmonary haemorrhage, pruritus, and venous embolism, while those in the SOC group were hematemesis, haematochezia, alanine aminotransferase increased, and aspartate aminotransferase increased (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.22](#)).

A total of 11 serious TEAEs led to death, of which none were considered as related to the study drug (see Section 0).

Study U313

During the Main Treatment Period, serious TEAEs were reported in 5 (4.6%) subjects in the edoxaban group and 3 (5.2%) subjects in the SOC group (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.7](#)). Serious TEAEs reported in >1 subject were cardiac failure (2 [1.8%] subjects in the edoxaban group and 1 [1.7%] subject in the SOC group) and pleural effusion (2 [1.8%] subjects in the edoxaban group). None of the serious TEAEs were considered to be related to the study drug (Module 5.3.5.1 DU176b-C-U313 CSR [Listing 16.2.7.2](#)). Two serious TEAEs led to death (see Section 0).

During the Extension Period plus 3 days, serious TEAEs were reported in 19 (13.2%) subjects (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.8](#)). Pyrexia was the only serious TEAE reported in >1 subject (ie, in 2 [1.4%] subjects).

Serious TEAEs considered to be related to the study drug were reported in 3 (2.1%) subjects: traumatic liver injury, myocardial ischaemia, and MI (Module 5.3.5.1 DU176b-C-U313 CSR [Listing 16.2.7.2](#)).

Study U157

No serious TEAEs were reported during the study.

Other Significant Adverse Events

Study U312

Treatment-emergent Adverse Events Leading to Discontinuation

During the Main Treatment Period plus Extension Period and On-treatment, TEAEs leading to study drug discontinuation were reported in 8 (5.5%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.8](#)).

Treatment-emergent AEs leading to study drug discontinuation were as follows:

- Edoxaban group – embolism venous (in 2 [1.4%] subjects); and cerebral venous sinus thrombosis, DVT, haematochezia, haemorrhagic stroke, intracranial pressure increased, peripheral embolism, and pruritus (each in 1 [0.7%] subject)
- SOC group – alanine aminotransferase increased, anaplastic astrocytoma, aspartate aminotransferase increased, and stoma site haemorrhage (each in 1 [0.7%] subject)

Most TEAEs leading to study drug discontinuation were not considered as related to the study drug; exceptions were as follows (Module 5.3.5.1 DU176b-D-U312 CSR [Listing 16.2.7.3](#)):

- Edoxaban group – pruritus and embolism venous, each reported in 1 subject
- SOC group – alanine aminotransferase increased and aspartate aminotransferase increased, each reported in 1 subject

Treatment-emergent Adverse Events Leading to Study Drug Interruption

During the Main Treatment Period plus Extension Period and On-treatment, TEAEs leading to study drug discontinuation were reported in 17 (11.7%) subjects in the edoxaban group and 15 (10.6%) subjects in the SOC group (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.7](#)).

Treatment-emergent AEs leading to study drug interruption reported in >1 subject were as follows:

- Thrombocytopenia, in 3 (2.1%) subjects and in 2 (1.4%) subjects in the edoxaban and SOC groups, respectively
- Febrile neutropenia, in 2 (1.4%) subjects in each treatment group
- Pancytopenia, in 2 (1.4%) subjects in the SOC group

Bleeding Events Confirmed by Clinical Events Committee Adjudication

During the Main Treatment Period plus Extension Period and On-treatment, 25 (17.2%) subjects in the edoxaban group and 24 (17.0%) subjects in the SOC group experienced at least 1 event confirmed by CEC adjudication as a bleeding event (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.1](#); see also [Section 0](#)). Specifically, 2 (1.4%) subjects in the edoxaban group and no subjects in the SOC group experienced a major bleeding event; 7 (4.8%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced a CRNM bleeding event; and 22 (15.2%) subjects in the edoxaban group and 20 (14.2%) subjects in the SOC group experienced a minor bleeding. Bleeding events were considered as serious in 3 (2.1%) subjects in the edoxaban group (menometrorrhagia, chest wall haematoma, and pulmonary haemorrhage, each in 1 [0.7%] subject) and 4 (2.8%) subjects in the SOC group (haematemesis, haematochezia, stoma site haemorrhage, and vomiting, each in 1 [0.7%] subject; Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.5](#)).

During the Overall Treatment Period, 26 (17.9%) subjects in the edoxaban group and 24 (17.0%) subjects in the SOC group experienced at least 1 event confirmed by CEC adjudication as a bleeding event (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.2](#)). In addition to the serious events described above for the Main Treatment Period plus Extension Period and On-treatment, a serious event of ureterolithiasis was reported in 1 (0.7%) subject in the edoxaban group (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.6](#)).

Liver Function

During the Main Treatment Period plus Extension Period and On-treatment, there were no notable differences between the treatment groups in the occurrence of elevated liver enzymes and TBL (Module 2.7.4 [Table 3.10](#)). Elevations in liver parameters that occurred in >5 subjects in either group were the following:

- ALT $\geq 3 \times$ ULN, in 15 (10.3%) subjects and 12 (8.5%) subjects in the edoxaban and SOC groups, respectively
- ALT $\geq 5 \times$ ULN, in 6 (4.1%) subjects and 6 (4.3%) subjects in the edoxaban and SOC groups, respectively
- AST $\geq 3 \times$ ULN, in 6 (4.1%) subjects and 4 (2.8%) subjects in the edoxaban and SOC groups, respectively
- ALT or AST $\geq 3 \times$ ULN, in 16 (11.0%) subjects and 12 (8.5%) subjects in the edoxaban and SOC groups, respectively
- ALT or AST $\geq 5 \times$ ULN, in 6 (4.1%) subjects and 6 (4.3%) subjects in the edoxaban and SOC groups, respectively

A summary of elevated liver enzymes and bilirubin abnormalities reported during the Overall Treatment Period is presented in Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.15](#).

During the Main Treatment Period plus Extension Period and On-treatment, adjudicated hepatic events were reported in 2 (1.4%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.11](#)). The nature of liver injury was hepatocellular in all cases. Results were the same for the Overall Treatment Period (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.12](#)).

During the Overall Treatment Period, investigator-reported hepatic events were recorded for 4 (2.8%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group (Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.3.2.13](#)). The known causes of the events were as follows: known hepatotoxic drug in 1 (0.7%) subject in the edoxaban group, known underlying liver disease in 1 (0.7%) subject in the SOC group, and other in 3 (2.1%) subjects in the edoxaban group and 2 (1.4%) subjects in the SOC group. There were no Hy's law cases in either treatment group.

Study U313

Treatment-emergent Adverse Events Leading to Study Drug Discontinuation

During the Main Treatment Period, TEAEs leading to study drug discontinuation were reported in 3 (2.8%) subjects in the edoxaban group: cardiac failure, coronary artery thrombosis, and arterial thrombosis (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.41](#) and [Listing 16.2.7.3](#)). None of these events were considered as related to the study drug, except arterial thrombosis. None of the subjects in the SOC group experienced TEAEs leading to study drug discontinuation.

During the Extension Period plus 3 days, TEAEs leading to study drug discontinuation were reported in 5 (3.5%) subjects (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.42](#)): atrial thrombosis, MI,

pyrexia, and cerebellar infarction. Of these TEAEs leading to study drug discontinuation, myocardial ischaemia and MI were considered as related to the study drug (Module 5.3.5.1 DU176b-C-U313 CSR Listing 16.2.7.3).

Treatment-emergent Adverse Events Leading to Study Drug Interruption

During the Main Treatment Period, TEAEs leading to study drug interruption were reported in 3 (2.8%) subjects in the edoxaban group (ie, toothache, injection site bruising, and ALT abnormal) and 3 (5.2%) subjects in the SOC group (ie, haematochezia, hyponatraemia, and epistaxis) (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.44](#)).

During the Extension Period plus 3 days, TEAEs leading to study drug interruption were reported in 10 (6.9%) subjects (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.45](#)). The only TEAE reported in >1 subject was epistaxis (in 2 [1.4%] subjects).

Bleeding Events Confirmed by Clinical Events Committee Adjudication

During the Main Treatment Period, a total of 4 (3.7%) subjects in the edoxaban group and 2 (3.4%) subjects in the SOC group experienced TEAEs confirmed by CEC adjudication as bleeding events (Module 2.7.4 [Table 3.11](#); see also Section 0). The only adjudicated bleeding event reported in >1 subject was epistaxis: in 3 (2.8%) subjects in the edoxaban group and 1 (1.7%) subject in the SOC group. None of the events were considered as serious (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.58](#)).

During the Extension Period plus 3 days, a total of 4 (2.8%) subjects experienced TEAEs confirmed by CEC adjudication as bleeding events: aphthous ulcer, haematochezia, menorrhagia, epistaxis, and haematoma (1 subject each; see also Section 0). None of the events were considered as serious (Module 5.3.5.1 DU176b-CU313 CSR [Table 14.3.2.59](#) and [Table 14.3.2.60](#)).

Thromboembolic Events Confirmed by Clinical Events Committee Adjudication

During the Main Treatment Period, 1 subject in the SOC group experienced TEAEs confirmed by CEC adjudication as TEs (ie, PE and DVT; Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.65](#)). The event of PE was considered as serious (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.69](#)).

During the Extension Period plus 3 days, TEAEs confirmed by CEC adjudication as TEs were reported in 5 (3.5%) subjects: atrial thrombosis, MI, myocardial ischaemia, cerebellar infarction, and cerebral haematoma (fatal haemorrhagic stroke) (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.67](#)).

The following events were CEC-confirmed serious events and were reported in 5 (3.5%) subjects: atrial thrombosis, MI, myocardial ischaemia, cerebellar infarction, and cerebral haematoma (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.2.71](#) and [Table 14.3.2.72](#)).

Liver Function

No notable differences between the treatment groups were identified in the occurrence of elevated liver enzymes and TBL test results.

During the Main Treatment Period, elevations in liver parameters that occurred in ≥ 2 subjects in either treatment group were as follows (see also Module 2.7.4 [Table 3.12](#)):

- ALT $\geq 3 \times$ ULN, in 2 (1.8%) subjects and 0 subjects in the edoxaban and SOC groups, respectively
- ALT or AST $\geq 3 \times$ ULN, in 2 (1.8%) subjects and 0 subjects in the edoxaban and SOC groups, respectively

- TBL $\geq 1.5 \times$ ULN, in 1 (0.9%) subject and 3 (5.2%) subjects in the edoxaban and SOC groups, respectively

There were no Hy's law cases in either group. None of the subjects had an adjudicated hepatic event (Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.1.16](#)).

During the Extension Period plus 3 days, there was 1 adjudicated hepatic event (ie, ALT or AST $\geq 8 \times$ ULN; Module 5.3.5.1 DU176b-C-U313 CSR [Table 14.3.1.17](#)).

Study U157

No TEAEs leading to discontinuation or other significant TEAEs were reported during the study.

Clinical Laboratory Evaluations

Clinical laboratory assessments (haematology and serum chemistry) were conducted as detailed in Module 2.7.4 [Table 1.4](#). There were no notable safety observations; mean baseline values and mean changes from Baseline were similar between the edoxaban group and SOC group.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs and physical examination were conducted in Studies U312, U313, and U157 (for details, refer to Module 2.7.4 Section [1.1.1.4](#) and Section [1.1.1.5](#)). There were no notable safety observations in Studies U312, U313, and U157. In Studies U312 and U313, mean baseline values and mean changes from Baseline were similar between the edoxaban group and SOC group.

Safety in Special Groups and Situations

Subgroup analyses of adjudicated major or CRNM bleeding events (Studies U312 and U313), major bleeding events (Study U312 only), and all bleeding events (Study U312 only) should be interpreted with caution because of the small numbers in each subgroup.

Postmarketing Data

A cumulative search of postmarketing reports for edoxaban use in the paediatric population (age <18 years) was conducted from the Global Safety Database. Nine serious and 24 nonserious cases were identified; the age range was from neonate to 18 years.

The serious cases included 1 fatal case (stillbirth). The father of the neonate started therapy with Lixiana 60 mg for DVT and clotting disorder (antiphospholipid antibody syndrome). Therapy with Lixiana was interrupted 3 to 4 days prior to sperm donation for in vitro fertilization in 2017. The mother gave stillbirth in 2018 in the eighth month of pregnancy. No further information is available for this case.

For the other 8 serious cases, there were no bleeding events involved, and company causality was not related for all except one. In that case, a 17-year-old female patient took Lixiana for an unknown indication and experienced vomiting, blurred vision, and headache.

Overall, the limited number of off-label use or medication error cases did not show any new safety signals or impact on the overall benefit-risk of edoxaban.

8.3. Discussion on clinical safety

In Study U312, results were comparable between the edoxaban and SOC groups for the primary safety objective. Edoxaban was generally safe and well tolerated in paediatric subjects for the treatment and secondary prevention of VTE. A total of 3 (2.1%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudication-confirmed major and CRNM bleeding

event during the Main Treatment Period and On-treatment (HR: 0.60, 95% CI: 0.139, 2.597). On the contrary, during the Overall Treatment Period, 10 (6.9%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudication-confirmed major/CRNM bleeding event (HR: 1.85, 95% CI: 0.637, 5.370), which means that during follow-up there were 7 major/CRNM bleedings in the edoxaban group and none in the SOC group. A time-varying risk of bleeding with edoxaban could not be confirmed based on the data presented. This is in line with data from other studies, such as ENGAGE AF-TIMI 48 with a mean study drug exposure of 806 days in the edoxaban 60 mg group or post-authorisation safety study ETNA-AF Europe, with a median treatment duration of 97.5 weeks during the 48-month follow-up period (see assessment of Q18 of the RSI).

Treatment-emergent AEs in study U312 occurred in 71.0% (103/145) of subjects in the edoxaban group and 67.4% (95/141) of subjects in the SOC group. The most frequently reported TEAEs (ie, $\geq 4\%$ of subjects in either group) were headache, vomiting, and pyrexia. The TEAEs of nasopharyngitis, vomiting, headache, dizziness, musculoskeletal chest pain, and rash occurred more frequently in the edoxaban group. The TEAEs of ecchymosis and drug hypersensitivity occurred more frequently in the SOC group. The incidences of all other reported TEAEs differed between the groups by $\leq 2.2\%$. Overall, no new safety signals related to edoxaban use were observed. In study U312, 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), seizure and respiratory failure (1 subject), and pleural effusion (1 subject). The deaths in the SOC group included adrenal insufficiency (1 subject); pneumococcal sepsis (1 subject); and cardiopulmonary failure, systemic inflammatory response syndrome, acute respiratory distress syndrome, and noncardiogenic pulmonary oedema (1 subject). None of the deaths were considered related to study drug. The mean values for the serum chemistry and haematology parameters evaluated were generally similar between the 2 groups at Baseline, and the mean changes from Baseline for each parameter were generally similar between the groups during the study. There were no clinically meaningful differences in vital signs between the groups (at Baseline and post-Baseline). During the Overall Treatment Period, the percentage of subjects who experienced serious TEAEs was 30.3% (44/145) in the edoxaban group and 26.2% (37/141) in the SOC group. Overall, 8 (5.5%) subjects in the edoxaban group experienced TEAEs leading to discontinuation of study drug vs. 3 (2.1%) subjects in the SOC group during the Main Treatment Period.

In study U313, results were similar between the 2 treatment groups for the primary safety objective. Two subjects, 1 in each treatment group, experienced a CRNM bleeding event in the Main Treatment Period (annualised rate: 0.04, edoxaban group; 0.07, SOC group). Edoxaban was generally safe and well tolerated in paediatric subjects with cardiac diseases at risk of TE complications. No new safety signals in this paediatric study population were observed. During the Main Treatment Period, TEAEs occurred in 46.8% of subjects in the edoxaban group and 41.4% of subjects in the SOC group. Treatment-emergent AEs considered drug related occurred in 6.4% of subjects in the edoxaban group and 1.7% of subjects in the SOC group. Two subjects died during the Extension Period of the study. Both events were severe and considered not related to study drug. During the Main Treatment Period, the percentage of subjects who experienced serious TEAEs was 4.6% (5/109) of subjects in the edoxaban group and 5.2% (3/58) in the SOC group. No subjects in either treatment group experienced a study drug-related serious TEAE. Overall, 2.8% (3/109) of subjects in the edoxaban group experienced TEAEs leading to discontinuation of study drug during the Main Treatment Period. One subject had a TEAE of arterial thrombosis leading to discontinuation of study drug that was considered by the investigator as study drug related. There were two children with Kawasaki disease in the U313 study that developed MI considered related to study medication by the investigator (1 Subject: who received warfarin 3 mg during main treatment period switched to edoxaban 45 mg during extension treatment; Another Subject on SOC (details unknown; active ingredient not

defined) 31 mg during main period received edoxaban (dose not recorded in the narrative) The events were poorly documented with respect to study medications, doses and narratives. The MAH provided narratives including study medications and doses given at the start of the trial and former medications the patients were taken at the onset of the MI (see assessment of Q18 of the RSI). The events were considered as not related to edoxaban (see assessment of Q18 of the RSI).

In Study U157, edoxaban was safe and well tolerated when administered orally in a single low dose or single high dose to paediatric subjects from 38 weeks gestation (0 months) to <18 years of age. Four subjects in Cohorts 1a/1b, 6 subjects in Cohorts 2a/2b, 1 subject in Cohorts 3a/3b, and 4 subjects in Cohorts 4a/4b experienced TEAEs, of which the majority were mild, resolved without any sequelae, and did not require any medical intervention. Given the small number of subjects in each group, the number of TEAEs in the low and high dose groups in each cohort was comparable. No severe TEAEs were observed. One subject in Cohorts 1a/1b, 2 subjects in Cohorts 2a/2b, 1 subject in Cohorts 3a/3b, and 1 subject in Cohorts 4a/4b experienced study drug-related TEAEs, of which all were mild. No subjects in Cohorts 5a/5b experienced any TEAEs. In the 12 to <18 years age cohort, 1 subject treated with high dose of edoxaban (Cohort 1b) had PT prolonged (without bleeding), which was considered to be related to edoxaban. In the 6 to <12 years age cohort, 1 subject treated with high dose of edoxaban (Cohort 2b) had aPTT prolonged (without clinical impact), which was considered to be related to edoxaban. There were no deaths during the study. No subjects experienced serious TEAEs or study drug-related serious TEAEs during the study, and there were no TEAEs leading to discontinuation of study drug. Two subjects experienced 3 serious AEs in the Screening Period and did not receive the study drug. No clinically meaningful changes in serum chemistry, haematology laboratory evaluations, or vital signs were observed.

In summary, during paediatric studies, edoxaban was generally safe and well tolerated, which is in line with the results reported in adults. No major safety issues arose.

9. PRAC advice

N/A.

10. Risk management plan

The WSA submitted an updated RMP (version 15.0, 21 Oct 2022) with this application. The main proposed RMP changes were the following:

Summary of significant changes in the RMP:

The following paragraphs describe changes from the previously submitted edoxaban EU RMP version 14.1.

- Part I Product(s) overview has been updated to include the information on paediatric population.
- Part II: Module SIII Clinical trial exposure and Part II: Module SV Post-authorisation experience have been updated with the new exposure data.
- Part II Module SVII, the missing information "Use in paediatric population", has been removed from the list of safety concerns. This part has also been updated to include safety data from DU176b-D-U312 (Hokusai VTE Paediatrics Study) and DU176b-C-U313 (ENNOBLE-ATE Study) related to bleeding events (Important identified risk).
- Part II Module SIII, Part V, VI, have been revised accordingly.
- The other changes are of minor nature.

PART I Product Overview

The MAH proposes to update text for paediatric population in SmPC section 4.2

“Paediatric population

Edoxaban is not recommended for use in children and adolescents from birth to 18 years of age with confirmed VTE (PE and/or DVT) event as the efficacy has not been established. Available data in VTE patients are described in sections 4.8, 5.1 and 5.2.”

Assessor’s comments: In light of the available paediatric data based on final results from Study DU176b-D-U312, the MAH has proposed to update the SMPC of Edoxaban in several sections. The proposed updated mention in the RMP is identical to that proposed in the SmPC in section 4.2.

PART II Safety Specification

10.1. Safety Specification

Clinical trial exposure

The MAH proposes to update the RMP with new exposure data.

SI II 1 Brief overview of development

Currently, edoxaban is approved in 67 countries and is marketed in 59 countries worldwide.

European Economic Area:

Approved and Marketed

Austria	Finland	Liechtenstein	Slovak Republic
Belgium	Germany	Lithuania	Slovenia
Bulgaria (Roteas)	Hungary	Luxembourg	Spain
Czech Republic	Iceland	Netherlands	Sweden
Croatia (Roteas)	Ireland	Norway	
Denmark	Italy	Portugal	
Estonia	Latvia	Romania (Roteas)	
Austria	Estonia	Italy	Norway
Belgium	Finland	Latvia	Portugal
Bulgaria (Roteas®)	Germany	Liechtenstein	Slovak Republic
Croatia (Roteas®)	Hungary	Lithuania	Spain
Czech Republic	Iceland	Luxembourg	Sweden
Denmark	Ireland	Netherlands	

Approved and Not Marketed

Cyprus	Greece	Malta	Poland
France			
Albania	France	Malta	Romania
Cyprus	Greece	Poland	Slovenia

Rest of World

Approved and Marketed

Albania	El Salvador	Malaysia	Taiwan
Azerbaijan	Guatemala	Mexico	Thailand
Bahrain	Honduras	Nicaragua	Turkey
Belize	Hong Kong	Panama	UAE
Brazil	Indonesia	Philippines	UK
Canada	Japan	Singapore	USA
China	Kazakhstan	Saudi Arabia	Vietnam
Costa Rica	Kyrgyzstan	South Korea	
Dom. Rep.	Macau	Switzerland	
Bahrain	Guatemala	Mexico	Taiwan
Belize	Honduras	Nicaragua	Thailand
Brazil	Hong Kong	Panama	Turkey
Canada	Indonesia	Philippines	UAE
China	Japan	Singapore	USA
Costa Rica	Kazakhstan	Saudi Arabia	UK
Dom. Rep.	Macau	South Korea	
El Salvador	Malaysia	Switzerland	

Approved and Not Marketed

Israel	Oman	Turkmenistan	
Azerbaijan	Israel	Kyrgyzstan	

Assessor's comments: The DLP of the new version 15.0 of the RMP dated the 30 September 2022. In the PSUSA covering the period from 22 oct 2021 to 21 oct 2022, it is indicated that "edoxaban is approved in 69 countries and is marketed in 60 countries worldwide". The difference in dates between the DLPs of the PSUR and the RMP may explain the differences in the number of countries where the product is authorized and marketed.

SIII.2 Clinical Trial Exposure

Cumulatively 46,25508 subjects have been treated within the clinical development programme (in ongoing and completed studies) until last DSUR cut-off (21-APR-2022) of this report, either as healthy subjects (2,140 healthy subjects) or patients (44068115 patients).

Estimates of overall cumulative subject exposure are provided in Table 6-1 Part II: Module SIII.1, based upon actual exposure data from completed/open-label studies and the enrolment/randomisation schemes for ongoing studies.

Table 1: Estimated Cumulative Subject Exposure in DU-176b Clinical Studies

Treatment	Number of Subjects
Edoxaban	29,367390
Comparator	16,14824
Placebo	717
Total	46,25508

Table 2: Age Group and Gender

Age group	Patients	
	M	F
<65	8,29869	3,93596
≥65	9,265	7,837
Total	17,56334	11,772833

Table 3: Ethnic Origin (Nonvalvular Atrial Fibrillation, Venous Thromboembolism, and Orthopaedic Surgery Indications)

Estimated Cumulative Subject Exposure to DU-176b in Completed Clinical Studies by Racial Group	
Racial Group	Number of Subjects
White	20,313
Asian	5,545
Black or African American	1,075
Unknown	284
Native Hawaiian or Other Pacific Islander	2
American Indian or Alaska native	1
Other	874
Total	28,094

Ethnic origin	Patients
Caucasian	20,398
Black	1,082
Asian	5,562
Other	887
Unknown	286
Total	28,215 ^a

^a Missing to the total of 29,390 edoxaban patients: ethnic origin not collected in some studies

Assessor's comments: These changes concern updates to exposure data in clinical trials up to 21 April 2022.

Post-authorisation experience

SV.1.2 Exposure

Cumulatively, from IBD through to the end of ~~second~~ first quarter 2022~~1~~, a total of ~~820,993~~ 884,920 patients are estimated to have received edoxaban for OS indication and ~~6,051,965~~ 7,885,754 patient-years of edoxaban exposure for NVAf and VTE indications.

Assessor's comments: Update of patient exposure data. No comments.

PART II: MODULE SVII Identified and potential risks

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

RMP version 15.0 (current) vs version 14.1

"Use in paediatric population" previously classified as missing information has been removed from the list of safety concerns.

~~There have been no added or reclassified safety concerns with edoxaban use in this version of the RMP.~~

SV VII.3.1 Presentation of important Identified Risk and Important potential risks

Bleeding events

DU176b-D-U312 (Hokusai VTE Paediatrics Study):

During the Main Treatment Period (randomization until the end of Month 3) and On-treatment (on study drug or within 3 days of interruption or discontinuation) , 3 (2.1%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC experienced at least 1 adjudicated confirmed major/CRNM bleeding event (HR: 0.60, 95% CI: 0.139, 2.597; Module 5.3.5.1 DU176b-D-U312 CSR Table 14.3.1.1).

During the Main Treatment Period and On-treatment, all major/CRNM bleeding events were localised in noncritical sites (upper and lower gastrointestinal tract bleeding, vaginal bleeding, epistaxis, and "other" bleeding; Module 5.3.5.1 DU176b-D-U312 CSR Table 14.3.1.19). All subjects experienced clinically overt bleeding events; in addition, 1 (0.7%) subject in the edoxaban group had a decrease in haemoglobin level of ≥ 2 g/dL, and 1 (0.7%) subject in the edoxaban group and 3 (2.1%) subjects in the SOC group had bleeding events that required surgery in an operating room or suite.

During the Main Treatment Period plus Extension Period and On-treatment, 8 (5.5%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudicated confirmed major/CRNM bleeding event (HR: 1.48, 95% CI: 0.484, 4.503; Module 5.3.5.1 DU176b D-U312 CSR Table 14.3.1.7).

During the Main Treatment Period plus Extension Period and On-treatment, 1 bleeding event occurred in a critical site (pulmonary haemorrhage in 1 subject in the edoxaban group), while all other bleeding events were localised in noncritical sites (upper and lower gastrointestinal tract bleeding, vaginal bleeding, epistaxis, and "other" bleeding; Module 5.3.5.1 DU176b D U312 CSR Table 14.3.1.25). All subjects experienced clinically overt bleeding events; in addition, 1 (0.7%) subject in the edoxaban group had a decrease in haemoglobin level of ≥ 2 g/dL, 1 (0.7%) subject in the edoxaban group required transfusion(s), 4 (2.8%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group required surgery in an operating room or suite.

During the Overall Treatment Period, 10 (6.9%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudicated confirmed major/CRNM bleeding event (HR: 1.85, 95% CI: 0.637, 5.370; Module 5.3.5.1 DU176b-D-U312 CSR Table 14.3.1.14).

DU176b-C-U313 (ENNOBLE-ATE Study):

As shown in Table 11 (0.9%) subject in the edoxaban group and 1 (1.7%) in the SOC group experienced a CRNM bleeding event (HR [95% CI]: 1.24 [0.88, 1.73]; p=0.2184; Module 5.3.5.1 DU176b-C-U313 CSR Table 14.3.1.1). Annualised rates were 0.04 for the edoxaban group and 0.07 for the SOC group.

The proportion of subjects with all bleeding event was similar in the edoxaban and SOC groups: 3.7% and 3.4%, respectively.

Table 1: Summary of Adjudicated Bleeding Events, Main Treatment Period – Study U313 (Safety Analysis Set)

Adjudicated Bleeding Events	Statistics	Edoxaban (N = 109)	SOC (N = 58)
Major/CRNM bleeding events	n (%)	1 (0.9)	1 (1.7)
	Annualised rate	0.04	0.07
	Rate difference (95% CI)	-0.03 (-0.18, 0.12)	
Major bleeding events	n (%)	0	0
	Annualised rate	-	-
	Rate difference (95% CI)	-	
All bleeding events (Major/CRNM/Minor)	n (%)	4 (3.7)	2 (3.4)
	Annualised rate	0.15	0.14
	Rate difference (95% CI)	0 (-0.24, 0.25)	

CI = confidence interval; CRNM = clinically relevant nonmajor; SAP = Statistical Analysis Plan; SOC = standard of care

Note: Annualised rate = number of subjects with events/total time at risk (years). For each subject, the “at risk” years = (the event or censoring – date of randomization + 1)/365.25. If a subject has multiple events, the time of the first event is used.

Note: 95% CI for rate difference is calculated by using Wald's method.^{Error! Reference source not found.}

Note: Percentages are based on the number of subjects in the Safety Analysis Set.

Source: Module 5.3.5.1 DU176b-C-U313 CSR Table 14.3.1.2.

Assessor's comments: The MAH has updated the RMP with the “bleeding events” safety results reported in the two studies DU176b-D-U312 (Hokusai VTE Paediatrics Study) and DU176b-C-U313 (ENNOBLE-ATE Study) provided in the type II variation procedure. No new adverse reactions were observed in paediatric clinical studies.

SVII.3.2 Presentation of the missing information

The MAH proposes to update the RMP by deleting the reference to use in the pediatric population as missing information

~~Missing information: Use in paediatric population~~
~~Evidence source:~~
~~Paediatric use was not studied in the clinical development programme.~~
~~Population in need of further characterisation:~~
~~The paediatric development programme is addressing this matter. Until reports of studies in children are available, the SmPC will describe lack of data in this population.~~
SmPC – Summary of Product Characteristics

Assessor's comments: Safety data were provided with the results of studies DU176b-D-U312 and DU176b-C-U313. No new safety concerns have been reported in paediatric clinical studies. The proposed update is acceptable.

10.2. Summary of the safety concerns

Table part II: Module SVII;1 : Summary of safety Concerns

Summary of Safety Concerns	
Important identified risks	Bleeding or Bleeding due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding e.g. aspirin, NSAIDs • Inappropriate administration of 60 mg dose/inadvertent overdose by use of 60 mg dose, eg, in combination with use of strong P-gp inhibitors; in patients with low body weight ≤ 60 kg; and in patients with moderate to severe renal impairment (CrCL 15–50 mL/min)
Important potential risks	Hepatic dysfunction
Important potential risks	Trend towards decreasing efficacy in NVAf subjects with high CCL
Missing information	Lack of reversal agent
Missing information	Paediatric use
Missing information	Reproductive and development toxicity (Pregnancy and lactation)
Missing information	Patients with hepatic impairment
Missing information	Patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease (CrCL < 15 mL/min or on dialysis)
Missing information	Patients with mechanical heart valves
Missing information	Combination with dual antiplatelet therapy
Missing information	Off-label use in Europe in populations or indications outside the approved indications per European SmPC

Assessor's comments: "Paediatric use" has been removed from the "Missing information". This is consistent with the final results of study DU176b-D-U312. Considering the data in the safety specification, the safety concerns listed above are appropriate.

10.3. Risk minimisation measures

Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Missing information • Lack of reversal agent • Paediatric use • Reproductive and development toxicity (Pregnancy and lactation) •	Routine risk communication: • SmPC Section 4.2 • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.6 • SmPC Section 4.9 • PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Prescription only medicine Other routine risk minimisation measures beyond the Product Information: • None

Additional risk minimisation measures

Table 2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Missing information		
Missing information: • Lack of reversal agent • Paediatric use • Reproductive and development toxicity (Pregnancy and lactation) • Patients with hepatic impairment • Patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease (CrCL <15 mL/min or on dialysis) • Patients with mechanical heart valves • Combination with dual antiplatelet therapy	Routine risk communication: • SmPC <i>section 4.2</i> • SmPC <i>section 4.3</i> • SmPC <i>section 4.4</i> • SmPC <i>section 4.6</i> • SmPC <i>section 4.9</i> • PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Prescription only medicine Other routine risk minimisation measures beyond the Product Information: • None Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Anticoagulation reversal programme (to address lack of reversal agent) • PASS (ETNA-AF-Europe [DSE-EDO-04-14-EU],

Off-label use in Europe in populations or indications outside the approved indications per European SmPC	Prescriber Guide	
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Assessor's comments: The proposal is consistent with Table part II: Module SVII;1 : Summary of safety Concerns. The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

10.4. Annexes

The annexes have been updated appropriately.

10.5 Overall conclusion on the RMP

☒ The changes to the RMP are not acceptable. RMP version 14.1 remains as the latest approved.

Assessor's comments: Due to the concerns raised in the framework of the Type II Procedure No. EMEA/H/C/WS2409 by the CHMP Rapporteur and the request to send a new proposal for paediatric indication and posology for the tablets (i.e.: adolescents), the proposed changes to the SmPC in section 4.2

Paediatric population

Edoxaban is not recommended for use in children and adolescents from birth to 18 years of age with confirmed VTE (PE and/or DVT) event as the efficacy has not been established. Available data in VTE patients are described in sections 4.8, 5.1 and 5.2."

will likely be modified.

Therefore, the proposed amendment to the RMP "PART I PRODUCT OVERVIEW" can only be validated once the conclusions of WS2409 have been approved.

All other proposed changes in the sections of the new RMP version 15.0 are acceptable. Consequently RMP version 14.1 remains approved.

New RMP following RSI August 2023

Regarding this type II Variation (RSI), the MAH submitted an updated RMP (version 16.1), based on the recently approved version 16.0 from procedure EMEA/H/C/XXXX/WS2483.

The main proposed RMP changes (version 16.1) were the following:

- Table Part I.1 Product Overview (Dosage in the EEA): Inclusion of proposed text for paediatric population
- Changes of minor nature

PART I Product Overview

The MAH proposes to update text for paediatric population in SmPC section 4.2

"Paediatric population

Edoxaban is not recommended for use in children and adolescents from birth to 18 years of age with confirmed VTE (PE and/or DVT) event as the efficacy has not been established. Available data in VTE patients are described in sections 4.8, 5.1 and 5.2."

Assessor's comments: In view of the responses provided by the MAH, the applicant's intention of not pursuing a paediatric indication and posology is finally endorsed by the Rapporteur.

The proposed updated mention in the RMP is identical to that proposed in the SmPC in section 4.2. The other minor changes concern updates to Annex 8 (summary of changes to the RMP) concerning the latest versions of the RMP 15.0/15.1/16.0/16.1.

Other changes regarding paediatric data included in the last RMP (version 16.0) have been approved from procedure EMEA/H/C/XXXX/WS2483.

Consequently, the proposed amendment RMP version 16.1 is acceptable. At the end of the procedure the applicant submitted version 17.0 identical with version 16.1 to provide format of the major version in line with the "Guidance on the format of the risk management plan (RMP) in the EU – in integrated format".

MS1 comments:

The PRAC Rapporteur's assessment is supported. In particular, it is supported to remove paediatric use from the summary of safety concerns, as this is not an indicated population and as the paediatric study is now completed.

MS2 comments:

We support Rapp's AR and have no further comments.

11. Changes to the Product Information

In light of the paediatric data described in the dossier, the MAH proposes updates to Sections 4.2, 4.8, 5.1, and 5.2 of the edoxaban Summary of Product Characteristics as follows:

- Section 4.2: This section has been updated to confirm edoxaban is not recommended in the paediatric population.
- Section 4.8: This section has been updated to confirm that no new adverse reactions were observed in paediatric clinical studies.
- Section 5.1: A summary of results from available efficacy and safety data of the pivotal paediatric clinical Study U312 has been implemented.
- Section 5.2: This section has been updated to include overall PK conclusions from paediatric clinical Studies U312, U313, and U157.

“4.2 Posology and method of administration

Posology

[...]

Paediatric population

~~The safety and efficacy of edoxaban in children and adolescents less than 18 years of age have not been established. No data are available.~~

Paediatric population

Edoxaban is not recommended for use in children and adolescents from birth to 18 years of age with confirmed VTE (PE and/or DVT) event as the efficacy has not been established. Available data in VTE patients are described in sections 4.8, 5.1 and 5.2.

Method of administration

[...]”

“4.8 Undesirable effects

“[...]

Paediatric population

The safety of edoxaban was evaluated in two Phase 3 studies (Hokusai VTE PEDIATRICS and ENNOBLE-ATE) in paediatric patients from birth to less than 18 years of age with VTE (286 patients, 145 patients treated with edoxaban) and cardiac diseases at risk of thrombotic events (167 patients, 109 patients treated with edoxaban). No adverse reactions other than those observed in adult patients (see Table 3) were reported in paediatric patients.

Reporting of suspected adverse reactions

[...]”

“5.1 Pharmacodynamic properties

[...]

Paediatric population

~~The European Medicines Agency has deferred the obligation to submit the results of studies with edoxaban in one or more subsets of the paediatric population in prevention of arterial thrombosis, treatment of thromboembolism and prevention of thromboembolism (see section 4.2 for information on paediatric use).~~

The safety, efficacy, pharmacokinetics and pharmacodynamics of edoxaban in paediatric subjects from birth to 18 years of age with VTE and cardiac diseases at risk of thrombotic events were evaluated in two Phase 3 studies (Hokusai VTE PEDIATRICS and ENNOBLE-ATE). The pivotal paediatric study, Hokusai VTE PEDIATRICS, is described below. In the pivotal study (Hokusai VTE PEDIATRICS), a Phase 3, open-label, randomised, multi-centre, controlled study to evaluate the pharmacokinetics and pharmacodynamics of edoxaban and compare the efficacy and safety of edoxaban with standard of care (SOC) anticoagulant therapy in paediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE), a total of 290 subjects were randomised into the study: 147 in the edoxaban group and 143 in the SOC group, of which 286 subjects took at least one dose of study medication (MITT): 145 subjects in the edoxaban group and 141 subjects in the SOC group.

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 during the first 3-month period (intended duration of treatment was 6 to 12 weeks for paediatric patients from birth to less than 6 months of age).

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) exceeded the predefined non-inferiority margin of 1.5, hence the non-inferiority of edoxaban versus SOC was not confirmed (see Table 12).

Table 12: Adjudicated Composite Primary Efficacy Endpoint – Main Treatment Period (mITT Analysis Set)

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

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.

The primary safety endpoint was a combination of major and CRNM bleeding events, occurring during the Main Treatment Period (3 months + 3 days).

The safety 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 (95 % CI): 0.60 (0.139, 2.597)]“.

For more information, please refer to the Summary of Product Characteristics.

Assessor's comments.

In response to MS comments on the SmPC, the Company has sent a modified version of sections 4.8, 5.1 and 5.2 on 06 October 2023. All changes detailed below are acceptable for the Rapporteur.

Section 4.8. Undesirable effects.

The Applicant proposes to maintain the text related to the primary safety endpoint and CRNM bleeding events in section 5.1., as this is consistent with the current SmPC guideline and the other DOAC's labels such as Xarelto, Pradaxa and Apixaban. This would further support harmonisation across the labels in the DOAC's class.

In order to accommodate the MS comment, the MAH has proposed to add information to Section 4.8, which is similar to Pradaxa EU SmPC (please see above, text highlighted in yellow): "Overall, the safety profile in children was similar as in the adult patient population (see Table 3). In total, 16.6% of paediatric patients treated with edoxaban for VTE experienced adverse reactions."

Section 5.1. Pharmacodynamic properties.

In response to MS comments, the Rapp has replaced the abbreviation SOC (standard of care) by "standard of care" and/or "control group", in order to avoid confusion with the same abbreviation included in section 4.8 for SOC (System Organ Class).

Also, the MAH has included two decimals instead of three in the description of the HR and corresponding 95% CIs for the primary endpoint.

The posology used for edoxaban in the paediatric pivotal trial is a relevant information, and therefore a description of the edoxaban doses used in the HOKUSAI-VTE paediatrics was added.

Section 5.2. Pharmacokinetic properties

"Children" has been replaced by "adolescents" (highlighted in yellow) after a comment from NL.

NL also commented that the PK information in section 5.2 would be as informative as possible for PK people and others involved. It was asked to the applicant to mention more specifically the age categories studied down to 0-<6 months, and 6-12 months and with which administered doses the same exposure as in adults was attained.

Per the Agency's comment, the MAH has added more detailed paediatric PK data to section 5.2. The number of paediatric subjects (N = 141) included in the population PK analysis and the related number per age category are provided. The observed geometric mean trough exposures in each age group in the two Phase 3 trials (Hokusai VTE PEDIATRICS and ENNOBLE-ATE) are added. In accordance to the SmPC Guideline results of pharmacokinetic studies in the different paediatric age groups are summarized and compared to adults, and uncertainties due to the large inter-individual variability and small sample size of paediatric pharmacodynamic data are also stated.

The implemented changes are appropriate for the Rapporteur.

Finally, in accordance to the SmPC Guideline, the MAH has included a reference to the uncertainty of the paediatric pharmacodynamics data due to the large inter-individual.

The implemented changes are appropriate for the Rapporteur.

See attached product information with tracked amendments and comments.

11.1.1. Quick Response (QR) code

N/A.

12. Request for supplementary information

12.1. Major objections

Clinical aspects

Efficacy

None.

Safety

None

RMP aspects

None.

12.2. Other concerns

Clinical aspects

Bioanalytical methods

1. The Applicant should submit a list with the GCP regulatory inspections conducted by US FDA or members States of the European Union in the clinical and the bioanalytical centre
2. For the bioanalytical report 141052AKR_DEN of study DU176b-A-U157, the bioanalytical report 160607ASMG_DEN of study DU176b-D-U312 and the bioanalytical report 180260AKR_DEN of study DU176b-D-U313, the applicant should clarify the number of subject samples in each run, since this information has not been found in the bioanalytical reports, and comment if the number of QCs is at least 5% of the analysed study samples
3. For the bioanalytical report 160607ASMG_DEN of study DU176b-D-U312, the applicant should discuss if in run 16 any sample was diluted for the parent compound DU-176 since dilution QCs failed in that run.
4. For the bioanalytical report 180260AKR_DEN of study DU176b-D-U313, the applicant should clarify if any sample was diluted in run 8 for the parent compound DU-176b.
5. The applicant should clarify the actual analyte that is measured, DU-176 (edoxaban) or DU-176b (edoxaban tosylate). As the same bioanalytical method is employed for the analysis of the study samples of the three studies (DU176b-A-U157, DU176b-D-U312 and DU176b-D-U313), the bioanalytical report should be consistent in the analyte that is measured. However, bioanalytical reports 141052AKR_DEN and 180260AKR_DEN refer to the quantitative determination of DU-176b and the bioanalytical report 160607ASMG_DEN refers to quantitative determination of DU-176. It is expected that the free form of the salt is being measured, but this would imply that two bioanalytical reports are incorrect. The Applicant should clarify if this may have impacted the accuracy of the reported concentrations (e.g. by using the wrong molecular weight of the analyte).

Pharmacokinetics & Pharmacodynamics

6. When comparing the population PK model of edoxaban in adult and pediatric patients, despite similar structural definition was assumed among both populations, large differences were detected on the estimates of the structural parameters of both models, that suggest that differences in the PK properties of edoxaban exist on absorption and distribution not explained by allometric effects. The Applicant is requested to discuss the possible mechanisms (covariates) that can explain these differences.
7. DV vs IPRED plot shows an under-prediction of inter-individual variability, since data points are not aligned around the identity line. The Applicant should clarify whether additional inter-individual random effects were tested on other PK parameters of the model.

8. The Applicant should provide the simulated exposure for each age, eGFR and body weight cohort with the proposed dosing regimens, including the median (50th percentile) and extreme percentiles (5th and 95th) of the pediatric (simulated) and adult patients (observed) in order to clarify whether similar exposure would be achieved.
9. Based on the PK/PD relationships that have been established across the three PD endpoints, showing that a moderate-to-high PD response of anti-Xa activity, prothrombin time and activated partial thromboplastin time is expected in the exposure range of 150-300 ng/mL of edoxaban, it would be highly informative to evaluate the optimal dosing regimens proposed able to achieve the PK range of 150-300 ng/mL in at least the 80% of the pediatric population for each age, eGFR and body weight cohort.

Efficacy

10. A paediatric indication could be potentially approvable on the basis of an extrapolation exercise from adults (EMA/199678/2016) (indication same as in adults: treatment and secondary prevention of VTE), a popPK model able to establish a paediatric dose (see OC of PK/PD) and exploratory efficacy and safety data from study U312 in children with VTE (the paediatric addendum on VTE prophylaxis and treatment, EMA/CHMP/763438/2017, does not require a formal hypothesis of non-inferiority at the time of designing VTE paediatric phase III trials). In this respect:
 - a. An extrapolation exercise should be proposed. The applicant is invited to justify that the consequences of inhibiting FXa is comparable in children and adults (i.e.: similar pharmacodynamics in adults and children). Also please address whether the exploratory results of efficacy in children are not heterogeneous compared with those reported in adults. For this purpose, a meta-analysis may be conducted in order to explore potential heterogeneity in efficacy between adults and children including HOKUSAI-VTE adults and Hokusai VTE PEDIATRICS, using total recurrent VTE as primary efficacy endpoint and Major and CRNMB as primary safety endpoint, for overall study period with rates adjusted by length of follow up (i.e.: events per month or per year).
 - b. The objective of this paediatric development should be to find a pediatric dose that provides a similar exposure than in adults for the tablets (in children aged 12 years and above) and granules (in children of less than 12 years) following a refinement of the pop-PK and PK/PD models (see also OCs of PK/PD). A paediatric posology should be proposed for the tablets (i.e.: adolescents) in the context of current WS procedure. A further extension application for the granules for oral suspension should be considered in the event of a potential positive outcome of current procedure in order to address the possibility of extending the VTE indication for children less than 12 years old. The applicant should also discuss whether the edoxaban 15 mg dose tablets could be suitable for children in the eventual absence of a paediatric formulation (i.e.: granules for suspension).
11. The applicant should also provide sensitivity analyses of Hokusai VTE pediatrics using as primary endpoints those used in EINSTEIN Junior with rivaroxaban (symptomatic recurrent VTE) [Male et al. Lancet Haematol. 2020;7:e18-e27] and DIVERSITY study with dabigatran (combined endpoint of complete thrombus resolution, absence of recurrent VTE and absence of death related to VTE) [Halton et al. Lancet Haematol. 2021;3:22-e33] in order to put into context comparable paediatric studies that have used different endpoints and hypotheses.
12. In the phase III U312 study (Hokusai VTE pediatrics) a significant number of index events (46 events) were not confirmed, but were included in the main analysis. These patients should have been excluded from the mITT and PP populations and the main analysis, and only included in sensitivity analyses. In this respect:

- a. Please, provide efficacy analyses including only confirmed cases of VTE at baseline (240: 129 in the edoxaban group and 111 in the SOC group).
 - b. An explanation why there are two-fold more unconfirmed cases of the index VTE in the SOC group (n= 30) than in the edoxaban group (n=16) would be welcomed.
 - c. The description of VTE location of index events is rather scarce (VTE is only differentiated into DVT or PE). Please, describe locations of index DVTs (i.e.: lower limbs, upper limbs, catheter-associated DVT, cerebral venous thrombosis, etc).
 - d. Please provide subgroup analyses of recurrent VTE according to location of index DVT/PE.
13. There are two patients that developed symptomatic recurrent DVT while on edoxaban (subjects iliac DVTCVC DVT) that are not mentioned in the table 4.8 of the Summary of Clinical Pharmacology in relationship with edoxaban levels. The applicant should provide PK data and discussions about these two cases if edoxaban levels were available.
14. In study U312, 21 of 26 primary efficacy events in the edoxaban group and 29 of the 31 events in the SOC group corresponded to “no change or extension of thrombotic burden”.
 - c. The applicant is invited to clarify how many of these events in each group required additional treatment (i.e.: a course of parenteral anticoagulation if the children were on oral anticoagulation, or an increase in the intensity of parenteral anticoagulation if the children were already on parenteral anticoagulation).
 - d. The applicant should also provide PK data (i.e.: edoxaban levels) in all primary efficacy events (not only for the symptomatic ones), and to discuss about a potential relationship between edoxaban levels and cases of “no change or extension of thrombotic burden”.
15. The U312 study population is poorly characterized for essential clinical data in relationship with main efficacy and safety endpoint results, like efficacy/safety by age ranges (e.g.: 12 to < 18 years; 6 to < 12 years; 2 to < 6 years; and < 2 years), type of index VTE (e.g.: DVT related to central venous catheter, cerebral venous sinus, lower limbs, PE) and type of risk factors (persistent, transient or both, cancer yes/no, CVC yes/no). In addition, the presence of cancer and chemotherapy with asparaginase are major prothrombotic risk factors that could result in different VTE rates and/or treatment effects. In this respect:
 - e. The applicant is requested to clarify how many patients were recruited into the U312 study with cancer and/or asparaginase chemotherapy by treatment group and to analyse any potential imbalances between treatments.
 - f. All these subpopulations mentioned in the heading should be further analyzed in subgroups for efficacy and safety. In particular, recurrent VTE events and major/CRNMB should be described in these important subgroups and summarized in tables, despite it is acknowledged that the number of events in subgroups will be low.
16. The net clinical benefit analysis (Table 3.16 of the summary of clinical efficacy) disfavoured edoxaban in study U312, but looking at the VTE events, major bleeding and CRNM bleeding events described in other sections, numbers were numerically lower in the edoxaban group versus SOC. Please, explain this apparent discrepancy.
17. In study U313 the results seem worse for patients who switched from SOC to edoxaban (i.e.: SOC-edoxaban arm) than for those who continued with edoxaban since the start of the study (i.e.: edoxaban-edoxaban arm). Please discuss whether switching from edoxaban to SOC could be inappropriate for patients well controlled on SOC.

Safety

18. In Study U312, a total of 3 (2.1%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudication-confirmed major and CRNM bleeding event during the Main Treatment Period and On-treatment (HR: 0.60, 95% CI: 0.139, 2.597). On the contrary, during the Overall Treatment Period, 10 (6.9%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudication-confirmed major/CRNM bleeding event (HR: 1.85, 95% CI: 0.637, 5.370), which means that during follow-up there were 7 major/CRNM bleedings in the edoxaban group and none in the SOC group. Please discuss whether the risk of bleeding with edoxaban could be time-varying and try to identify any other cause that could explain this finding.
19. There were two children with Kawasaki disease in the U313 study that developed MI considered related to study medication by the investigator (one subject: warfarin 3 mg switched to edoxaban 45 mg during extension treatment; one subject: SOC 31 mg, active ingredient not defined, followed by edoxaban dose not recorded in the narrative). The events are poorly documented with respect to study medications, doses and narratives. Please provide narratives including study medications and doses given at the start of the trial and former medications the patients were taken at the onset of the MI. An assessment by the Sponsor about causality relationship should also be tempted including a discussion about a potential relationship between edoxaban and MI from adult and paediatric studies.

RMP aspects

None.

13. Assessment of the responses to the request for supplementary information

13.1. Major objections

Clinical aspects

N/A.

RMP aspects

N/A.

13.2. Other concerns

Clinical aspects

Question 1. The Applicant should submit a list with the GCP regulatory inspections conducted by US FDA or members States of the European Union in the clinical and the bioanalytical centre

Summary of the WSA's response

The history of FDA GCP inspections for the is shown in Table 1. The site has not been inspected by the member states of the European Union.

Table 1: List of GCP Inspections Conducted by the FDA

Inspection Dates	Results
27 Aug 1997	No findings
31 Mar 1998	No findings
03-05 Dec 2002	No findings
12-14 Nov 2003	1 finding
07-08 Mar 2005	No findings
06-09 and 12-14 Sep 2011	2 findings
13-17 Feb 2012	No findings
15-19 Sep 2014	No findings
25-29 Jun 2018	No findings

FDA = Food and Drug Administration; GCP = Good Clinical Practice

Assessment of the WSA's response

The MAH provided a list of the FDA inspections conducted in the bioanalytical site located at. The latest inspection was conducted in June 2018, and concluded with no findings. This is acceptable.

Additionally, the MAH has clarified that no EU inspections have been conducted.

Conclusion

Issue solved.

Question 2. For the bioanalytical report 141052AKR_DEN of study DU176b-A-U157, the bioanalytical report 160607ASMG_DEN of study DU176b-D-U312 and the bioanalytical report 180260AKR_DEN of study DU176b-D-U313, the applicant should clarify the number of subject samples in each run, since this information has not been found in the bioanalytical reports, and comment if the number of QCs is at least 5 % of the analysed study samples

Summary of the WSA's response

The key SOPs that governed the sample analysis at the Q 2 Solutions bioanalytical laboratory are shown in Table 2.

Table 2: Key SOPs for the Sample Analysis at Q² Solutions

Study	Sample Analysis SOP
DU176b-A-U157	U157 - ADV_OP_TX0005 Revision 6
DU176b-D-U312	U312 - ADV_OP_TX0005 Revision 10
DU176b-D-U313	U313 - ADV_OP_TX0005 Revision 12

SOP = standard operating procedure

All 3 SOP versions that were applicable required the number of quality control (QC) samples to be ≥5% of the study samples within a run.

The minimum number of QC samples analysed within a run would be 12 (4 QC levels, with replicates of at least 3 for each level). The 12 QC samples would cover up to 240 samples. The maximum number of injections for a sample analysis run does not exceed 192 injections (comprising two 96-well plates), which includes calibrators, QC samples, matrix blanks, and study samples.

The Applicant can therefore confirm that the number of QC samples included would exceed 5% of the subject samples analysed in each run.

Assessment of the WSA's response

The MAH has not provided a clear list of the total number of samples analysed per run for each bioanalytical report. However, the MAH has clarified that for each analytical run, the maximum number of injections was 192 (comprising two 96-well plates). Thus, the number of QCs included per run (12), exceeded 5% of the sample studies analysed per run. This is acceptable according to the recommendations of the ICH M10 Guideline.

Conclusion

Issue solved.

Question 3. For the bioanalytical report 160607ASMG_DEN of study DU176b-D-U312, the applicant should discuss if in run 16 any sample was diluted for the parent compound DU-176 since dilution QCs failed in that run.

Summary of the WSA's response

The objective of Run 16, as summarised in report 160607ASMG_DEN Table 1, was to analyse samples from 3 subjects. The dilution QC results did not pass for DU-176 (160607ASMG_DEN Table 2), while they were acceptable for D21-2393 (160607ASMG_DEN Table 3). The failed dilution QC results did not impact the DU-176 results reported. Detailed explanations are provided below:

- Case 1, 1 sample was re-analysed in Run 16 for D21-2393 since the initial analysis in Run 12 had a result of below quantitation limit (BLQ) due to dilution (see 160607ASMG_DEN Table 10, which describes the repeat analysis of D21-2393). The failed dilution QC results for DU-176 had no impact for this sample.
- Case 2 DU-176 first pass analysis was conducted for 2 samples without dilution in Run 16. The results were 18.1 and 54.4 ng/mL (160607ASMG_DEN Table 8) and were BLQ (382 ng/mL) of the assay. The failed dilution QC results for DU-176 had no impact for these 2 samples.
- Case 3, DU-176 first pass analysis was conducted for 2 samples without dilution in Run 16. The results were 8.68 ng/mL and 245 ng/mL (160607ASMG_DEN Table 8) and were BLQ (382 ng/mL) of the assay. The failed dilution QC results for DU-176 had no impact for these 2 samples.

Assessment of the WSA's response

The MAH has clarified that, for Run 16, the dilution QCs failed for DU-176 (Report 160607ASMG_DEN - Table 2), but were acceptable for D21-2393 (Report 160607ASMG_DEN- Table 3). The MAH has provided a detailed explanation arguing that none of the five samples analysed in Run 16 were diluted for DU-176, and thus the failed QCs had no impact on the reported concentrations. This explanation is acceptable.

Conclusion

Issue solved.

Question 4. For the bioanalytical report 180260AKR_DEN of study DU176b-D-U313, the applicant should clarify if any sample was diluted in run 8 for the parent compound DU-176b.

Summary of the WSA's response

The objective of Run 8, as summarised in 180260AKR_DEN Table 1, was to analyse samples from Subjects. Both first pass analysis and re-analysis samples were included in this run. The dilution QC results did not pass for DU-176 (180260AKR_DEN Table 2), while they were acceptable for D21-2393 (180260AKR_DEN Table 3).

The Sponsor asked Q2 Solutions bioanalytical laboratory whether there were any samples analysed with dilution in Run 8 for DU-176. The laboratory responded that there were samples analysed with dilution for DU-176b in Run 8. However, due to dilution QC failure in this run, the results for those samples were deactivated. Those affected samples were subsequently repeated within Run 9. The 7 samples analysed with dilution in Run 8 are listed in Table 3.

Table 3: List of Samples Analysed with Dilution in Run 8

Subject ID	Study ID	Accesssion Number
Case 1	DU176b-C-U313	AP507393E06
Case 2	DU176b-C-U313	AP918327D08
Case 3	DU176b-C-U313	EP680524E06
Case 4	DU176b-C-U313	EP209459E06
Case 5	DU176b-C-U313	EP680506E06
Case 6	DU176b-C-U313	EP300880E06
Case 7	DU176b-C-U313	EP528462E06

ID = identifier

When a run is rejected for not meeting the acceptance criteria for calibration standards or QC, the samples would be re-analysed in later runs. Typically, samples re-analysed for under such situations are not included in the repeat analysis table of the sample analysis report. However, the failure of the run and the reason of the failure should be reported.

Since Run 8 failed the dilution QCs, it was considered acceptable that the repeat analysis table (180260AKR_DEN Table 9) did not include those diluted samples that were not accepted in Run 8 but repeated later in Run 9. While the reported DU-176 concentration data were not affected, the Sponsor accepts that the run summary table (180260AKR_DEN Table 1) should indicate that 8 samples did not pass dilution QC acceptance criteria. The Sponsor proposes to implement this practice for future sample analysis studies performed at the laboratory

Assessment of the WSA's response

The MAH indicated that there were samples analysed with dilution for DU-176b in Run 8. However, due to dilution QC failure in this run, the results for those samples were deactivated. Those affected samples were subsequently repeated within Run 9, however, the reanalysis was not reported in the repeat analysis table of the sample analysis report. The MAH proposes to implement this practice for future sample analysis studies performed at the laboratory, and this is acceptable.

Conclusion

Issue solved.

Question 5. The applicant should clarify the actual analyte that is measured, DU-176 (edoxaban) or DU-176b (edoxaban tosylate). As the same bioanalytical method is employed for the analysis of the study samples of the three studies (DU176b-A-U157, DU176b-D-U312 and DU176b-D-U313), the bioanalytical report should be consistent in the analyte that is measured. However, bioanalytical reports 141052AKR_DEN and 180260AKR_DEN refer to the quantitative determination of DU-176b and the bioanalytical report 160607ASMG_DEN refers to quantitative determination of DU-176. It is expected that the free form of the salt is being measured, but this would imply that two bioanalytical reports are incorrect. The Applicant should clarify if this may have impacted the accuracy of the reported concentrations (e.g. by using the wrong molecular weight of the analyte).

Summary of the WSA's response

The free form of edoxaban (DU-176) was measured in each study. The Analytical Method Summary document (appended to each bioanalytical report) describes the analytes measured. There is no impact to the accuracy of the reported concentrations. The Sponsor will ensure that in future bioanalysis of edoxaban, the analyte name will be consistent to reflect that the free form is measured.

Assessment of the WSA's response

The MAH clarified that for all studies, the free form of edoxaban (DU-176) was measured, confirming that there is no impact to the accuracy of the reported concentrations. The MAH is encouraged to amend the bioanalytical reports 141052AKR_DEN and 180260AKR_DEN, so that they refer to DU-176 instead of DU-176b.

Conclusion

Issue solved.

Question 6. When comparing the population PK model of edoxaban in adult and paediatric patients, despite similar structural definition was assumed among both populations, large differences were detected on the estimates of the structural parameters of both models, that suggest that differences in the PK properties of edoxaban exist on absorption and distribution not explained by allometric effects. The Applicant is requested to discuss the possible mechanisms (covariates) that can explain these differences.

Summary of the WSA's response

The MAH agrees with the Assessor that the paediatric and adult PopPK analyses (model estimates are summarised in Table 1 and Table 2) suggested that the difference between paediatric and adult subjects in absorption and distribution of edoxaban might not be well captured with the current absorption rate constant and the fixed body weight exponent for volume of 1.0.

Also, the edoxaban absorption rate of oral suspension in paediatric subjects might be different from that of tablets in adult subjects. The differences and possible mechanisms for major PK model parameter estimates are discussed below.

Table 1: Population PK Model Estimates in a Paediatric Patient (Body Weight = 70 kg and eGFR = 110 mL/min/1.73 m²)

PK Parameter	Paediatric PopPK Model Estimate (RSE)	Shrinkage of Etas (%)
Apparent clearance, CL/F (L/h) ^a	44.19 (3%)	NA
Absorption rate constant, Ka (1/h)	0.365 (10%)	NA
Apparent central compartment volume, V2/F (L)	44 (22%)	NA
Apparent inter-compartmental clearance, Q2/F (L/h)	15.7 (16%)	NA
Apparent peripheral compartment volume, V3/F (L)	262.1 (11%)	NA
Hill coefficient of maturation function, HILL	3.4 (Fixed)	NA
Post-menstrual age at half max of the maturation function, TM50 (weeks)	47.7 (Fixed)	NA
eGFR effect on clearance	0.264 (27%)	NA
Formulation effect on absorption	-0.232 (24%)	NA
IIV	Estimate	η-shrinkage (%)
IIV Clearance	34% (7%)	13.3
IIV Central compartment volume	36% (25%)	67.4
IIV Inter-compartmental clearance	49% (30%)	53.7
Residual variability	Estimate	
Proportional error	0.41 (5%)	NA
Additive error (ng/mL)	0.69 (78%)	NA

eGFR = estimated glomerular filtration rate; IIV = inter-individual variability; NA = not applicable;

PK = pharmacokinetic(s); PopPK = population pharmacokinetic(s); RSE = relative standard error;

^a $CL/F = CL/F_{\text{Typ}} * (WT/70)^{0.75} * (eGFR/110)^{0.246} * [PMA^{3.4}/(47.7^{3.4} + PMA^{3.4})]$; CL/F_{Typ} is the estimated CL/F for a patient with eGFR = 110 mL/min/1.73 m² and body weight = 70 kg; PMA= post-menstrual age in weeks

Assessment of the WSA's response

Table 2: Parameter Estimates of the Final Adult PopPK Model (run130)

Parameter	Estimate (%RSE ^a)	
<i>Structural model</i>		
Apparent non-renal clearance (CL _{nr} /F), L/h	15.2 (2.20)	
Apparent non-renal clearance (CL _{nr} /F) study A-U141, L/h (̐ ₁₆)	18.3 (3.73)	
Apparent central volume of distribution (Vc/F), L	209 (1.61)	
Apparent peripheral volume of distribution (Vp/F), L	92.3 (2.66)	
Apparent inter-compartmental clearance (Q/F), L/h	5.91 (3.44)	
First order absorption rate constant (K _a), h ⁻¹	3.36 (4.74)	
Fractional change in K _a study A-U141, h ⁻¹ (̐ ₁₅) ^b	-0.690 (1.19)	
Lag time (T _{lag}), h	0.250 fixed ^c (ne ^d)	
<i>Covariate effects</i>		
CL _{cr} on CL _r , slope 1 (̐ ₁₁) ^e	0.202 (2.22)	
CL _{cr} on CL _r , slope 2 (̐ ₁₂) ^e	0.0321 (4.74)	
Scaling parameter for CL _{cr} on CL _r , slope 2 in Phase 3, % change (̐ ₁₉) ^e	274 (8.02)	
P-gp inhibitors on CL (Phase 1 only, ̐ ₁₇), % change ^f	33.4 (9.39)	
P-gp inhibitors on F (Phase 1 only, ̐ ₁₈), % change ^f	125 (5.19)	
Scaling parameter for race on Vc/F (̐ ₂₀), % change for Asians ^g	22.6 (13.6)	
Scaling parameter for Q/F in Phase 3 (̐ ₂₁), % change for patients ^h	64.6 (19.5)	
<i>Inter-individual variability</i>		<i>Shrinkage^k of etas (%)</i>
CL/F ⁱ , %CV	14.9 (7.10)	57.2
Scaling parameter CL/F-Vc/F (̐ ₉) ⁱ	1.56 (2.47)	
Vc/F ⁱ , %CV	23.2 (ne)	57.2
Vp/F ⁱ , %CV	52.7 (8.57)	58.7

Conclusion

Parameter		Estimate (%RSE ^a)
Scaling parameter Q/F·Vp/F (θ_{10}) ⁱ	1.00 fixed (ne)	
Q/F ⁱ , %CV	52.7 (ne)	58.7
Correlation η_1 and η_2 ⁱ	42.7 (13.7)	
Tlag, %CV	58.5 (7.83)	30.4
Inter-individual variability on residual variability, %CV	33.3 (6.89)	23.2
<i>Inter-occasion variability</i>		<i>Shrinkage^k of eta (% at occasion 1; 2; 3; 4; 5)</i>
CL/F, %CV	9.78 fixed (ne)	65.7; 78.5; 72.3; 41.5; 2.38
Vc/F, %CV	26.9 fixed (ne)	58.8; 66.4; 69.9; 24.9; -30.7
ka, %CV	101 fixed (ne)	70.4; 65.0; 78.4; 40.5; 43.2
		<i>Shrinkage^k of epsilon (%)</i>
Proportional residual error, %CV	14.2 (2.80)	8.04
Incremental proportional residual error in Phase 3, %CV	Residual variability	
Objective function value	-4890.854/na ^j	
Condition number	134/na ^j	

CL_{CR} = creatinine clearance; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; P-gp = P-glycoprotein; PopPK = population pharmacokinetic(s); RSE = relative standard error

^a For inter-individual and inter-occasion variability, %RSEs are given for the corresponding variance and covariance terms.

^b The fractional change in typical Ka: Typical Ka_{study A-U141} = Typical value of Ka × (1 + θ_{15})

^c Tlag was fixed to the estimate obtained for the Phase 1 model.

^d ne = not estimated

^e Typical CL/F = CL_w/F · (WT/70)^{3/4} + θ_{11} · CL_{cr}

If CL_{cr} > 90 and Phase 1: Typical CL/F = CL_w/F · (WT/70)^{3/4} + (θ_{11} - θ_{12}) · 90 + θ_{12} · CL_{cr}

If CL_{cr} > 90 and Phase 3: Typical CL/F = CL_w/F · (WT/70)^{3/4} + (θ_{11} - (θ_{12} · θ_{19}) · 90 + (θ_{12} · θ_{19}) CL_{cr}

^f Only for Phase 1 studies: If concomitant P-gp inhibitor: Typical parameter = Typical value of parameter * (1 + θ)

^g The fractional change in Vc/F for Asians: Typical Vc/F_{Asian} = Typical Vc/F_{Non-Asian} · (1 + θ_{20})

^h The fractional change in Q/F for patients: Typical Q/F_{patients} = Typical Q/F_{Patients} * (1 + θ_{21})

ⁱ CL/F = θ_1 · (WT/70)^{3/4} · e ^{η_1} ; Vc/F = θ_2 · (WT/70) · e ^{η_1 · θ_9}

Vp/F = θ_3 · (WT/70) · e ^{η_2} ; Q/F = θ_4 · (WT/70)^{3/4} · e ^{η_2 · θ_{10}}

^j na=not applicable

^k PsN output was used to obtain shrinkage values.

Apparent clearance (CL/F): Per the CHMP guideline on the evaluation of the PK of medicinal products in patients with decreased renal function (EMA/CHMP/83874/2014), it is preferred to estimate renal function with estimated eGFR as compared with CrCl. Therefore, eGFR was incorporated in the clearance equation of the paediatric PopPK model. In contrast, CrCl was used to estimate renal clearance of edoxaban in the adult PopPK model because the guideline was not available at the time of the adult PopPK model development. To simplify the comparison, a paediatric subject with a body weight of 70 kg and equal CrCl and eGFR of 110 mL/min/1.73 m² was assumed. The CL/F estimated by the paediatric PopPK model is 44.19 L/h. The CL/F estimated by the adult PopPK model is 15.2 + 0.202 × 110 = 37.42 L/h. The CL/F estimated by the paediatric model is only 18% higher than that estimated by the adult model. Actually, CrCl is slightly higher than eGFR because creatinine is secreted by the proximal tubule in addition to being filtered by the glomerulus. Thus, a paediatric subject with an eGFR of 110 mL/min/1.73 m² should have a CrCl > 110 mL/min/1.73 m², which may explain the lower CL/F estimated by the adult PopPK model (37.42 L/h versus 44.19 L/h).

Central volume of distribution (Vc/F): The paediatric and adult PopPK model-estimated Vc/F values are 44 and 209 L, respectively. A 4-fold difference in Vc/F was observed between the models. It is recognised that Vc/F can be affected by many factors such as PK sampling time points and sampling

intensity. It is challenging to do intensive PK sampling in paediatric patients. In Study 157, only 4 to 7 PK samples were collected from each paediatric patient. In Studies 312 and 313, only 2 sparse PK samples were collected from each patient. Because of the sparseness of the PK data during the initial absorption phase, the C_{max} of edoxaban in paediatric patients might not be accurately characterised. Furthermore, the formulation may also affect the C_{max} of edoxaban in paediatric patients and the model estimate of V_c/F. As shown in Figure 1, the paediatric subjects enrolled in the Study 157 high-dose groups showed median AUC comparable to that in adult patients receiving a 60 mg QD dose but higher median C_{max} than that in adult patients. The PopPK model-estimated AUC_{0-24h,ss} values across 5 age cohorts were comparable to or lower than that observed in adult patients, and the model-estimated C_{max,ss} of children aged 12 to <18 years was lower than that observed in adult patients (Table 3). However, the model-estimated C_{max,ss} values for the 4 younger cohorts who took oral suspension formulation were higher than that observed in adult patients. The PopPK and covariate analyses showed that the oral suspension formulation caused a faster oral absorption and higher C_{max} of edoxaban in paediatric patients but did not affect the bioavailability. The higher C_{max} of edoxaban in paediatric patients might result in a lower V_c/F. Based on the adult exposure-response analysis, it is not evident that C_{max} is a predictor of efficacy or safety.

Figure 1: Comparison of Median Exposure in the Paediatric Subjects in High-dose Groups of Study 157 Versus Median Exposure in Adult Subjects Receiving 60 mg QD Dose

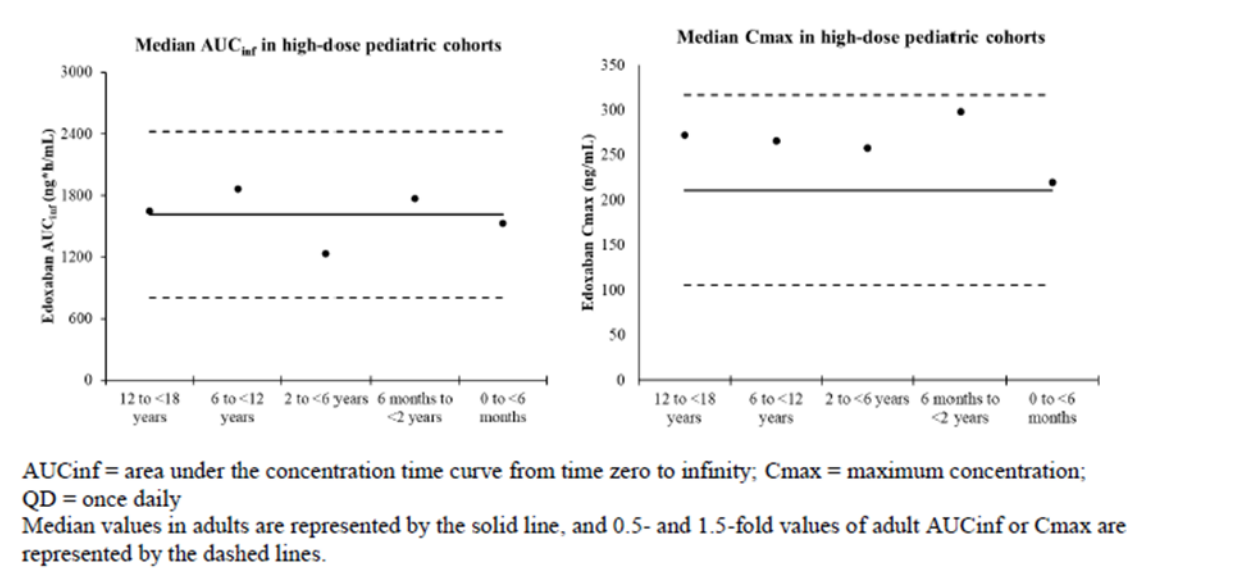


Table 3: Summary of PopPK Model-estimated Pharmacokinetics Exposures for Paediatric Patients by Age Cohort (Studies 312 and 313)

	0 to <6 months	6 months to <2 years	2 to <6 years	6 to <12 years	12 to <18 years	Paediatric Overall	Adult VTE Patients ^a
	(N = 9)	(N = 19)	(N = 36)	(N = 38)	(N = 39)	(N = 141)	(N = 3106)
C _{max,ss} (ng/mL)							
Mean (SD)	282 (70.4)	314 (90.4)	274 (85.8)	295 (58.6)	191 (39.5)	262 (81.4)	212 (49.4)
Median	283	299	295	294	189	265	211
[Min, Max]	[154, 399]	[161, 532]	[16.4, 402]	[139, 433]	[105, 299]	[16.4, 532]	[68.8, 362]
AUC _{0-24h,ss} (ng•h/mL)							
Mean (SD)	1710 (713)	1700 (919)	1290 (611)	1550 (622)	1210 (363)	1420 (637)	1652 (318)
Median	1640	1600	1270	1510	1150	1320	1613
[Min, Max]	[640, 3140]	[679, 3960]	[58.2, 3100]	[629, 3990]	[613, 2490]	[58.2, 3990]	[732, 3141]

AUC_{0-24h,ss} = area under the concentration time curve from time zero to 24 hours after dosing in the steady state; C_{max,ss} = maximum concentration in the steady state; Max = maximum; Min = minimum; PopPK = population pharmacokinetic(s); QD = once daily; SD = standard deviation; VTE = venous thromboembolism

^a Adult subjects received 60 mg QD.

Apparent peripheral volume of distribution (V_p/F): The total volume of distribution (V_c/F + V_p/F) values estimated by the paediatric and adult PopPK models are 306 and 301 L, respectively, which are comparable. The paediatric and adult PopPK model-estimated V_p/F values are 262 and 92 L, respectively. The high estimate of V_p/F by the paediatric PopPK model might be caused by the low estimate of V_c/F.

Apparent inter-compartmental clearance (Q/F): The paediatric and adult PopPK model estimated Q/F values are 15.7 and 5.9 L/h, respectively. The high estimate of Q/F by the paediatric PopPK model was likely caused by the high estimate of V_p/F.

Oral absorption rate constant (K_a): The paediatric and adult PopPK model-estimated K_a values are 0.365 and 3.36 h⁻¹, respectively. A lag time of 0.25 hours was included in the adult PopPK model while no lag time was included in the paediatric PopPK model. The different formulations used in adult and paediatric subjects and different physiological characteristics (ie, stomach volume and gastric pH) between adult and paediatric subjects might cause different oral absorption rates of edoxaban.

In summary, the PopPK analysis showed that differences in the PK properties of edoxaban exist on absorption and distribution between paediatric and adult subjects. Furthermore, the CL/F of edoxaban in paediatric subjects is substantially affected by body weight, renal function, and age.

Thus, it would require to develop weight-, age-, and renal function-based doses to achieve edoxaban exposures in paediatric patients comparable to those in adult patients.

Assessment of the WSA's response

The Applicant acknowledge that the absorption and distribution of edoxaban does not seem to be properly captured with the current model as there are significant differences between absorption and distribution parameters between both adult and paediatric models.

When comparing the population PK model of edoxaban in adult and paediatric patients, there are differences on Apparent CL/F (37.42 vs 44.19), K_a (3.36 vs 0.365), V_c (209 vs 44), V_p (92.3 vs 262), and Q/F (5.9 vs 15.7).

The Applicant has partially provided the explanation of these differences, although no clear justification regarding additional factors to allometry has been given.

Regarding the differences in CL/F, eGFR was included to estimate renal function in the paediatric Pop PK model, on the other hand, CrCl was used in the adult model. The CL/F parameters were calculated for a subject of 70 kg and CrCl and eGFR of 110ml/min/1.73m². Despite the differences in the

covariate selected for renal function between both populations, pediatric patients show higher CL/F value compared to adults. Such relationship is age, body-weight and renal function dependent, so additional evidence should be provided in case dose recommendations in younger pediatric patients.

Concerning the Vc/F, the sparse PK sampling in the paediatric studies makes it difficult to properly characterize the C_{max} in this population, and makes it difficult to properly calculate the Vc/F. In the paediatric population, Vc/F is 4-fold lower than the Vc/F in the adult population, which may biased the Vp/F. For that reason Q/F is higher in the paediatric population due to the high value of Vp/F. In general, the lack of adequate experimental characterization of the alpha- and beta-disposition phases may compromise the estimation of Vp/F and Q/F.

The differences in the K_a are explained by the different formulation used as well as the differences in physiological characteristics, although a 10-fold difference is observed.

Overall, the explanations are partially endorsed, although additional efforts would be required to fully understand whether the hypothesis are plausible. As a consequence, paediatric doses for each paediatric subgroup should be based on age, weight and renal function in order to investigate if those patients achieve edoxaban exposures that are comparable to adult (Please refer to question 8).

Conclusion

Issue solved

Question 7. DV vs IPRED plot shows an under-prediction of inter-individual variability, since data points are not aligned around the identity line. The Applicant should clarify whether additional interindividual random effects were tested on other PK parameters of the model.

Summary of the WSA's response

Inter-individual random effects were tested on 3 PK parameters: CL/F, Vc/F (V₂/F), and Q/F. The eta-shrinkages related to IIV for CL/F, Vc/F, and Q/F were 13.3%, 67.4%, and 53.7%, respectively (Table 1). The high eta-shrinkages for Vc/F and Q/F indicate that the individual parameter estimates were considerably shrunken toward the typical values and had only limited value for usage as diagnostics. The high shrinkages were likely due to the sparse PK sampling design in the paediatric studies. High shrinkages for Vc/F (57.2%) and Q/F (58.7%) were also observed in the adult PopPK model of edoxaban (Table 2). Since shrinkage influences Bayesian individual exposure predictions, which depend on individual parameter estimates, predicted variability in some exposure measures (eg, C_{max}) will likely be lower than observed variability in systemic exposure.

Due to the wide distribution of C_{max} in paediatric patients, we have assessed IIV on K_a during base model development. The estimate of IIV on K_a was very small (0.000042) and did not improve the model. Thus, the IIV on K_a was fixed to 0 in the model.

Assessment of the WSA's response

The Applicant has provided the required explanation. IIV was assessed on K_a during base model development, but its estimation was close to the null value and not significant.

Conclusion

Issue not further pursued.

Question 8. The Applicant should provide the simulated exposure for each age, eGFR and body weight cohort with the proposed dosing regimens, including the median (50th percentile) and extreme percentiles (5th and 95th) of the paediatric (simulated) and adult

patients (observed) in order to clarify whether similar exposure would be achieved.

Summary of the WSA's response

The information is summarised in Table 4 and Table 5. The MAH agrees with the Assessor that the paediatric dosing regimens tested in Studies 312 and 313 may lead to an under-exposure in paediatric patients compared to adult patients. To accurately match the drug exposure in adult patients, a 20% to 50% dose increase may be needed for individual age-, eGFR-, and body weight-based subgroups.

Table 4: Simulated AUC_{0-24h,ss} of Edoxaban for Adolescent Patients by Body Weight

	Adolescents (12 to <18 years)			Adult VTE Patients ^a
Body weight	<30 kg	30 kg to <60 kg	≥60 kg	
N	70	391	556	3106
Mean ± SD (ng•h/mL)	1690 ± 1030	1240 ± 449	1190 ± 441	1652 (318)
Median [5 th , 95 th] (ng•h/mL)	1470 [704, 4270]	1170 [661, 2070]	1120 [593, 2040]	1613 [1204, 2246]

AUC_{0-24h,ss} = area under the concentration time curve from time zero to 24 hours after dosing in the steady state; eGFR = estimated glomerular filtration rate; QD = once daily; SD = standard deviation; VTE = venous thromboembolism

Note: Paediatric subjects with body weight <30 kg received 30 mg QD. Paediatric subjects with body weight between 30 and <60 kg received 45 mg QD (eGFR >50% of normal) or 30 mg QD (eGFR between 30% and 50% of normal). Paediatric subjects with body weight ≥60 kg received 60 mg QD (eGFR >50% of normal) or 45 mg QD (eGFR between 30% and 50% of normal).

^a Adult subjects received 60 mg QD.

Table 5: Simulated AUC_{0-24h,ss} of Edoxaban for Paediatric Patients by Age and eGFR

	0 to <6 months		6 months to <2 years		2 to <6 years		6 to <12 years		12 to <18 years		Adult VTE Patients
eGFR % of normal	30-50	>50	30-50	>50	30-50	>50	30-50	>50	30-50	>50	NA
Dose	0.4 mg/kg	0.8 mg/kg	0.75 mg/kg	1.5 mg/kg	0.7 mg/kg	1.4 mg/kg	0.8 mg/kg	1.2 mg/kg	45 or 30 mg ^a	60, 45 or 30 mg ^a	60 mg QD
N	61	1184	19	1017	8	1014	10	1000	19	998	3106
Mean (SD) ng•h/mL	660 (242)	1390 (634)	883 (331)	1430 (617)	754 (371)	1340 (527)	1220 (522)	1310 (521)	916 (269)	1250 (522)	1652 (318)
Median [5 th , 95 th] ng•h/mL	632 [334, 1070]	1280 [569, 2590]	888 [432, 1250]	1320 [661, 2620]	586 [465, 1370]	1270 [647, 2330]	1280 [483, 1960]	1210 [619, 2230]	811 [630, 1340]	1170 [636, 2130]	1613 [1204, 2246]

AUC_{0-24h,ss} = area under the concentration time curve from time zero to 24 hours after dosing in the steady state; eGFR = estimated glomerular filtration rate; NA = not applicable; QD = once daily; SD = standard deviation; VTE = venous thromboembolism

^a Dose is adjusted by body weight.

Assessment of the WSA's response

The Applicant provided the requested simulations. The paediatric doses tested in the studies lead to an under-exposure in paediatric patients compared to adult patients, especially in adolescent patients with high body weight (Table 4) and paediatric patients across different age and eGFR values (Table 5). Due to the absence of an exposure-safety analysis in pediatric patients, dose selection should be established based on achieving similar exposure range compared to the adult patients. In that sense, additional simulation-based analyses should be conducted in order to justify the dose selection regimen in paediatric patients able to achieve similar exposure compared to the adult patients. However, given that the MAH is still not recommending the use of edoxaban in children and, from a clinical standpoint, there are reasons to agree on that, due to potential lack of efficacy (see

assessment of MAH answer to Q10 and Q11), these additional simulation-based analyses are not further pursued. On the other hand, given that one of the reasons given by the applicant not to recommend the use of edoxaban in children is that the use of tablets in children may be associated to a 20-30% underexposure compared to the use of edoxaban 60 mg in adults, section 5.2 of the SmPC should be amended to reflect this (see Rapporteur's proposal in the attached PI with track changes).

Conclusion

Issue solved (not further analyses pursued).

Question 9. Based on the PK/PD relationships that have been established across the three PD endpoints, showing that a moderate-to-high PD response of anti-Xa activity, prothrombin time and activated partial thromboplastin time is expected in the exposure range of 150-300 ng/mL of edoxaban, it would be highly informative to evaluate the optimal dosing regimens proposed able to achieve the PK range of 150-300 ng/mL in at least the 80% of the paediatric population for each age, eGFR and body weight cohort.

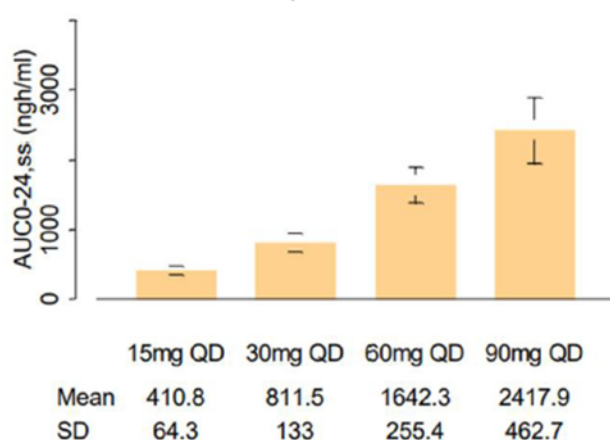
Summary of the WSA's response

The MAH agrees with the Assessor that a moderate-to-high pharmacodynamic response of anti-Xa activity, prothrombin time, and activated partial thromboplastin time is expected in the plasma edoxaban concentration range of 150 to 300 ng/mL. As shown in Figure 2, according to the dose-exposure relationship in adult patients, a dose >120 mg QD is needed to achieve steady state C_{avg} >150 ng/mL or AUC_{0-24h} >3600 ng•h/mL in adult patients (the dose interval was 24 hours and $C_{avg} = AUC_{0-24h}/24$). In the previous adult clinical programme, 60 mg QD was determined as the efficacious and safe dose in adult VTE patients. Therefore, in the current paediatric programme, the paediatric doses were proposed to match edoxaban exposure in adult VTE patients receiving a 60 mg QD dose. Achieving C_{avg} of edoxaban >150 ng in 80% of the paediatric population was not targeted.

Furthermore, the exposure-response analysis for safety (clinically relevant bleeding) conducted in nonvalvular atrial fibrillation patients does not support a dose >60 mg. As shown in Figure 3, $C_{avg,ss}$ >100 ng/mL or $AUC_{0-24h,ss}$ >2400 ng•h/mL is associated with an increased major bleeding risk.

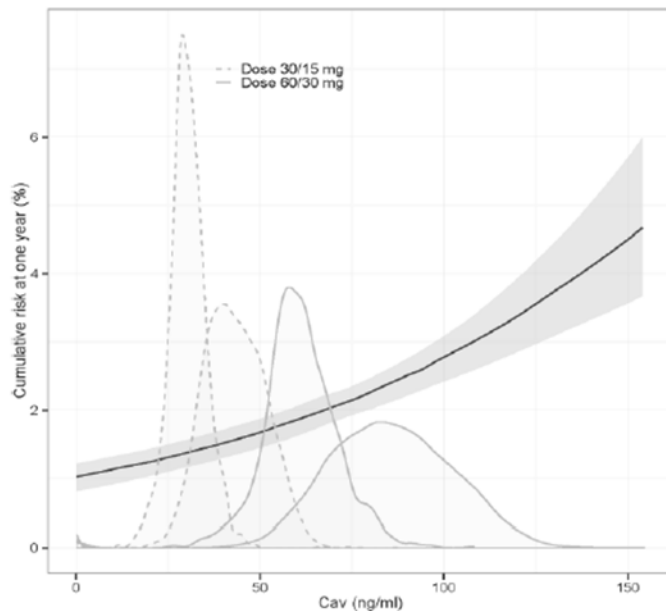
Therefore, the paediatric doses of edoxaban were proposed to match 0.5- and 1.5-fold of the median exposure ($AUC_{0-24h,ss} = 806.5$ to 2419.5 ng•h/mL or $C_{avg,ss} = 33.6$ to 101 ng/mL) in adult VTE patients receiving a 60 mg QD dose.

Figure 2: Mean $\pm$ SD AUC of Edoxaban in Adult Patients by Dosing Regimen (Study TMPP002)



AUC = area under the concentration time curve; $AUC_{0-24,ss}$ = area under the concentration time curve from time zero to 24 hours after dosing in the steady state; QD = once daily; SD = standard deviation

Figure 3: Probability of Clinically Relevant Bleeding Event Occurring Within 1 Year in an Adult NVAF Patient Treated With Edoxaban Versus Plasma Cavg of Edoxaban (Study TMPP009)



Cav = average concentration; NVAF = non-valvular atrial fibrillation; QD = once daily

From left to right, the 4 distributions represent 4 dosing groups: starting at 30 mg QD with dose reduction to 15 mg QD, 30 mg QD, starting with 60 mg QD with dose reduction to 30 mg QD, and 60 mg QD.

Assessment of the WSA's response

The Applicant acknowledge that moderate-to-high PD response of anti-Xa activity, prothrombin time and activated partial thromboplastin time is expected in the exposure range of 150-300 ng/mL of edoxaban. In order to achieve that exposure a dose regimen greater than 120 mg QD is needed. This is not supported by the previous adult VTE program or the exposure-response analysis for safety, where higher bleeding events were predicted as Cave increases. Therefore, the selection of the exposure range of 60 mg QD of edoxaban for pediatric patients is endorsed, despite the efficacy could be compromised. The explanation given by the Applicant is endorsed.

Conclusion

Issue solved

Question 10. A paediatric indication could be potentially approvable on the basis of an extrapolation exercise from adults (EMA/199678/2016) (indication same as in adults: treatment and secondary prevention of VTE), a popPK model able to establish a paediatric dose (see OC of PK/PD) and exploratory efficacy and safety data from study U312 in children with VTE (the paediatric addendum on VTE prophylaxis and treatment, EMA/CHMP/763438/2017, does not require a formal hypothesis of non-inferiority at the time of designing VTE paediatric phase III trials). In this respect:

- a) An extrapolation exercise should be proposed. The applicant is invited to justify that the consequences of inhibiting FXa is comparable in children and adults (i.e.: similar pharmacodynamics in adults and children). Also please address whether the exploratory results of efficacy in children are not heterogeneous compared with those reported in adults. For this

purpose, a meta-analysis may be conducted in order to explore potential heterogeneity in efficacy between adults and children including HOKUSAI-VTE adults and Hokusai VTE PEDIATRICS, using total recurrent VTE as primary efficacy endpoint and Major and CRNMB as primary safety endpoint, for overall study period with rates adjusted by length of follow up (i.e.: events per month or per year).

- b) The objective of this paediatric development should be to find a pediatric dose that provides a similar exposure than in adults for the tablets (in children aged 12 years and above) and granules (in children of less than 12 years) following a refinement of the pop-PK and PK/PD models (see also OCs of PK/PD). A paediatric posology should be proposed for the tablets (i.e.: adolescents) in the context of current WS procedure. A further extension application for the granules for oral suspension should be considered in the event of a potential positive outcome of current procedure in order to address the possibility of extending the VTE indication for children less than 12 years old. The applicant should also discuss whether the edoxaban 15 mg dose tablets could be suitable for children in the eventual absence of a paediatric formulation (i.e.: granules for suspension).

Summary of the WSA's response

The MAH acknowledges the suggestion from CHMP regarding the potential of filing for the paediatric indication; however, based on review of the data available, the MAH does not intend to seek a paediatric indication for edoxaban as the benefit-risk profile remains uncertain.

The MAH would like to highlight that prior to initiating the paediatric development programme, the PIP was discussed and agreed with the PDCO. The agreed PIP comprised 3 edoxaban clinical studies:

- One Phase 1 dose-finding study, DU176b-A-U157: "A phase 1, open-label, single-dose, non-randomized study to evaluate pharmacokinetics and pharmacodynamics of edoxaban in pediatric patients" (referred to as Study U157)
- Two Phase 3 studies:
 - Treatment of VTE registrational study, DU176b-D-U312: "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)" (hereafter referred to as Study U312)
 - Prophylaxis of arterial thromboembolism study, DU176b-C-U313: "An open-label, randomized, parallel-group, multicenter, observational trial to evaluate the safety and efficacy of edoxaban tosylate in children from 38 weeks gestational age to less than 18 years of age with cardiac diseases at risk of thromboembolic events" (hereafter referred to as Study U313)

The pivotal study for the paediatric clinical programme, Study U312, was conducted in paediatric patients with confirmed VTE. The study was designed with the agreement of the PDCO to demonstrate the NI of edoxaban versus SOC treatment and used an NI margin of 1.5 extrapolated from the adult Hokusai VTE study (Study DU176b-D-U305; hereafter referred to as Study U305). As indicated in the Study U312 CSR, the study did not meet the primary efficacy objective of demonstrating the NI of edoxaban to SOC.

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 with 2 (1.4%) subjects in the SOC group.

There was 1 (0.7%) unexplained death in each group for which VTE could not be ruled out. There was no change or extension of thrombotic burden based on imaging in 21 (14.5%) subjects in the edoxaban group and 29 (20.6%) subjects in the SOC group. The HR (edoxaban/SOC) was 1.01 with 2-sided 95% CI of (0.594, 1.719). The upper bound of the 95% CI (ie, 1.719) was above the prespecified NI margin of 1.5. Therefore, the study failed to show NI of edoxaban compared with SOC.

As the study did not achieve the primary efficacy objective, the benefit-risk profile of edoxaban could not be ascertained in the paediatric population studied.

a. Extrapolation

Refinement of PopPK and PK/PD models for dose extrapolation

In Study 312, two sparse PK samples were collected on the day of the fifth dose of edoxaban (Day 5 + 3 days). Predose PK samples were collected from all subjects participating in the PK/PD assessment (N = 69). Postdose PK samples were taken at either any time between 0.5 and 3 hours after dosing or at any time between 3 and 8 hours after dosing. In Study U313, two sparse PK samples (predose and any time between 1 and 3 hours after dosing) were collected from 73 subjects during the Month 1 Visit. The PD sampling times for measurement of PT, aPTT, and anti-FXa were at the same time as the PK samples.

The sparse PK sampling design during the initial oral absorption phase in the paediatric studies did not permit precise estimation of several population- and individual-level PK parameters, as demonstrated by the high ETA shrinkage (shrinkage of ETA of approximately 60% for Vc/F and Q2/F; see response to [Question 6](#) and [Question 7](#)). The MAH attempted estimation of the IIV on the Ka during the development of the base model. However, the estimate of IIV on Ka was very small (0.000042) and did not improve the model fit in a statistically significant manner. Furthermore, the exposure-response analysis conducted in adult VTE subjects showed that the probability of recurrent VTE decreased with increasing edoxaban Cavg or AUC.¹ On the other hand, no statistically significant exposure-response relationships were found for clinically relevant bleeding or MACE in adult VTE subjects. These findings justified the use of AUC instead of Cmax for extrapolation and exposure matching in the paediatric VTE population. Since the edoxaban population and individual CL/F values needed for AUC calculation seemed to be well estimated in the paediatric PopPK model (ETA-shrinkage for the IIV on CL/F = 13.3% and relative standard error of CL/F population estimate = 3%), further refinement of the model was deemed to be unnecessary.

The MAH investigated the PK/PD relationship of edoxaban in paediatric subjects. Anti-FXa activity, aPTT, and PT all exhibited exposure-dependent responses to edoxaban in children of different ages and adult subjects ([Figure 1](#), [Figure 3](#), and [Figure 4](#), respectively). Edoxaban exhibited similar PK relationships for anti-FXa activity between paediatric and adult subjects; however, anti-FXa activity is considered a marker of edoxaban (and DOACs) exposure (PK) and not directly related to clinical outcomes.^{2,3,4}

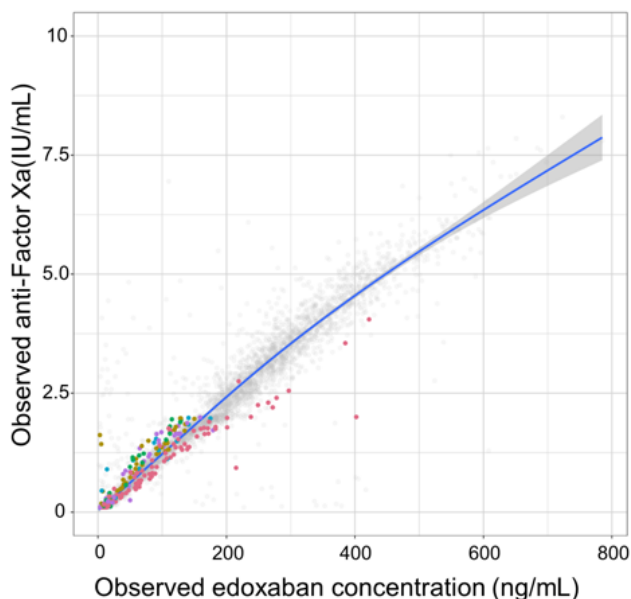
In contrast, both PT and aPTT are considered markers of the PD of edoxaban. However, the considerable variation in the PD biomarkers PT and aPTT for edoxaban (see below), especially in the lower age cohort of subjects, contributes more uncertainty when considered alongside the Study U312 results (ie, the low number of symptomatic recurrent VTE events in both groups in the study and the study not meeting the primary objective of demonstrating NI). As such, the MAH concludes that the benefit-risk profile remains uncertain for edoxaban use in paediatric patients.

FXa inhibition in children and adults

The relationship between anti-FXa activity or PT and plasma edoxaban concentration was compared between paediatric subjects across 5 age cohorts and adult subjects with VTE enrolled in the Hokusai VTE adult study (Study U305). Because aPTT data were not collected in Study U305, the aPTT and PK data collected from healthy adult subjects enrolled in the Phase 1 studies were used for the paediatric and adult PK-aPTT relationship comparison.

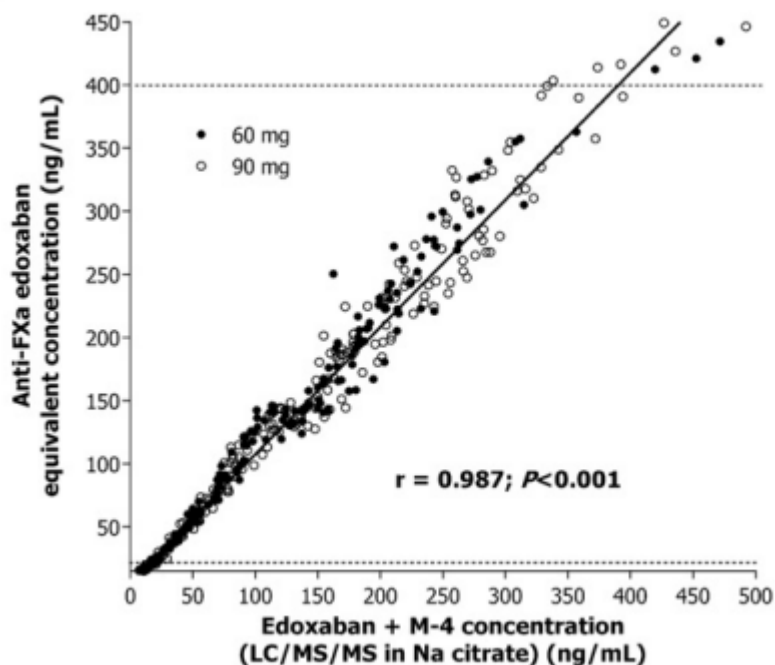
As shown in [Figure 1](#), the anti-FXa activity data were generally comparable between paediatric subjects and adult subjects in the plasma edoxaban concentration range of 0 to 200 ng/mL. It is expected to see a linear correlation for anti-FXa activity and plasma edoxaban concentrations in both paediatric and adult subjects. A prior study showed that a commercially available anti-FXa chromogenic assay accurately estimated plasma edoxaban concentrations in adult healthy subjects taking edoxaban 60 and 90 mg QD doses.⁵ A good correlation was observed between plasma concentrations of edoxaban and its metabolite concentrations determined by anti-FXa assay and liquid chromatography-mass spectroscopy. The slope and intercept of anti-FXa and plasma edoxaban concentration correlation curve are dependent on the anti-FXa chromogenic assay rather than the age or demographic characteristics of study subjects ([Figure 2](#)).

Figure 1: Comparison of Anti-FXa Versus Edoxaban Concentration in Adults and Children



Note: The blue line represents the LOESS fit of adult data

Figure 2: Correlation Between Anti-FXa Edoxaban Equivalent Concentration and Edoxaban + Active Metabolite (M4)



FXa = factor Xa; LC/MS/MS = liquid chromatography coupled with tandem mass spectrometry; M4 = active metabolite

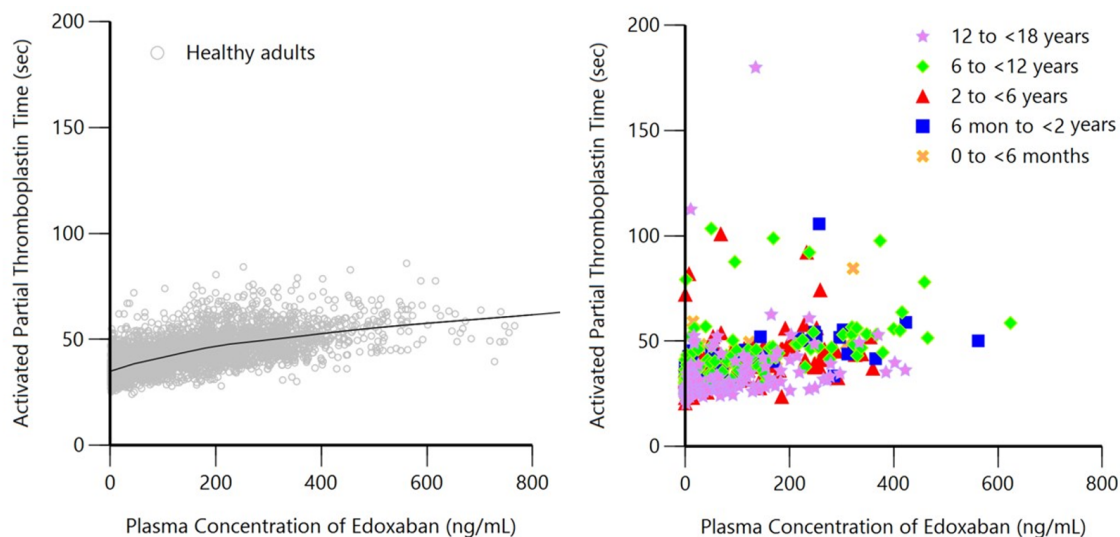
Source: He et al, 2017⁵

Thus, overlaid anti-FXa and plasma edoxaban concentration curves should not be used to support a similar PK/PD relationship between paediatric and adult subjects. Anti-FXa level cannot be used as a direct marker of clinical efficacy for any specific oral direct Xa inhibitor.⁶

To assess PD similarity between paediatric and adult subjects, aPTT and PT should be used. However, due to the small sample size and large IIV in the paediatric aPTT and PT data, the similarity in the PD relationship for aPTT or PT between paediatric and adult subjects could not be formally evaluated (Figure 3 and Figure 4, respectively).

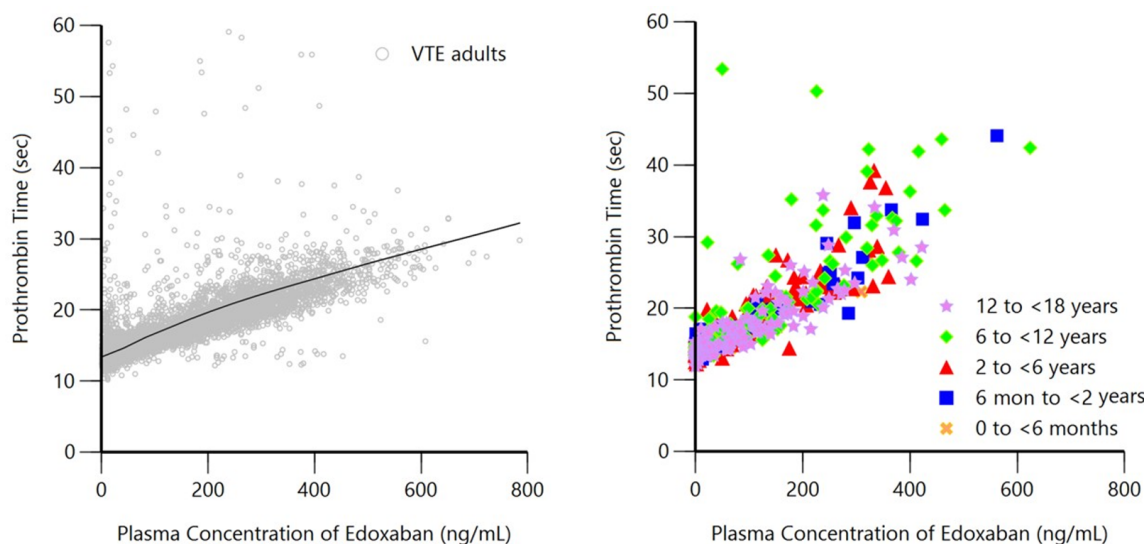
As described above, the considerable variation in the PD biomarkers PT and aPTT for edoxaban, especially in the lower age cohorts, contributes additional uncertainty when considered alongside the Study U312 results (ie, the low number of symptomatic recurrent VTE events in both groups in the study and the study not meeting the primary objective of demonstrating NI); hence, the benefit-risk profile remains uncertain for edoxaban use in paediatric patients.

Figure 3: Comparison of PD Biomarker aPTT Versus Edoxaban Concentration in Adults and Children



aPTT = activated partial thromboplastin time; PD = pharmacodynamic(s)

Figure 4: Comparison of PD Biomarker PT Versus Edoxaban Concentration in Adults and Children



PD = pharmacodynamic(s); PT = prothrombin time

Investigation of potential heterogeneity in efficacy between adults and children

To explore potential heterogeneity in efficacy and safety between adults and children included in the Hokusai-VTE adult study (Study U305) and Hokusai VTE paediatric study (Study U312), a meta-analysis was performed using CEC-confirmed total recurrent VTE as the primary efficacy endpoint and major or CRNM bleeding as the primary safety endpoint for the overall study period, with rates adjusted by length of follow up (ie, percentage of subjects with events per year). The meta-analysis was performed based on summary statistics, and a test of the heterogeneity between the 2 studies was performed.

The distribution of VTE events in paediatric patients is bimodal, with the majority of events occurring in neonates and infants^{7,8} and in adolescents.⁹ In contrast to VTE in adults, VTE in children is rarely truly idiopathic in nature.¹⁰ Approximately $\geq 90\%$ of children with VTE have a serious underlying disorder (eg, cancer, congenital heart disease, nephrotic syndrome, etc; a precipitation factor [CVC, infection, trauma, or surgery] and/or a hereditary prothrombotic condition). Apart from better awareness for VTE, the widely observed increase in childhood VTE is mainly due to the medical progress in the treatment and/or interventions of critically ill children. The typical location of VTE in neonates and infants differs from that in adults and adolescents. In neonates and young children, VTE occurs more often (60%) in the upper extremity venous system (versus only 2% in adults). This reflects the common placement of CVC (the most frequent precipitating factor of VTE in children) via the internal jugular or subclavian veins. Loss of catheter patency and loss of central venous access have important consequences in children with cancer and other serious medical conditions.¹⁰ Non-extremity DVT (eg, cerebral sinus vein thrombosis and renal or portal VTE) is also more frequent in children than in adults.^{11,12} The location of the clots results in fewer classic VTE symptoms and may also impair the effective/precise diagnosis with standard measures (ie, compression ultrasound cannot be performed in these locations).

Although both studies have common efficacy endpoints of recurrent VTE events and death where VTE could not be ruled out, there are differences between them that should be noted. The population in Study U305 included elderly patients with different comorbidities compared with Study U312, which was conducted in paediatric patients with different comorbidities (ie, hypercoagulability conditions, malignancy, genetic disorders, etc with different comedications including chemotherapy and predisposing factors for developing TE events). For example,

- In Study U305, 32.8% of subjects (2704/8240 subjects) were ≥ 65 years of age, and 13.4% of subjects (1104/8240 subjects) were ≥ 75 years of age. A history of hypertension was reported for 39.6% of subjects (3262/8240 subjects), dyslipidaemia for 22.1% of subjects (1817/8240 subjects), diabetes for 10.5% of subjects (864/8240 subjects), and cancer for 9.4% of subjects (771/8240 subjects; DU176b-D-U305 CSR [Table 14.1.3.5](#)), concluding different concomitant comorbidities and risk factors.
- In Study U312, hypertension was reported for 3.8% of subjects (11/286 subjects), diabetes mellitus for 0.3% of subjects (1/286 subjects), and hyperlipidaemia for 1.0% of subjects (3/286 subjects; dyslipidaemia was not reported; DU176b-D-U312 CSR [Table 14.1.2.4](#)), highlighting the different patient population with different comorbidities.
- It should also be recognised that the incidence and prevalence of VTE events is lower (much lower in the younger age cohorts) when compared with the incidence and prevalence of VTE in adult patients.¹³

Performing a meta-analysis would provide limited information due to the huge difference in sample size between the 2 studies. When pooling the studies, the final outcome would be reflective of the

findings for Study U305. Noting these reservations, the MAH has provided the meta-analysis for information in an Annex to the response to question 10.

Alternatively, to investigate potential heterogeneity, [Table 3](#) provides a summary of the annualised rates of adjudicated symptomatic recurrent VTE and major or CRNM bleeding in Studies U312 and 305. The annualised rate provides more validity, especially with the lower number of reported events in Study U312.

The annualised rate of symptomatic recurrent VTE was higher for edoxaban in paediatric subjects in Study U312 than in adult subjects in Study U305 (15.6% versus 3.5%, respectively), whereas the annualised rate of symptomatic recurrent VTE was more similar for the SOC groups across the studies (6.4% and 3.9%, respectively). The rate ratio estimate (95% CI) for the annualised rate of symptomatic VTE on SOC versus edoxaban was 0.41 (0.08, 2.13) for paediatric subjects in Study U312 and 1.12 (0.89, 1.42) for adult subjects in Study U305.

The annualised rate estimates of symptomatic recurrent VTE on edoxaban were compared between the 2 studies.

- The ratio (Study U305/Study U312) for the symptomatic recurrent VTE was 0.22 with 95% CI (0.09, 0.54); *P* value = 0.0010. These results show that the adult subjects on edoxaban had a significantly lower rate of symptomatic recurrent VTE compared with the paediatric subjects, indicating potential heterogeneity in efficacy between the 2 studies.

The annualised rate of major or CRNM bleeding was similar across both populations. The rate ratio estimate (95% CI) for the annualised rate of major or CRNM bleeding on SOC versus edoxaban was 1.70 (0.41, 7.13) for paediatric subjects in Study U312 and 1.15 (1.01, 1.32) for adult subjects in Study U305.

The annualised rate estimates of major or CRNM bleeding on edoxaban were compared between the 2 studies.

- The ratio (Study U305/Study U312) of major or CRNM bleeding on edoxaban was 1.24 with 95% CI (0.40, 3.87); *P* value = 0.7062. No potential heterogeneity was found in major or CRNM bleeding (the 95% CI for the ratio spanned unity), indicating similar rates in adults and children.

Hence, the rate of symptomatic recurrent VTE on edoxaban appeared different (ie, higher) in children compared with adults, whereas the risk of bleeding was similar in children and adults.

Table 3: Comparison of Annualized Rate for CEC Confirmed Symptomatic Recurrent VTE and Major or CRNM Bleeding in the Main Treatment Period – Studies U312 and 305 (Safety Analysis Set)

	Study U312		Study U305	
	Edoxaban (N = 145)	SOC (N = 141)	Edoxaban (N = 4118)	SOC (N = 4122)
Symptomatic recurrent VTE (n, %)	5 (3.4%)	2 (1.4%)	130 (3.2%)	146 (3.5%)
Annualised rate	15.6%	6.4%	3.5%	3.9%
Rate ratio estimate (95% CI) ^a	0.41 (0.08, 2.13)		1.12 (0.89, 1.42)	
Major or CRNM bleeding events (n, %)	3 (2.1%)	5 (3.5%)	405 (9.8%)	461 (11.2%)
Annualised rate	8.7%	14.9%	10.9%	12.5%
Rate ratio estimate (95% CI) ^a	1.70 (0.41, 7.13)		1.15 (1.01, 1.32)	

	Difference in Annualized Rate Ratio between Studies (U305 to U312; Edoxaban Subjects Only)	
Symptomatic recurrent VTE (95% CI) ^a ; p-value ^b	0.22 (0.09, 0.54); 0.0010	
Major or CRNM bleeding events (95% CI) ^a ; p-value ^b	1.24 (0.40, 3.87); 0.7062	

CI = confidence interval; CRNM = clinically relevant nonmajor; LS = least squares; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

^a Estimates of Annualized Rate Ratio, SOC to edoxaban, are generated fitting a Poisson model to the annualised rate of events to total patient-years at risk, adding to the model an offset equal to the natural log of exposure years. Exponentiated LSmean difference estimates for rate ratio and confidence intervals.

^b The *P* value for difference of LS means.

Notes: The Main Treatment Period is defined as from randomisation to the Month 3 Visit + 3 days.

Annualised rate = # subject with event/Total time at risk (years). Total time at risk is the sum, across subjects, of the number of "at risk" years. For each subject, the "at risk" years = (the event or censoring – date of randomisation + 1)/365.25. If a subject has multiple events, the time of the first event is used.

There is still a scarcity of data on the relationship between age and long-term clinical outcomes of patients with VTE. In the current real-world VTE registry, there was no significant difference in the risk of major bleeding depending on different age groups, while younger patients showed an excess risk for recurrent VTE compared with older patients.¹⁴

Overall, comparing across the studies shows that the risk of symptomatic recurrent VTE on edoxaban appears different (ie, higher) in children compared with adults (mainly due to different etiopathogenesis for VTE occurrence and different underlying medical comorbidities), indicating heterogeneity in the incidence of VTE between the adult and the paediatric populations; whereas the risk of major or CRNM bleeding was similar in the 2 populations.

These results indicate that there is potential heterogeneity in efficacy outcome between adults and children on edoxaban. A full assessment of the risk given this discrepancy between children and adults is difficult given the very low number of symptomatic recurrent events observed in children in Study U312. As such, the MAH concludes that the benefit-risk profile for edoxaban remains uncertain for the paediatric indication.

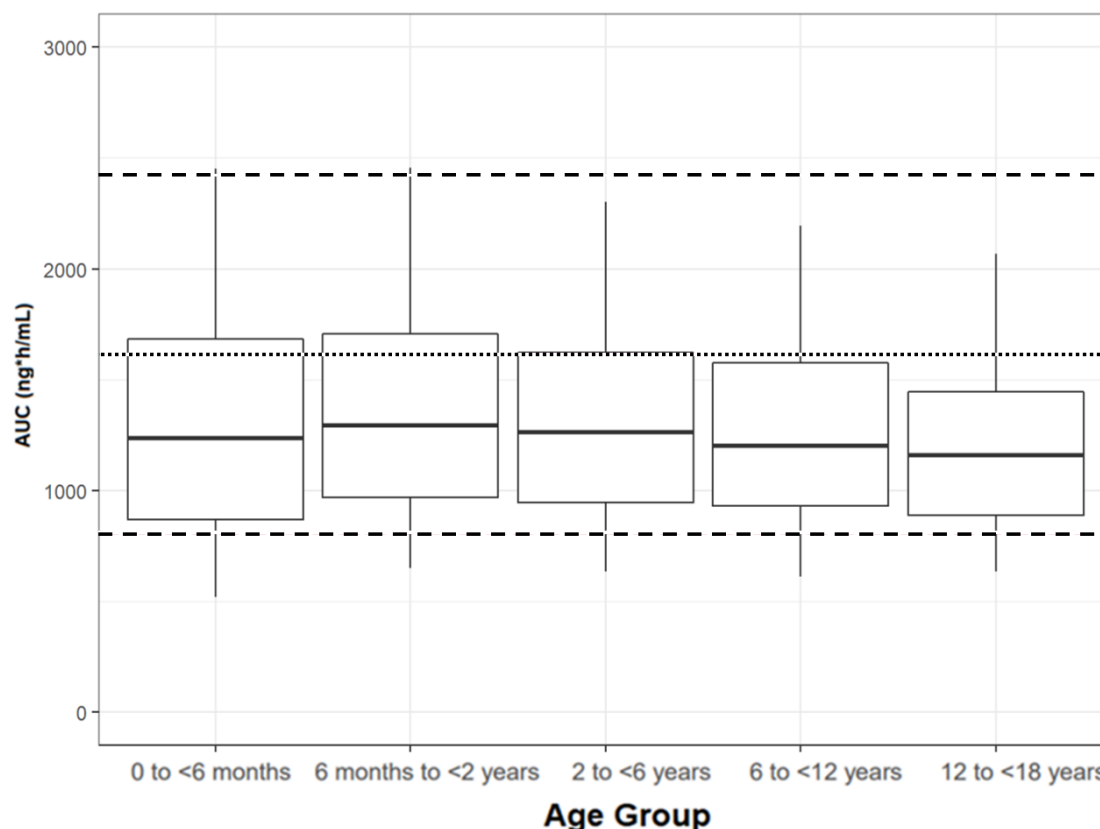
b. Proposal for Paediatric Dose and Posology

The MAH agrees with the Assessors that the proposed dosing regimens in paediatric patients could lead to an underexposure in paediatric patients compared with adult patients (Figure 5).

Per the post hoc PopPK simulation, the median AUC_{0-24h,ss} values for 0 to <0.5 years, 0.5 to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years of age cohorts are 1250, 1310, 1270, 1210, and 1160 ng*h/mL, respectively, which are 19% to 28% lower than the median AUC_{0-24h,ss} (1613 ng*h/mL) of adult VTE subjects receiving the 60 mg QD dose. The proposed doses for adolescents with body weight of 30 to <60 kg and ≥60 kg resulted in median AUC_{0-24h,ss} values of 27% and 31%, respectively, lower than that of adult VTE subjects receiving the 60 mg QD dose.

To accurately match the drug exposure in adult patients, a 20% to 50% dose increase could be needed for individual age-, eGFR-, and body weight-based subgroups.

Figure 5: Simulations by Age Group Using the Dose Regimen Tested in Clinical Studies



AUC = area under the concentration-time curve

Note: The upper and lower dash lines represent 50% and 150% of the median AUC of adult subjects, respectively. The dotted line represents the median AUC of adult subjects.

The relative oral bioavailability of granules for oral suspension versus tablets was assessed in healthy adult subjects (Study DU176b-A-U154). As shown in [Table 4](#), two 30-mg tablets and a 10-mL oral suspension (6 mg/mL) had similar exposure in healthy adult subjects, but the C_{max} of the oral suspension was 13% lower than that of the tablets. The relative bioavailability of oral suspension and tablets was not evaluated in any paediatric studies. The pooled PopPK analysis using data from 3 paediatric studies estimated the oral absorption rate of tablets to be 23% lower than that of oral suspension, but the formulation had no statistically significant effect on the oral bioavailability in the model. In the whole paediatric clinical development programme, only 6 children aged 6 to <12 years were administered at least 1 edoxaban dose as tablets (30 mg tablets and/or 15 mg tablets); however, PK data were not collected from these subjects ([Table 5](#) and [Table 6](#)). No children under 6 years of age were administered the tablet formulation. Therefore, it is unknown whether the tablet and granule formulations are bioequivalent in subjects younger than 12 years.

Table 4: Relative Bioavailability of Oral Suspension (6 mg/mL × 10 mL) and Tablets (30 mg × 2 Tablets) in Fasting State in Healthy Adult Subjects (Study DU176b-A-U154)

Dependent Variable	Ln(Geo LSM)		Geo LSM		Ratio ^a (%)	90 % CI	
	Suspension	Tablet	Suspension	Tablet		Lower	Upper
C _{max} (ng/mL)	5.3233	5.4643	205.0546	236.1083	86.85	72.97	103.27
AUC _{last} (ng.h/mL)	7.4492	7.4890	1718.5265	1788.2344	96.10	90.30	102.27

Dependent Variable	Ln(Geo LSM)		Geo LSM		Ratio ^a (%)	90 % CI	
	Suspension	Tablet	Suspension	Tablet		Lower	Upper
AUCinf (ng.h/mL)	7.4705	7.5107	1755.5143	1827.4883	96.06	90.43	102.04

AUCinf = area under the concentration-time curve from time zero to infinity; AUClast = area under the concentration-time curve from time zero to the last measurable concentration; CI = confidence interval; Cmax = maximum concentration; Geo LSM = geometric least squares mean

^a Edoxaban suspension/edoxaban tablet

Table 5: Edoxaban Use in Children **≥6** Years of Age by Formulation, Study, and Age Cohort

	Study 157 (Single Dose)		Study 312		Study 313	
	6 to <12 y (N = 13)	12 to <18 y (N = 15)	6 to <12 y (N = 23)	12 to <18 y (N = 85)	6 to <12 y (N = 54)	12 to <18 y (N = 43)
Oral granules	13 (100%)	0 (0%)	23 (100%)	0 (0%)	53 (98.1%)	2 (4.6%)
Tablet	0 (0%)	15 (100%)	0 (0%)	85 (100%)	6 (9.3%)	43 (100%)

Table 6: Listing of Subjects Under 12 Years of Age Administered ≥ 1 Edoxaban Dose as Tablets

Age Cohort: 6 to <12 Years	Edoxaban Formulation Administered
U313-	Subjects taking both oral granules and tablets (N = 5)
U313-	43 to 45 mg for granules and 45 mg for tablets
U313-	36.6 to 37.2 mg for granules and 45 mg for tablets
U313-	45 to 60 mg for granules and 45 mg for tablets
U313-	45 mg for both granules and tablets
U313-	45 mg for both granules and tablets
U313-	Subject taking tablets only (N = 1)
U313-	30 mg for tablets

Overall, there are inadequate PK/PD, efficacy, or safety data to support the use of the edoxaban 30 mg or 15 mg tablets in patients younger than 12 years. It may not be possible to achieve the correct weight-calculated dose via administration of tablets, leading to overdosing or underdosing in some subjects. The target dose for subjects aged 6 to <12 years is 1.2 mg/kg. Only subjects weighing 18 or 36 kg would receive the correct dose when administered edoxaban tablets, as illustrated in [Table 7](#).

Table 7: Edoxaban Exposure by Body Weight for 30-mg and 15-mg Tablets

Body Weight	30-mg Tablet	15-mg Tablet
<18 kg	NA	>1.2 mg/kg
18 kg	NA	1.2 mg/kg
>18 to >36 kg	>1.2 mg/kg	<1.2 mg/kg
36 kg	1.2 mg/kg	NA
>36 kg	<1.2 mg/kg	NA

NA = not applicable

Overall, regarding dose and posology, similar exposure as obtained in adults was not achieved using the proposed dose regimen of edoxaban tablets in subjects 12 to <18 years of age (rather, it could lead to an approximately 20% to 30% underexposure in paediatric compared to adult patients). It is unknown whether the tablet and granule formulations are bioequivalent in patients younger than 12 years. There are inadequate PK/PD, efficacy, or safety data to support the use of the edoxaban 30 mg or 15 mg tablets in patients younger than 12 years of age.

Overall Summary

The MAH does not recommend edoxaban to be used for a paediatric indication due to uncertainty about benefit-risk profile of edoxaban in the paediatric population as summarised below.

- Study U312 was specifically designed to compare edoxaban to SOC in a paediatric population. Its failure to demonstrate NI provides uncertainty with regard to the use of edoxaban in this population.
- A comparison of Studies U305 and U312 shows a lower annualised rate of symptomatic recurrent VTE occurrence in adults compared to children on edoxaban (annualised rate ratio [adults/paediatric] of 0.22 [95% CI: 0.09, 0.54]; P value = 0.0010), which also adds uncertainty that edoxaban would offer at least an equal benefit to approved SOC in children. A full assessment of the risk given this discrepancy between children and adults is difficult given the very low number of symptomatic recurrent events observed in children in Study U312. The risk of major or CRNM bleeding was similar in the 2 populations.
- As expected, edoxaban exhibits similar PK relationships for anti-FXa activity between paediatric and adult subjects. Anti-FXa level cannot be used as a direct marker of clinical efficacy for any specific oral direct Xa inhibitor.⁶
- The PD biomarkers PT and aPTT show considerable variation for edoxaban in paediatric subjects, especially in the lower age cohorts, which contributes further uncertainty when considered alongside the study results (the low number of symptomatic recurrent VTE events reported in the Study U312 and the study not meeting the primary objective of demonstrating NI). Therefore, the MAH concludes that the benefit-risk profile for edoxaban in the paediatric indication remains uncertain.

Currently, numerous treatment options are available for paediatric VTE, including the direct oral anticoagulants rivaroxaban and dabigatran, in addition to the traditional therapy with heparin (eg, enoxaparin/unfractionated heparin/fondaparinux, etc) and the VKAs (eg, warfarin, acenocoumarol, etc). Given the treatment options available for paediatric patients and the uncertainty that edoxaban offers at least an equivalent benefit to SOC in this patient population, the MAH does not consider that a recommendation for formulation development is warranted.

Edoxaban does not fulfil an unmet medical need in terms of treatment options for paediatric VTE. The benefit-risk profile for edoxaban in children remains uncertain with the results of Study U312; therefore, the MAH does not support an edoxaban paediatric indication.

The MAH proposes to include relevant information regarding outcomes for the paediatric clinical studies, which were performed in compliance with the PIP in the product information as part of this variation application.

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Assessment of the WSA's response

The applicant has provided and discussed some key pitfalls of the paediatric development of edoxaban in children. Regarding dose and posology, similar exposure as obtained in adults was NOT achieved using the proposed dose regimen of edoxaban tablets in subjects 12 to <18 years of age (rather, it could lead to an approximately 20% to 30% underexposure). This was translated into a higher annualized rate of recurrent symptomatic VTE with edoxaban vs. SOC in the meta-analysis provided (15.6% vs. 6.4% in the study U312 in children), while in the adult study U305, the trend was the opposite in favour of edoxaban (3.5% vs. 3.9%). In addition, in sensitivity analyses, using the endpoint of symptomatic recurrent VTE as defined in the EINSTEIN-Jr study, edoxaban would have been declared inferior to SOC with statistical significance (HR: 2.34; 95% CI: 0.453 to 12.054) (see also assessment of Q11). Therefore, a potential lack of efficacy of edoxaban due to underexposure in children at the doses tested in study U312 is a real possibility.

In addition, it is unknown whether the tablet and granule formulations are bioequivalent in patients younger than 12 years. There are inadequate PK/PD, efficacy, or safety data to support the use of the edoxaban 30 mg or 15 mg tablets in patients younger than 12 years of age. Therefore, establishing a paediatric posology is challenging and subject to significant uncertainty with the data available.

Finally, there are several treatment options for paediatric VTE (i.e.: rivaroxaban, dabigatran, heparins and VKAs). Given the treatment options available for paediatric patients and the uncertainty that edoxaban offers at least an equivalent benefit to SOC in this patient population, the MAH does not consider that a recommendation for formulation development is warranted.

It is unfortunate that the paediatric PIP has failed in achieving the goal of establishing an appropriate effective and safe dose that provides a similar exposure as in adults. Given the uncertainties about the benefit-risk profile of edoxaban in the paediatric population and the difficulties in establishing an appropriate paediatric dose, the Rapporteur finally shares the MAH intention of not recommending the use of edoxaban in children.

Conclusion

Issue solved (no further information pursued).

Question 11. The applicant should also provide sensitivity analyses of Hokusai VTE pediatrics using as primary endpoints those used in EINSTEIN Junior with rivaroxaban (symptomatic recurrent VTE) [Male et al. Lancet Haematol. 2020;7:e18-e27] and DIVERSITY study with dabigatran (combined endpoint of complete thrombus resolution, absence of recurrent VTE and absence of death related to VTE) [Halton et al. Lancet Haematol. 2021;322-e33] in order to put into context comparable paediatric studies that have used different endpoints and hypotheses.

Summary of the WSA's response

The requested sensitivity analyses for edoxaban are provided in Table 8 and Table 9, with the corresponding results from the published studies.

For the endpoint of symptomatic recurrent VTE as used in the EINSTEIN-Jr study, the comparison of edoxaban versus SOC was HR: 2.34; 95% CI: (0.453, 12.054) and for rivaroxaban versus SOC was HR: 0.40; 95% CI: (0.11, 1.41).

For the composite endpoint of complete thrombus resolution, absence of recurrent VTE, and absence of VTE-related death as used in the DIVERSITY study, the difference between SOC vs edoxaban was -0.0115; 90% CI: (-0.1022, 0.0792) and the difference between SOC versus dabigatran was -0.04; 90% CI: (-0.14 to 0.07).

Table 8: Sensitivity Analysis of Symptomatic Recurrent VTE

Study Treatment Group	Symptomatic Recurrent VTE ^a
Hokusai-VTE paediatric study	
Edoxaban (N = 145)	5 (3.4%)
SOC (N = 141)	2 (1.4%)
Hazard ratio (95% CI) ^b	2.34 (0.453, 12.054)
EINSTEIN-Jr study ¹	
Rivaroxaban (N = 335)	4 (1%)
SOC ^c (N = 165)	5 (3%)
Hazard ratio (95% CI)	0.40 (0.11, 1.41)

CI = confidence interval; SOC = standard of care; VTE = venous thromboembolism

^a Proportion with symptomatic recurrent VTE assessed by the central independent adjudication committee

^b Hazard ratio (95% CI) corresponds to the time to first event (days) in symptomatic recurrent VTE

^c Heparin or VKA.

Table 9: Sensitivity Analysis of Proportion with Complete Thrombus Resolution, Absence of Recurrent VTE, and Absence of VTE-related Death

Study Treatment Group	Composite Endpoint ^a	Complete Thrombus Resolution	Freedom from Recurrent VTE	Freedom from VTE-related Death
Hokusai-VTE paediatric study				
Edoxaban (N = 145)	50 (34.5%)	51 (35.2%)	132 (91.0%)	135 (93.1%)
SOC (N = 141)	47 (33.3%)	47 (33.3%)	127 (90.1%)	127 (90.1%)
Mantel-Haenszel weighted difference (90% CI)	-0.0115 (-0.1022, 0.0792) <i>P</i> = 0.00031 ^b			
DIVERSITY study ²				
Dabigatran (N = 177)	81 (46%)	81 (46%)	170 (96%)	177 (100%)
SOC (N = 90) ^c	38 (42%)	38 (42%)	83 (92%)	89 (99%)
Mantel-Haenszel weighted difference (90% CI)	-0.04 (-0.14, 0.07) <i>P</i> < 0.0001 ^d			

CI = confidence interval; SOC = standard of care; VTE = venous thromboembolism

^a Proportion with complete thrombus resolution, absence of recurrent VTE, and absence of VTE-related death

^b Difference in rates SOC minus Edoxaban, Mantel-Haenszel weighted difference

^c Low molecular weight heparins, unfractionated heparin, vitamin K antagonists, or fondaparinux, used according to investigators' judgment and standard clinical practice

^d Difference in rates (SOC minus dabigatran, Mantel-Haenszel weighted difference) with age group as a stratification factor.

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Assessment of the WSA's response

The applicant has provided the sensitivity analyses requested. For the endpoint of symptomatic recurrent VTE as used in the EINSTEIN-Jr study, the comparison of edoxaban versus SOC was HR 2.34 (95% CI: 0.453 to 12.054) and for rivaroxaban versus SOC was HR: 0.40; 95% CI: (0.11, 1.41). Therefore, by using symptomatic VTE as primary endpoint, edoxaban would have been declared inferior to SOC with statistical significance.

For the composite endpoint of complete thrombus resolution, absence of recurrent VTE, and absence of VTE-related death as used in the DIVERSITY study, the difference between SOC vs edoxaban was -1.15%; 90% CI: (-10.22 to 7.92; non-inferiority margin of absolute differences of 20% was used; non-inferiority *P* = 0.00031) and the difference between SOC versus dabigatran was -4% (90% CI: -14% to 0). Therefore, using the primary endpoint of the DIVERSITY study, edoxaban would have

been declared non-inferior to SOC in HOKUSAI-VTE paediatrics study, while dabigatran was declared non-inferior to SOC, and almost superior to SOC with borderline statistical significance to SOC in the DIVERSITY study, as the upper 90%CI for the absolute difference in the primary endpoint was 0.

These sensitivity analyses highlight the heterogeneity in conclusions about benefit-risk that are apparent depending on the efficacy endpoint used in children. In general, the efficacy of edoxaban vs SOC in study U312 in children using different primary endpoints seems lower than that achieved by rivaroxaban in the EINSTEIN-Jr study and by dabigatran in the DIVERSITY study. In fact, edoxaban would have been declared inferior to SOC using the primary endpoint of symptomatic VTE as defined in the EINSTEIN-JR study

Conclusion

Issue solved.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 12. In the phase III U312 study (Hokusai VTE paediatrics) a significant number of index events (46 events) were not confirmed, but were included in the main analysis. These patients should have been excluded from the mITT and PP populations and the main analysis, and only included in sensitivity analyses. In this respect:

- a) Please, provide efficacy analyses including only confirmed cases of VTE at baseline (240: 129 in the edoxaban group and 111 in the SOC group).
- b) An explanation why there are two-fold more unconfirmed cases of the index VTE in the SOC group (n= 30) than in the edoxaban group (n=16) would be welcomed.
- c) The description of VTE location of index events is rather scarce (VTE is only differentiated into DVT or PE). Please, describe locations of index DVTs (i.e.: lower limbs, upper limbs, catheter-associated DVT, cerebral venous thrombosis, etc).
- d) Please provide subgroup analyses of recurrent VTE according to location of index DVT/PE.

Summary of the WSA's response

The MAH would like to clarify that in-line with the Study [DU176b-D-U312 Study Protocol \(Version 4.0\)](#) and [Statistical Analysis Plan \(SAP; Version 3.0\)](#), the primary efficacy analysis was based on the mITT Analysis Set, which included all subjects in the Randomised Analysis Set who received at least 1 dose of randomised study drug. The mITT Analysis Set comprised 286 subjects (edoxaban 145 subjects and SOC 141 subjects).

A Per Protocol analysis was prespecified as a sensitivity analysis in the SAP. The Per Protocol Analysis Set was defined as all subjects in the mITT Analysis Set who were sufficiently compliant with the protocol (ie, without major protocol deviations). Per the SAP, major deviations from the protocol included: taking the incorrect treatment during the entire study period, not satisfying the eligibility criteria, index VTE not confirmed by the CEC, delayed SAE reporting or informed consent etc. Full details of the major protocol deviations were documented in the protocol deviations plan version 9.0, dated 06 May 2022.

In total, 47 subjects in the mITT Analysis Set were excluded from the Per Protocol Analysis Set, which comprised 239 subjects (edoxaban 129 and SOC 110). Subjects whose index events were not confirmed by CEC adjudication were excluded from the Per Protocol Analysis Set. The results for the

Per Protocol Analysis Set were provided in the U312 CSR and were consistent with the results for the mITT Analysis Set (see DU176b-D-U312 CSR [Table 14.2.1.2](#)).

a) Efficacy Analyses Including Only Confirmed Cases of VTE at Baseline

As requested by the CHMP, the MAH has provided an analysis excluding the subjects whose index events were not confirmed by CEC adjudicators (edoxaban 129 subjects versus SOC 111 subjects).

During the Main Treatment Period, the frequency of subjects meeting the composite primary endpoint was 19 (14.7%) subjects in the edoxaban group and 19 (17.1%) subjects in the SOC group. The HR of the composite primary efficacy endpoint was 0.95; 95% CI: (0.500, 1.818). The upper bound of the 95% CI was 1.818, which was above the prespecified NI margin of 1.5.

The frequency of CEC adjudication-confirmed symptomatic recurrent VTE was 5 (3.9%) subjects in the edoxaban group and 2 (1.8%) subjects in the SOC group ([Table 10](#)).

Table 10: Adjudication-Confirmed Composite Primary Efficacy Endpoint in the Main Treatment Period – Study U312 (Subjects with Confirmed VTE at Baseline)

	Edoxaban (N = 129)	SOC (N = 111)
Subjects with events (n, %)	19 (14.7)	19 (17.1)
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 for 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 (15.3)
Time to first event (days)		
HR ^{a,b}	0.95	
2-sided 95% CI for HR ^{a,b}	(0.500, 1.818)	
2-sided <i>P</i> -value ^b	0.8849	

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

^a Edoxaban-to-SOC HR. Edoxaban is considered noninferior to SOC if the upper limit of the 95% CI is <1.5. If noninferiority is established, edoxaban is considered superior to SOC if the upper limit of the 95% CI is <1.0.

^b Based on the Cox proportional hazards regression model including treatment and age group as covariates

Notes: 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.

The Main Treatment Period is defined as from randomisation to the Month 3 Visit + 3 days.

Percentages are based on the total number of subjects randomised to the particular group.

b) Reasons for Unconfirmed Cases of the Index VTE

Study U312 was an event-driven Phase 3, prospective, randomised, open-label, blinded endpoint evaluation (PROBE), parallel-group study in subjects with confirmed VTE. The independent adjudication CEC was blinded to study treatment for event adjudication. The distribution of investigator-reported VTE events as unconfirmed events by the CEC (30 cases in the SOC group and 16 cases in the edoxaban group) is likely a chance finding.

c) Location of Index DVT

The requested summary is provided in [Table 11](#). The distribution of locations of index VTE was similar across the treatment groups in Study U312.

Index DVTs were most commonly located in the lower extremities. Overall, 43.2% of subjects with DVT (54/125 subjects; 50 with DVT only, and 4 with DVT and PE) in the edoxaban group and 38.8% of subjects with DVT (47/121 subjects; 44 with DVT only, and 3 with DVT and PE) in the SOC group had DVT located in the lower extremities. The next most common locations were cerebral venous sinus thrombosis reported for 21.6% of subjects with DVT (27/125 subjects; all with DVT only) in the edoxaban group and 17.4% of subjects with DVT (21/121 subjects; all with DVT only) in the SOC group, and upper extremities for 18.4% of subjects with DVT (23/125 subjects; 22 with DVT only, and 1 with DVT and PE) in the edoxaban group and 20.7% of subjects with DVT (25/121 subjects; 24 with DVT only, and 1 with DVT and PE) in the SOC group.

Table 11: Location of Index DVT– Study U312 (mITT Analysis Set)

	Edoxaban (N = 145)	SOC (N = 141)
Type of index events (n, %)		
PE without DVT	20 (13.8)	20 (14.2)
DVT with or without PE	125 (86.2)	121 (85.8)
Location of index DVT (n, %)		
Index event: DVT	N = 119	N = 116
Upper extremities	22 (15.2)	24 (17.0)
Lower extremities	50 (34.5)	44 (31.2)
Catheter related thrombosis	8 (5.5)	9 (6.4)
Cerebral venous sinus thrombosis	27 (18.6)	21 (14.9)
Hepatic vein/vena cava vein	1 (0.7)	0
Renal vein	0	1 (0.7)
Splanchnic vein	1 (0.7)	1 (0.7)
Missing	10 (6.9)	19 (13.5)
Index event: PE with DVT	N = 6	N = 5
Upper extremities	1 (0.7)	1 (0.7)
Lower extremities	4 (2.8)	3 (2.1)
Renal vein	0	1 (0.7)
Missing	1 (0.7)	0

DVT = deep vein thrombosis; mITT = Modified Intent-to-Treat; PE = pulmonary embolism; SOC = standard of care
Note: Percentages are based on the total number of subjects randomised to the particular group.

d) Subgroup Analyses of Recurrent VTE According to Location of Index DVT/PE

A summary of adjudication-confirmed VTE by location of index event and DVT characteristics (catheter and not catheter-related) is provided in [Table 12](#). However, due to the low number of subjects with events, it was not possible to draw any conclusions.

The 2 subjects with unexplained death where VTE could not be ruled out both had index events of PE only.

Table 12: Subgroup Analysis of Adjudication-Confirmed VTE in the Main Treatment Period by Location/Type of Index DVT/PE– Study U312 (mITT Analysis Set)

	Edoxaban (N = 145)	SOC (N = 141)	HR (95 % CI) ^{a,b}
Subjects with adjudication-confirmed VTE events (n, %)	5 (3.4)	2 (1.4)	2.34 (0.453, 12.054)
Index event Location/type (n, %)			
PE without DVT	1 (0.7)	1 (0.7)	NA
DVT only			
Upper extremities	1 (0.7)	0	NA
Lower extremities	3 (2.1)	0	NA
PE with DVT			
Lower extremities	0	1 (0.7)	NA

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; mITT = Modified Intent-to-Treat; NA = not available; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

^a Edoxaban-to-SOC HR.

^b Based on the Cox proportional hazards regression model including treatment and age group as covariates

Notes: The Main Treatment Period is defined as from randomisation to the Month 3 Visit + 3 days. Percentages are based on the total number of subjects randomised to the particular group.

REFERENCES

Not applicable.

Assessment of the WSA's response

The MAH has provided an analysis excluding the subjects whose index events were not confirmed by CEC adjudicators (i.e.: including edoxaban 129 subjects versus SOC 111 subjects). During the Main Treatment Period, the frequency of subjects meeting the composite primary endpoint was 19 (14.7%) subjects in the edoxaban group and 19 (17.1%) subjects in the SOC group. The HR of the composite primary efficacy endpoint was 0.95; 95% CI: (0.500, 1.818). The upper bound of the 95% CI was 1.818, which was above the prespecified NI margin of 1.5. Therefore, the analysis excluding patients with an index event not confirmed by CEC adjudicators yielded very similar results to those included in the main analysis. The frequency of CEC adjudication-confirmed symptomatic recurrent VTE was 5 (3.9%) subjects in the edoxaban group and 2 (1.8%) subjects in the SOC group. On the other hand, the applicant states that the imbalance between groups in the distribution of investigator-reported VTE events as unconfirmed events by the CEC (30 cases in the SOC group and 16 cases in the edoxaban group) is likely a chance finding.

The MAH has clarified that the type of index event was DVT with or without PE in 125 (86.2%) of 145 children of the edoxaban group and 121 (85.8%) of 141 children in the SOC group, while the remaining cases, 20 (13.8%) in the edoxaban group and 20 (14.2%) in the SOC group were PE without DVT.

DVTs were most frequently localized in the lower extremities (50 and 44 cases in the edoxaban and SOC groups, respectively), upper extremities (22 vs 24), and cerebral venous sinus (27 vs. 21). The number of catheter-related thrombosis as index VTE event was low in the edoxaban and SOC groups (8 vs. 9). A summary of adjudication-confirmed VTE by location of index event and DVT characteristics (catheter and not catheter-related) has been provided, but due to the low number of subjects with events, it is not possible to draw any conclusions.

Conclusion

Issue solved.

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 13. There are two patients that developed symptomatic recurrent DVT while on edoxaban (case 1 iliac DVT, case 2CVC DVT) that are not mentioned in the table 4.8 of the Summary of Clinical Pharmacology in relationship with edoxaban levels. The applicant should provide PK data and discussions about these two cases if edoxaban levels were available.

Summary of the WSA's response

Among the 145 subjects in the edoxaban group of Study U312, PK samples were collected from 69 subjects (per the protocol, samples were not required to be collected from all subjects). Unfortunately, PK samples were not collected from Case 1 or Case 2 (Module 5.3.5.1 DU176b-D-U312 CSR [Listing 16.2.2.3](#)). Based on their age (17 years), body weight (54.7 kg and 55.9 kg, respectively), and normal renal function, both subjects received the 45 mg QD dose when they developed DVT.

REFERENCES

Not applicable.

Assessment of the WSA's response

The MAH has clarified that PK samples were not collected from Case 1 or Case 2 PK samples were not collected from Case 1 or Case 2

Conclusion

Issue solved.

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 14. In study U312, 21 of 26 primary efficacy events in the edoxaban group and 29 of the 31 events in the SOC group corresponded to "no change or extension of thrombotic burden".

- a) The applicant is invited to clarify how many of these events in each group required additional treatment (i.e.: a course of parenteral anticoagulation if the children were on oral anticoagulation, or an increase in the intensity of parenteral anticoagulation if the children were already on parenteral anticoagulation).
- b) The applicant should also provide PK data (i.e.: edoxaban levels) in all primary efficacy events (not only for the symptomatic ones), and to discuss about a potential relationship between edoxaban levels and cases of “no change or extension of thrombotic burden”.

Summary of the WSA's response

a) Events Requiring Additional Treatment

The subjects with no change or extension of thrombotic burden during the Main Treatment Period are listed in [Table 13](#) together with details of anticoagulant use. One subject started additional anticoagulation before the primary efficacy outcome assessment in the edoxaban group. In the SOC group, 3 subjects started additional anticoagulation before the primary efficacy outcome assessment and 1 subject started additional anticoagulation on the same day as the primary efficacy outcome assessment.

Table 13: Listing of Subjects with No Change or Extension of Thrombotic Burden During the Main Treatment Period of Study U312 and Concomitant Anticoagulation Use

Treatment Subject	Anticoagulation Use After Day 1
Edoxaban	
Case 1	None
Case 2	None
Case 3	None
Case 4	None
Case 5	None
Case 6	None
Case 7	None
Case 8	None
Case 9	None
Case 10	None
Case 11	None
Case 12	No concomitant use of anticoagulation in the Main Treatment Period. Heparin 25000 IU on Day 240. Primary efficacy assessment was on Day 92.
Case 13	None
Case 14	None
Case 15	None
Case 16	None
Case 17	None
Case 18	None
Case 19	No concomitant use of anticoagulation in the Main Treatment Period. Acetylsalicylic acid 100 mg QD prophylaxis ongoing from Day 393. Primary efficacy assessment was on Day 94.

Treatment Subject	Anticoagulation Use After Day 1
Case 20	None
Case 21	Enoxaparin 40 mg QD ongoing from Day 32. Primary efficacy assessment was on Day 99.
SOC	
Case 22	None
Case 23	No concomitant use of anticoagulation in the Main Treatment Period. Enoxaparin 20 mg BID from Day 87 to Day112. Primary efficacy assessment was on Day 87.
Case 24	None
Case 25	None
Case 26	None
Case 27	No concomitant use of anticoagulation in the Main Treatment Period. Acetylsalicylic acid 100 mg QD ongoing from 2009. Primary efficacy assessment was on Day 100.
Case 28	Enoxaparin 30 mg BID from Day 1 to Day 19. Primary efficacy assessment was on Day 104.
Case 29	None
Case 30	No concomitant use of anticoagulation in the Main Treatment Period. Tinzaparin sodium 3000 IU from Day -10 to Day3. Primary efficacy assessment was on Day 92.
Case 31	None
Case 32	None
Case 33	None
Case 34	None
Case 35	Heparin 3500 IU in 50 mL ongoing from Day -13. Primary efficacy assessment was on Day 89.
Case 36	No concomitant use of anticoagulation in the Main Treatment Period. Dipyridamole 0.2/tablet BID ongoing from Day 38 and Acetylsalicylic acid 15 mg BID ongoing from Day 59. Primary efficacy assessment was on Day 91.
Case 37	No concomitant use of anticoagulation in the Main Treatment Period. Dipyridamole 5 mg BID from Day 92 to Day 104, and from Day 209 to Day 239. Acetylsalicylic acid 15 mg BID from Day 92 to Day 208 and 20 mg from Day 209 to Day 239. Primary efficacy assessment was on Day 92.
Case 38	None
Case 39	Heparin 2.5 mL TID from Day 38 to Day 46, 2.5 mL QD on Day 47. Enoxaparin 40 mg QD on Day 43. Acetylsalicylic acid 81mg QD from Day 43 to Day 44. Warfarin 2 mg QD on Day 44. Primary efficacy assessment was on Day 95.
Case 40	None
Case 41	None
Case 42	None
Case 43	None
Case 44	None
Case 45	None

Treatment Subject	Anticoagulation Use After Day 1
Case 46	Enoxaparin sodium 140 mg QD ongoing from Day 141. Primary efficacy assessment was on Day 92.
Case 47	None
Case 48	None
Case 49	None
Case 50	None

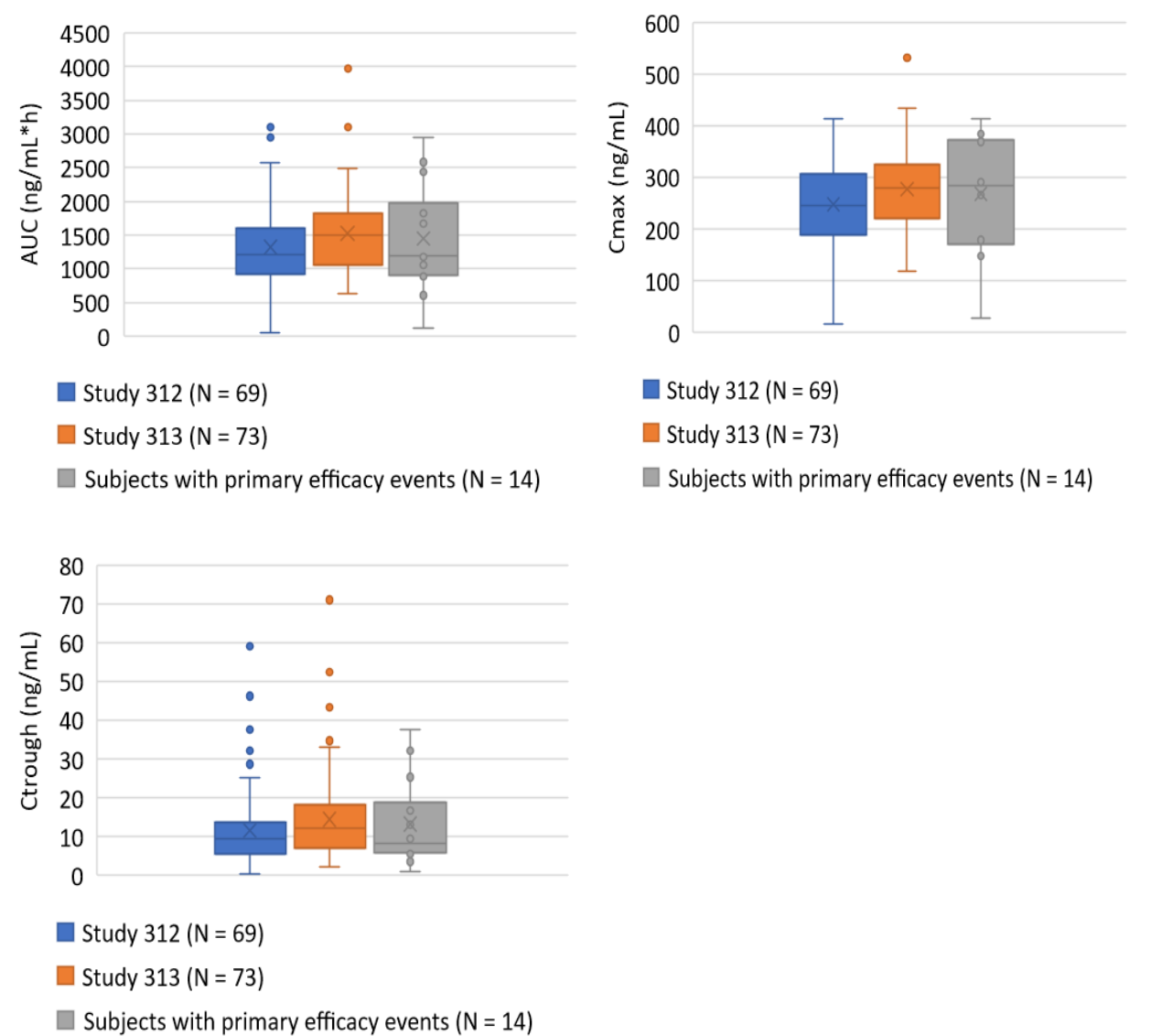
BID = twice daily; CSR = clinical study report; QD = once daily; SOC = standard of care; TID = three times daily
Source: Module 5.3.5.1 DU176b-D-U312 CSR [Listing 16.2.6.2](#), [Listing 16.2.3.6](#)

b) Edoxaban Levels in Subjects with Primary Efficacy Events

Plasma edoxaban levels are not available for all subjects in Study U312 (the PK Analysis Set included 69 subjects of the 145 subjects treated with edoxaban). As noted by the Assessors, the majority of subjects with an efficacy outcome had no change or extension of thrombotic burden. Among the 26 subjects with primary efficacy events in the edoxaban group, PK samples were collected from 14 subjects (2 subjects with symptomatic recurrent VTE, 1 death where VTE could not be ruled out and 11 subjects with no change or extension of thrombotic burden).

The PopPK model-estimated steady-state AUC, C_{max} , and C_{trough} of the 14 subjects with PK data are summarised in [Figure 6](#) and [Table 14](#). The median and average exposures of edoxaban of the 14 subjects were slightly higher than that of subjects enrolled in Study U312 and comparable to that of subjects enrolled in Study U313. No relationship between edoxaban levels and primary efficacy events was observed.

Figure 6: Boxplot of the PK Parameters of Subjects with Primary Efficacy Events During the Main Treatment Period (N = 14) Versus Subjects in Study 312 (N = 69) and Study 313 (N = 73) with PK Data Available.



AUC = area under the concentration-time curve; Cmax= maximum concentration; Ctough = minimum plasma concentration; PK = pharmacokinetic

Table 14: PK Parameters of Subjects with Primary Efficacy Events During Main Treatment Period (N = 14) Versus Subjects in Study 312 with PK Data Available (N = 69)

Subject (N = 14)	Age Group (years)	Dose (mg)	AUC (ng / mL * h)	Cmax (ng / mL)	Ctough (ng / mL)
Primary event: symptomatic VTE					
Case 1	>12 to ≤18	60	1179	189	9.42
Case 2	>0.5 to ≤2	8.7	2442	392	25.30

Subject (N = 14)	Age Group (years)	Dose (mg)	AUC (ng / mL * h)	Cmax (ng / mL)	Ctrough (ng / mL)
Primary event: no change or extension of thrombotic burden					
Case 3	>0.5 to ≤2	10.35	1217	293	6.91
Case 4	>2 to ≤6	1.4	129	27	0.98
Case 5	>12 to ≤18	45	905	179	5.54
Case 6	>2 to ≤6	20.58	1823	370	14.31
Case 7	>2 to ≤6	10.5	606	149	3.50
Case 8	>6 to ≤12	45	1672	292	16.59
Case 9	>12 to ≤18	60	887	149	6.71
Case 10	>6 to ≤12	32.4	1056	277	5.71
Case 11	>0.5 to ≤2	12.9	2946	413	37.54
Case 12	>2 to ≤6	16.8	1147	267	7.20
Case 13	>6 to ≤12	60	1730	370	13.05
Primary event: death where VTE could not be ruled out					
Case 14	>6 to ≤12	32	2581	385	32.17
Study 312 (N = 69)					
Mean ± SD	NA	NA	1319 ± 608	248 ± 87	11.59 ± 9.98
Median (min, max)	NA	NA	1217 (58, 3137)	246 (16, 413)	9.37 (0.24, 59.0)

AUC = area under the concentration-time curve; Cmax= maximum concentration; CSR = clinical study report; Ctrough = minimum plasma concentration; max = maximum; min = minimum; NA = not applicable; PK = pharmacokinetic; PopPK = population PK; SD = standard deviation; VTE = venous thromboembolism

Source: Module 5.3.5.1 DU176b-D-U312 CSR U312 [Listing 16.2.2.3](#), [Listing 16.2.5.1](#), [Listing 16.2.6.2](#); PopPK modelling and simulation report [Table 27](#)

REFERENCES

Not applicable.

Assessment of the WSA's response

The MAH has provided the data requested. One subject (Case 13) of 21 children (4.8%) with “no change or extension of thrombotic burden” in the edoxaban group started additional anticoagulation before the primary efficacy outcome assessment. In the SOC group, 3 of 29 children (10.3%) with “no change or extension of thrombotic burden” started additional anticoagulation before the primary efficacy outcome assessment and 1 additional subject in the SOC started additional anticoagulation on the same day as the primary efficacy outcome assessment.

On the other hand, Among the 26 subjects with primary efficacy events in the edoxaban group, PK samples were collected from 14 subjects (2 subjects with symptomatic recurrent VTE, 1 death where VTE could not be ruled out and 11 subjects with no change or extension of thrombotic burden). The median and average exposures of edoxaban of the 14 subjects were slightly higher than that of subjects enrolled in Study U312 and comparable to that of subjects enrolled in Study U313. No

relationship between edoxaban levels and primary efficacy events was observed.

Conclusion

Issue solved.

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 15. The U312 study population is poorly characterized for essential clinical data in relationship with main efficacy and safety endpoint results, like efficacy/safety by age ranges (e.g.: 12 to < 18 years; 6 to < 12 years; 2 to < 6 years; and < 2 years), type of index VTE (e.g.: DVT related to central venous catheter, cerebral venous sinus, lower limbs, PE) and type of risk factors (persistent, transient or both, cancer yes/no, CVC yes/no). In addition, the presence of cancer and chemotherapy with asparaginase are major prothrombotic risk factors that could result in different VTE rates and/or treatment effects. In this respect:

- a) The applicant is requested to clarify how many patients were recruited into the U312 study with cancer and/or asparaginase chemotherapy by treatment group and to analyse any potential imbalances between treatments.
- b) All these subpopulations mentioned in the heading should be further analyzed in subgroups for efficacy and safety. In particular, recurrent VTE events and major/CRNMB should be described in these important subgroups and summarized in tables, despite it is acknowledged that the number of events in subgroups will be low.

Summary of the WSA's response

a. Subjects in Study U312 with Cancer and/or Asparaginase Chemotherapy

[Table 15](#) summarises the numbers of subjects with each medical history reported in the neoplasms benign, malignant and unspecified system organ class. A medical history in the neoplasms benign, malignant and unspecified system organ class was reported for 19.3% of subjects (28/145 subjects) in the edoxaban group and 22.0% of subjects (31/141 subjects) in the SOC group. Similar proportions of subjects had a history of cancer in the edoxaban and SOC groups of Study U312.

The subjects who received either prior or concomitant treatments in the ATC class Other antineoplastic agents are listed in [Table 16](#).

Overall, 6.9% of subjects in the edoxaban group (10/145 subjects) had received asparaginase (or pegaspargase/crisantaspase), whereas 3.5% of subjects in the SOC group (5/141 subjects) had received asparaginase (or pegaspargase).

[Table 17](#) summarises the number of subjects receiving asparaginase, pegaspargase, or crisantaspase by prior and concomitant use during the study.

Table 15: Subjects with Cancer in Study U312 (mITT Analysis Set)

	Edoxaban (N = 145)	SOC (N = 141)
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	Edoxaban (N = 145)	SOC (N = 141)
Medical history of "Neoplasms benign, malignant and unspecified (incl cysts and polyps)", n (%)	28 (19.3)	31 (22.0)
Acute lymphocytic leukaemia	7 (4.8)	5 (3.5)
Hodgkin's disease	2 (1.4)	3 (2.1)
Osteosarcoma	2 (1.4)	1 (0.7)
Anaplastic large-cell lymphoma	0	2 (1.4)
B precursor type acute leukaemia	1 (0.7)	1 (0.7)
Craniopharyngioma	1 (0.7)	1 (0.7)
Haemangioma	1 (0.7)	1 (0.7)
Lymphangioma	1 (0.7)	1 (0.7)
Non-Hodgkin's lymphoma	1 (0.7)	1 (0.7)
Precursor B-lymphoblastic lymphoma	2 (1.4)	0
T-cell type acute leukaemia	1 (0.7)	1 (0.7)
Adrenocortical carcinoma	0	1 (0.7)
Anaplastic astrocytoma	0	1 (0.7)
Bone giant cell tumour	0	1 (0.7)
Brain neoplasm benign	0	1 (0.7)
Brain neoplasm malignant	0	1 (0.7)
Diffuse large B-cell lymphoma	1 (0.7)	0
Embryonal rhabdomyosarcoma	0	1 (0.7)
Ewing's sarcoma	0	1 (0.7)
Germ cell neoplasm	1 (0.7)	0
Histiocytic necrotising lymphadenitis	0	1 (0.7)
Hodgkin's disease nodular sclerosis	1 (0.7)	0
Langerhans' cell histiocytosis	0	1 (0.7)
Leukaemia	1 (0.7)	0
Medullary thyroid cancer	1 (0.7)	0
Medulloblastoma	0	1 (0.7)
Metastases to bone	0	1 (0.7)
Metastases to kidney	0	1 (0.7)
Metastases to lung	0	1 (0.7)
Metastases to meninges	0	1 (0.7)
Metastases to pleura	1 (0.7)	0
Metastases to spine	1 (0.7)	0
Neurofibrosarcoma	0	1 (0.7)
Ocular neoplasm	0	1 (0.7)
Optic glioma	1 (0.7)	0

CSR = clinical study report; mITT = Modified Intent-to-Treat; SOC = standard of care

Note: Percentages are based on the total number of subjects randomised to the particular group.

Source: Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.1.2.4](#)

Table 16: Listing of Subjects Treated with Other Antineoplastic Agents (Prior or Concomitant Administration) in Study U312 (mITT Analysis Set)

Subject	Other Antineoplastic Agents
Edoxaban group	
Case 1	Pegaspargase and crisantaspase
Case 2	Cisplatin
Case 3	Cisplatin
Case 4	Hydroxycarbamide
Case 5	Asparaginase, imatinib, and dasatinib
Case 6	Cisplatin, carboplatin
Case 7	Cisplatin
Case 8	Asparaginase
Case 9	Asparaginase
Case 10	Asparaginase
Case 11	Asparaginase
Case 12	Asparaginase, pegaspargase, and rituximab
Case 13	Rituximab
Case 14	Asparaginase and pegaspargase
Case 15	Asparaginase and pegaspargase
Case 16	Asparaginase
SOC group	
Case 17	Pegaspargase
Case 18	Hydroxycarbamide and imatinib
Case 19	Mitotane, topotecan, and cisplatin
Case 20	Carboplatin
Case 21	Carboplatin
Case 22	Cisplatin
Case 23	Cisplatin
Case 24	Pegaspargase
Case 25	Pegaspargase
Case 26	Carboplatin
Case 27	Asparaginase
Case 28	Asparaginase

CSR = clinical study report; mITT = Modified Intent-to-Treat; SOC = standard of care

Source: Module 5.3.5.1 DU176b-D-U312 CSR [Listing 16.2.3.5](#)

Table 17: Subjects Treated with Asparaginase, Pegaspargase, or Crisantaspase (Prior or Concomitant Administration) in Study U312 (mITT Analysis Set)

	Edoxaban (N = 145)	SOC (N = 141)
Prior treatment with		
Asparaginase	6 (4.1)	1 (0.7)
Pegaspargase	3 (2.1)	1 (0.7)
Concomitant treatment with		
Asparaginase	5 (3.4)	1 (0.7)
Pegaspargase	3 (2.1)	3 (2.1)
Crisantaspase	1 (0.7)	0

CSR = clinical study report; mITT = Modified Intent-to-Treat; SOC = standard of care

Note: Percentages are based on the total number of subjects randomised to the particular group.

Source: Module 5.3.5.1 DU176b-D-U312 CSR [Table 14.1.2.5](#), [Table 14.1.2.6](#)

b. Recurrent VTE events and Major/CRNM Bleeding for Important Subgroups in Study U312

Results for the requested subgroups are summarised in [Table 18](#) for confirmed symptomatic recurrent VTE and in [Table 19](#) for major and CRNM bleeding. Due to the low number of subjects with events, it was not possible to draw any conclusions for either symptomatic recurrent VTE or major or CRNM bleeding events across the subgroups.

Table 18: Adjudication-confirmed Symptomatic Recurrent VTE in the Main Treatment Period by Important Subgroups – Study U312 (mITT Analysis Set)

	Edoxaban (N = 145)	SOC (N = 141)	HR (95 % CI) ^a
Symptomatic recurrent VTE (n, %)	5 (3.4)	2 (1.4)	
Age cohort			
<2 years	1 (0.7)	0	NA
2 to <6 years	0	0	NA
6 to <12 years	1 (0.7)	1 (0.7)	NA
12 to <18 years	3 (2.1)	1 (0.7)	0.41 (0.063, 2.636)
Index event location			
PE only	1 (0.7)	1 (0.7)	NA
DVT only			
DVT upper extremities	1 (0.7)	0	NA
DVT lower extremities	3 (2.1)	0	NA
PE with DVT			
DVT lower extremities	0	1 (0.7)	NA
Type of index DVT			
Catheter-related	1 (0.7)	0	NA
Not catheter-related	3 (2.1)	1 (0.7)	0.41 (0.063, 2.636)
Missing	1 (0.7)	1 (0.7)	NA

	Edoxaban (N = 145)	SOC (N = 141)	HR (95 % CI) ^a
Risk factor			
Persistent	4 (2.8)	0	NA
Transient	1 (0.7)	2 (1.4)	NA
Cancer			
Yes	2 (1.4)	0	NA
No	3 (2.1)	2 (1.4)	1.00 (0.096, 10.368)
Central venous catheter			
Yes	1 (0.7)	0	NA
No	4 (2.8)	2 (1.4)	0.71 (0.033, 15.302)

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; mITT = Modified Intent-to-Treat; NA = not available; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism

^a Edoxaban-to-SOC HR based on the Cox proportional hazards regression model including treatment and age group as covariates.

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

Table 19: Adjudicated Major and CRNM Bleeding in the Main Treatment Period by Important Subgroups – Study U312 (mITT Analysis Set)

	Edoxaban (N = 145)	SOC (N = 141)	HR (95 % CI) ^a
Confirmed bleeding events			
Major or CRNM bleeding	3 (2.1)	5 (3.5)	0.58 (0.137, 2.420)
Major bleeding ^b	1 (0.7)	0	NA
CRNM bleeding ^b	3 (2.1)	5 (3.5)	0.57 (0.136, 2.400)
Age cohort			
<2 years	1 (0.7)	1 (0.7)	0.98 (0.143, 6.787)
2 to <6 years	0	1 (0.7)	NA
6 to <12 years	0	0	NA
12 to <18 years	2 (1.4)	3 (2.1)	0.78 (0.236, 2.598)
Risk factor			
Persistent	2 (1.4)	1 (0.7)	2.02 (0.417, 9.839)
Transient	1 (0.7)	4 (2.8)	0.25 (0.050, 1.215)
Cancer			
Yes	1 (0.7)	1 (0.7)	1.65 (0.287, 9.467)
No	2 (1.4)	4 (2.8)	0.46 (0.132, 1.564)
Central venous catheter			
Yes	1 (0.7)	0	NA
No	2 (1.4)	5 (3.5)	0.39 (0.119, 1.267)

CI = confidence interval; CRNM = clinically relevant nonmajor; HR = hazard ratio; mITT = Modified Intent-to-Treat; NA = not available; SOC = standard of care

^a Edoxaban-to-SOC HR based on the Cox proportional hazards regression model including treatment and age group as covariates.

^b Case 11 had multiple separate events of Epistaxis: 1 was adjudicated as Major bleeding, and 2 were adjudicated as CRNM bleeding.

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

REFERENCES

Not applicable.

Assessment of the WSA's response

Approximately 19.3% of children in the edoxaban group and 22% in the SOC group had a medical history of neoplasms. Overall, 6.9% of subjects in the edoxaban group and 3.5% of subjects in the SOC group had received asparaginase (or pegaspargase). Results for the requested subgroups have been summarised in Table 16 (documented symptomatic recurrent VTE) and in Table 17 (major and CRNM bleeding). Some HRs in Table 16 seem to be inconsistent with events rates used, but these calculations are not relevant for the application. Due to the low number of subjects with events, it is not possible to draw any conclusions for either symptomatic recurrent VTE or major or CRNM bleeding events across the subgroups. Therefore, the issue is no further pursued.

Conclusion

Issue solved

Question 16. The net clinical benefit analysis (Table 3.16 of the summary of clinical efficacy) disfavoured edoxaban in study U312, but looking at the VTE events, major bleeding and CRNM bleeding events described in other sections, numbers were numerically lower in the edoxaban group versus SOC. Please, explain this apparent discrepancy.

Summary of the WSA's response

The noted discrepancies are due to the different periods considered most appropriate for the various endpoints.

- The primary efficacy events were summarised for the Main Treatment Period (defined as from randomisation to the Month 3 visit + 3 days).
- Major and CRNM bleeding was summarised for the Main Treatment Period and on-treatment, where on-treatment was defined as on study drug, within 3 days of study drug interruption, discontinuation and last dose of study drug.
- The net clinical outcome analysis considers the Overall Treatment Period (from randomisation to the date of the last dose of study drug + 30 days) and therefore includes the primary efficacy events that occurred during the extension period, during periods of drug interruptions of more than 3 days, or during the additional 27 days after the last dose of study treatment compared with the analyses of the primary efficacy and safety events.

The major driver for the different results between the net clinical outcome and the primary safety and efficacy endpoints was an additional 5 subjects in the edoxaban group with major or CRNM bleeding that occurred during the extension period, and 2 subjects in the edoxaban group with major or CRNM bleeding that occurred while the subjects were not on-treatment ([Table 20](#)).

Table 20: Summary of Components of Primary Efficacy and Safety Endpoints

Endpoint (Analysis Set)	Period Components	Edoxaban (N = 145)	SOC (N = 141)
Composite endpoint (consisting of symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden [MITT])	Main Treatment Period	26 (17.9)	31 (22.0)
	Symptomatic recurrent VTE (n, %)	5 (3.4)	2 (1.4)
	PE nonfatal	0	1 (0.7)
	DVT nonfatal	4 (2.8)	0
	Unexplained death for which VTE cannot be ruled out (n, %)	1 (0.7)	1 (0.7)
	No change or extension of thrombotic burden based on imaging	21 (14.5)	29 (20.6)
Major and CRNM bleeding (safety, same as MITT)	Main Treatment Period and on-treatment	3 (2.1)	5 (3.5)
Net clinical benefit (MITT)	Overall Treatment Period	16 (11.0)	7 (5.0)
	Subjects with symptomatic recurrent VTE (n, %)	6 (4.1)	1 (0.7)
	Subjects with death as a result of VTE (n, %)	1 (0.7)	1 (0.7)
	Subjects with major bleeding (n, %)	2 (1.4)	0
	Subjects with CRNM bleeding (n, %)	9 (6.2)	5 (3.5)
	Subjects with major and CRNM bleeding (n, %)	10 (6.9)	5 (3.5)

CRNM = clinically relevant nonmajor; DVT = deep vein thrombosis; MITT = modified intent-to-treat; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolic event

Note: For the composite endpoint of symptomatic VTE, death is counted among recurrent VTE. For net clinical benefit deaths are not counted as symptomatic recurrent VTE but are summarised separately.

REFERENCES

Not applicable.

Assessment of the WSA's response

The MAH has clarified that the noted discrepancies are due to the different periods considered most appropriate for the various endpoints. The major driver for the different results between the net clinical outcome and the primary safety and efficacy endpoints was an additional 5 subjects in the edoxaban group with major or CRNM bleeding that occurred during the extension period, and 2 subjects in the edoxaban group with major or CRNM bleeding that occurred while the subjects were not on-treatment (see also assessment of Q18).

Conclusion

Issue solved.

Question 17. In study U313 the results seem worse for patients who switched from SOC to edoxaban (i.e.: SOC-edoxaban arm) than for those who continued with edoxaban since the start of the study (i.e.: edoxaban-edoxaban arm). Please discuss whether switching from edoxaban to SOC could be inappropriate for patients well controlled on SOC.

Summary of the WSA's response

The design of the Study U313 protocol was randomisation for the main period to either edoxaban or SOC. All subjects who entered the extension period were given edoxaban for the duration of the extension period (Protocol Version 3.0). Subjects who enrolled in the protocol earlier than Version 3.0 and continued to the extension period with SOC anticoagulants were given edoxaban once the site approved Protocol Version 3.0. The intent of the extension period was to gather additional safety data on edoxaban (Study U313 CSR Section 6.1.2).

For the efficacy endpoints during the Main Treatment Period, 1 (1.7%) subject in the SOC treatment group experienced 2 TE (annualised rate of 0.07). These events were a DVT with a PE. During the extension period + 30-day follow-up, 5 subjects experienced TEs; 2 subjects experienced an adjudication-confirmed stroke, 2 subjects experienced an MI, and 1 subject experienced intracardiac thrombus (Table 21). The events were a DVT with a PE.

The annualised rate of TE in the extension period of Study U313 was 0.06 events per year (including 1 subject who had not switched from SOC to edoxaban), which was similar to that reported for SOC during the Main Treatment Period (0.07 events per year). Therefore, the MAH considers that there is no evidence to suggest that switching from SOC to edoxaban would be inappropriate.

Table 21: Analysis of Adjudication-confirmed Secondary Efficacy Endpoints in Study U313 (mITT Analysis Set)

Endpoint	Statistics	Edoxaban	SOC
Main Treatment Period		(N = 109)	(N = 58)
TE, subjects with events	n (%)	0	1 (1.7)
	Annualised rate	0	0.07
	Rate difference (95% CI)	-0.07 (-0.22, 0.07)	
DVT	n (%)	0	1 (1.7)
PE	n (%)	0	1 (1.7)
Death as a results of TE	n (%)	0	0
All-cause mortality	n (%)	0	0
Extension Period + 30 days follow-up		(N = 144)	
TE, subjects with events	n (%)	5 (3.5)	
	Annualised rate	0.06	
Stroke	n (%)	2 (1.4)	
Intracardiac thrombus	n (%)	1 (0.7)	
MI	n (%)	2 (1.4)	
Death as a results of TE	n (%)	0	
All-cause mortality	n (%)	2 (1.4)	
	Annualised rate	0.03	

CI = confidence interval; CSR = clinical study report; DVT = deep vein thrombosis; MI = myocardial infarction; mITT = modified intent-to-treat; PE = pulmonary embolism; SAP = statistical analysis plan; SEE = systemic embolic event; SOC = standard of care; TE = thromboembolic event.

Notes: TEs included DVT, PE, stroke, SEE, intracardiac thrombus, MI, asymptomatic intracardiac thrombus identified by cardiac imaging, and death as a result of TE.

Annualised rate = number of subjects with event/total time at risk (years). Total time at risk is the sum, across subjects, of the number of "at risk" years. For each subject, the "at risk" years = (the event or censoring – date of randomisation + 1)/365.25. If a subject has multiple events, the time of the first event is used.

The 95% CI for rate difference was calculated by using Wald's method. Details are described in the SAP Addendum (27 Jul 2020).

The extension period is defined as from the day after the Month 3 Visit to the date of the last dose of study drug.

Source: Module 5.3.5.1 DU176b-C-U313 CSR Table 14.2.1.1, Table 14.2.1.2.

Details of the 5 subjects developing TE events during the extension period +30 days follow-up are presented in the detailed narrative in Module 5.3.5.1 DU176b-C-U313 CSR Section 14.3.3.

It should be noted that all subjects who developed the events in the Extension Period developed due to the progression of their underlying medical conditions transitioning from SOC to edoxaban and can be explained by the following:

- Development of MI in patients with Kawasaki's disease, a known complication irrespective of the anticoagulant therapy
- Subjects with congenital tricuspid valve atresia, transposition of the great vessels, Fontan surgery, and basal ganglia infarction, subject developing cerebellar infarction (acute infarction of the left cerebellar hemisphere and right inferior occipital lobe, and vermis)
- Subject with Fontan surgery, pulmonary atresia with intact septum, partial cavopulmonary bypass, intraventricular right thrombus, cerebral thrombosis, embolic stroke, and total cavopulmonary bypass developing severe right atria thrombosis.

Due to the rarity of the TE phenomenon in this patient population, TE episodes during the extension period were rare. This study was unique as a substantial portion of the cohort were at risk for arterial thrombosis within GCA. These GCA's are themselves relatively rare in the Kawasaki disease population (4 to 8%) treated during the acute episodes with intravenous gamma globulin. The development of intimal hyperplasia primarily at the proximal and distal ends of the GCA exacerbates abnormal fluid haemodynamics, which promotes clotting. Thus, patients with GCA carry the highest risk classification for the development of coronary artery thrombosis and myocardial ischaemia and or infarction. In this study, 2 subjects with GCA at very high risk developed treatment emergent TE episodes both with MI during the extension period. There was no comparative SOC group. However, an observational study showed that the cumulative incidence of coronary artery thrombosis with LMWH was $5.7 \pm 3.0\%$, with warfarin $6.7 \pm 3.7\%$, and with no anticoagulation $20.6 \pm 3.0\%$ ($P < 0.001$) at 2.5 years after the start of thromboprophylaxis.⁰ Thus, the incidence of coronary artery thrombosis in subjects with GCA in the extension period falls within these parameters.

The Study U313 trial results should be considered with respect to study limitations. Due to the rarity of heart disease in children compared to adult populations, the study was not adequately powered for any efficacy assessment. For the same reason, the study cohort was heterogenous and subjects with varying types of heart disease were included. Although enrolment was stratified for specific diagnoses to maintain similarity between treatment groups in the main period, subgroups were too small for reliable independent analyses. Furthermore, thrombosis risk varies substantially among these subgroups.

Overall, Study U313 showed high tolerability in children without major bleeding and showed rare occurrence of thrombosis in patients on warfarin-maintained INR within therapeutic range only 40% of the time, similar to findings in other studies. Of note, all reported events were unrelated to the study medication but were attributed to progression of the underlying medical condition. Switching from

SOC treatment to edoxaban in the extension period did not result in any increased reporting of the TE events.

REFERENCES

Manlhiot C, Newburger JW, Low T, et al. Low-molecular-weight heparin vs warfarin for thromboprophylaxis in children with coronary artery aneurysms after kawasaki disease: a pragmatic registry trial. *Can J Cardiol.* 2020;36(10):1598-607.

Assessment of the WSA's response

The MAH has provided brief narratives of the 5 subjects developing TE events during the extension period +30 days follow-up in study U313. All reported events were unrelated to the study medication but were attributed to progression of the underlying medical condition. Therefore, it is unlikely that switching from SOC treatment to edoxaban in the extension period is the fundamental cause of the increased reporting in TE events.

Conclusion

Issue solved.

SAFETY

Question 18. In Study U312, a total of 3 (2.1%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudication confirmed major and CRNM bleeding event during the Main Treatment Period and On-treatment (HR: 0.60, 95% CI: 0.139, 2.597). On the contrary, during the Overall Treatment Period, 10 (6.9%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudication confirmed major/CRNM bleeding event (HR: 1.85, 95% CI: 0.637, 5.370), which means that during follow-up there were 7 major/CRNM bleedings in the edoxaban group and none in the SOC group. Please discuss whether the risk of bleeding with edoxaban could be time-varying and try to identify any other cause that could explain this finding.

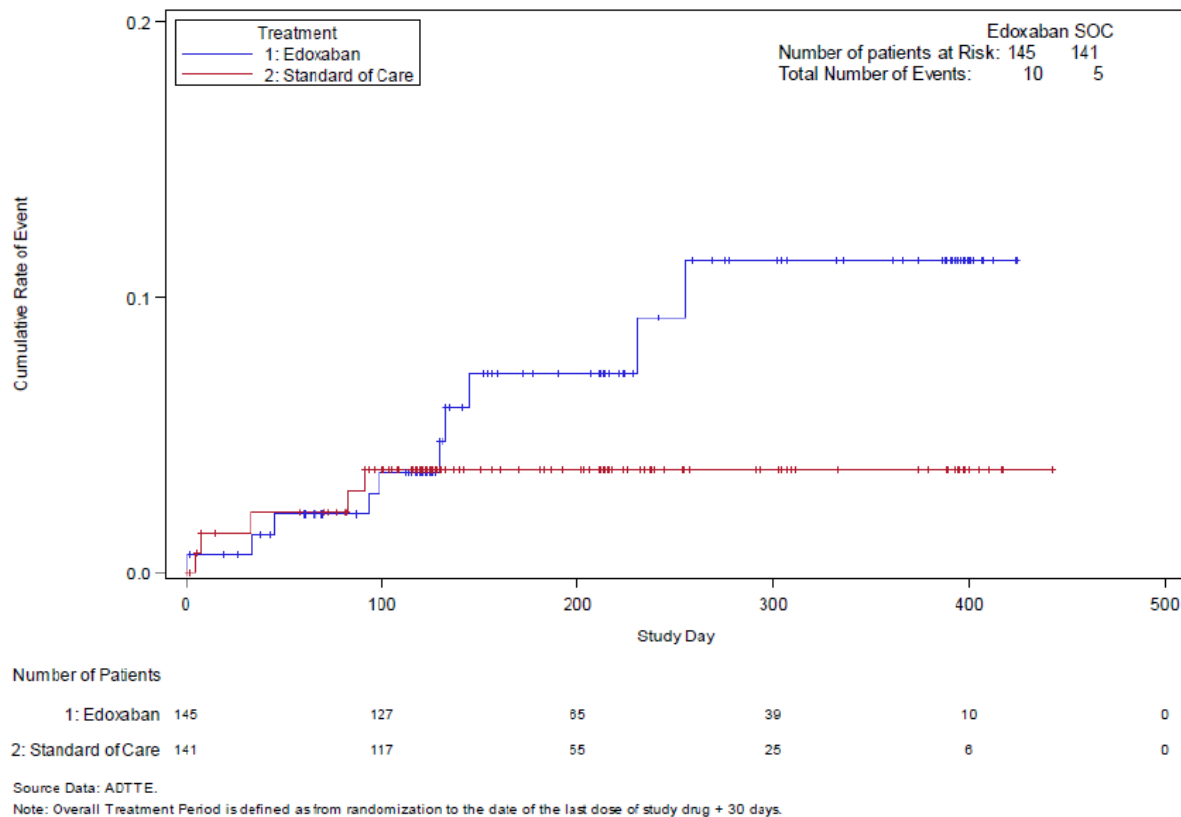
Summary of the WSA's response

The results of the safety analysis for Study U312 revealed that during the Main Treatment Period (from randomisation to Month 3 visit + 3 days) and On-treatment, at least 1 adjudication-confirmed major and CRNM bleeding event occurred in 3 subjects in the edoxaban group and in 5 subjects in the SOC group. Meanwhile, there were 10 subjects in the edoxaban group and 5 subjects in the SOC group who experienced at least 1 adjudication-confirmed major/CRNM bleeding event during the Overall Treatment Period (from randomisation to the date of the last dose of study drug + 30 days, which therefore includes the extension period, periods of drug interruptions of more than 3 days, and the additional 27 days after the last dose of study drug).

With increasing duration, over the study period, a higher incidence of bleeding events was observed with edoxaban than with SOC. However, compliance data indicated that compliance with edoxaban dosing was higher than with SOC. For the edoxaban group, 92.4% of subjects had 80% to 120% treatment compliance during the Overall Treatment Period ([Table 14.1.4.1](#)). For the 38 subjects who received treatment with warfarin, a mean percent time of 44.5% was within the INR therapeutic range of 2.0 to 3.0, approximately 46% was within the INR ranges of >2.0, and approximately 9% had an INR range >3.0 ([Table 14.1.4.3](#)). For the 52 subjects who received treatment with enoxaparin, the mean percent times with anti-FXa levels of <0.5, 0.5 to 1.0, and >1.0 were 24.98%, 59.48%, and 15.54%, respectively ([Table 14.1.4.4](#)).

Figure 1 shows the rate of major and CRNM bleeding events over the course of the study days for edoxaban and SOC treatments. During periods of edoxaban interruption or after discontinuation by the investigator for TE events, subjects were prescribed other anticoagulants (ie, LMWH or unfractionated heparin). Thus, safety endpoints were assessed using the On-treatment Period to allow an assessment of the relationship of the event to edoxaban.

Figure 1: Kaplan-Meier Plot for Time to First Event of Major and CRNM Bleeding Event – Overall Treatment Period



CRNM = clinically relevant non-major; SOC = standard of care

The Overall Treatment Period covers the period from randomisation to the date of the last dose of study drug (Main Treatment Period and Extension Period) plus 30 days (Follow-up).

Review of the patient profiles and of the details of the bleeding events allows allocation of the occurrence of major/CRNM bleeding events by period. Most of the identified bleeding events were assessed as not related to edoxaban.

- In the edoxaban group, during the Main Treatment Period, a total of 5 major/CRNM bleeding events occurred in 3 subjects. During the Extension Period (treatment from the end of the Main Treatment Period in Month 3 up through the end of Month 12), a total of 6 major/CRNM bleeding events occurred in 6 subjects during the edoxaban treatment. In the Follow-up period, 2 major/CRNM bleeding events occurred in 2 subjects (approximately 100 days after the last dose of edoxaban). One subject had major/CRNM bleeding events in the Main Treatment Period and in the Extension Period.
- In the SOC group, 5 major/CRNM bleeding events occurred in 5 subjects during the Main Treatment Period. No major/CRNM bleeding events occurred in the Extension Period or Follow-up period in the SOC group.

The number of subjects in the Safety Analysis Set completing the study (Treatment Period plus 30-day Follow-up or Main Treatment Period and Extension Period plus 30-day Follow-up) was higher in the edoxaban group: 131 subjects (90.3%) compared with 119 subjects (84.4%) in the SOC group. The same was true for the number of subjects completing the 3-month Main Study Period, the Extension Period, and the 30-day Follow-up: 77 subjects (53.1%) in the edoxaban group compared with 64 subjects (45.4%) in the SOC group.

Thus, in the edoxaban group, more subjects were included in the Overall Treatment Period. As shown in [Figure 1](#), at each time point from Study Day 100, more subjects were treated with edoxaban than with SOC. This may be a reason for more major/CRNM bleeding events with edoxaban in the Overall Treatment Period.

Analysis of the subjects' profile data (eg, medical history and concomitant medications) did not reveal any abnormalities or patterns that could explain the increased major/CRNM bleeding events with edoxaban that occurred after the Main Treatment Period. Although as was reported in the U312 CSR, subjects in the edoxaban group were sicker subjects than those in the SOC group (history of metastatic malignancy or underlying medical conditions predisposing them to an increased risk of developing TE events). The higher level of compliance with edoxaban compared with SOC may also have contributed to the higher number of major/CRNM bleeding on edoxaban.

During the Main Treatment Period, a change of study drug dosing (study drug interrupted or discontinuation of the drug) was required for 4 of the 5 major/CRNM bleeding events in the SOC group. In the edoxaban group, only one (tracheal bleeding, assessed as not related) of the 5 major/CRNM bleeding events during the Main Treatment Period required a change of study drug dosing (study drug interrupted). Amongst the additional major/CRNM bleeding events in the edoxaban group after the Main Treatment Period and during Extension Period or Follow-up, only 2 of the total 8 major/CRNM bleeding events required interruption of the study drug. The drug interruptions due to these events were brief, and in both cases, edoxaban was resumed after the events subsided. Of note, the 2 affected subjects were taking concomitant medications that may have contributed to an increased risk of bleeding (Clexane [enoxaparin sodium] and acetylsalicylic acid).

Although major/CRNM bleeding events were slightly lower in the edoxaban group compared with the SOC group in the Main Treatment Period of Study U312 (3 vs 5 events, respectively), major/CRNM bleeding events occurred more frequently with edoxaban compared with SOC in the Extension Period (6 vs 0 [1 of these subjects had also experienced a CRNMB in the Treatment Period]). Two subjects had major CRNMB in the follow-up period. However, the type and location of the major/CRNM bleeding events varied, and these events were not considered severe enough to warrant discontinuation of study medication. A time-varying risk of bleeding with edoxaban could not be confirmed based on the data presented. This is in line with data from other studies, such as ENGAGE AF-TIMI 48 with a mean study drug exposure of 806 days in the edoxaban 60 mg group or post-authorisation safety study ETNA-AF Europe, with a median treatment duration of 97.5 weeks during the 48-month follow-up period. There was no indication of an increased bleeding risk with longer duration of edoxaban treatment.

Assessment of the WSA's response

Major/CRNM bleeding events were slightly lower in the edoxaban group compared with the SOC group in the Main Treatment Period of Study U312 (3 vs 5 events, respectively), but major/CRNM bleeding events occurred more frequently with edoxaban compared with SOC in the Extension Period (6 vs 0 [1 of these subjects had also experienced a CRNMB in the Treatment Period]). However, the type and location of the major/CRNM bleeding events varied, and these events were not considered severe enough to warrant discontinuation of study medication, which is reassuring.

A potential explanation of the higher number of bleedings with edoxaban during the extension period is that treatment compliance was higher with edoxaban and also more patients completed the extension phase in the edoxaban group [77 subjects (53.1%) in the edoxaban group compared with 64 subjects (45.4%) in the SOC group]. Thus, in the edoxaban group, more subjects were included in the Overall Treatment Period. This may be a reason for more major/CRNM bleeding events with edoxaban in the Overall Treatment Period.

A time-varying risk of bleeding with edoxaban could not be confirmed based on the data presented. This is in line with data from other studies, such as ENGAGE AF-TIMI 48 with a mean study drug exposure of 806 days in the edoxaban 60 mg group or post-authorisation safety study ETNA-AF Europe, with a median treatment duration of 97.5 weeks during the 48-month follow-up period. There was no indication of an increased bleeding risk with longer duration of edoxaban treatment.

Conclusion

Question 19. There were two children with Kawasaki disease in the U313 study that developed MI considered related to study medication by the investigator (one subject: warfarin 3 mg switched to edoxaban 45 mg during extension treatment; one subject: SOC 31 mg, active ingredient not defined, followed by edoxaban dose, not recorded in the narrative). The events are poorly documented with respect to study medications, doses and narratives. Please provide narratives including study medications and doses given at the start of the trial and former medications the patients were taken at the onset of the MI. An assessment by the Sponsor about causality relationship should also be tempted including a discussion about a potential relationship between edoxaban and MI from adult and paediatric studies.

Summary of the WSA's response

Overall Discussion:

Due to the rarity of the TE phenomenon in this patient population, TE episodes during the extension period were rare. This study was unique as a substantial portion of the cohort were at risk for arterial thrombosis within giant coronary aneurysms (GCAs). These GCAs are themselves relatively rare in the Kawasaki disease (4% to 8%) population treated during the acute episodes with intravenous gamma globulin. Development of intimal hyperplasia primarily at the proximal and distal ends of the GCA exacerbates abnormal fluid haemodynamics, which promotes clotting. Thus, patients with GCA carry the highest risk classification for development of coronary artery thrombosis and myocardial ischemia and/or infarction. In this study, two GCA patients at very high risk developed treatment-emergent TE episodes both with MI during the extension study.

There was no comparative SOC group. However, an observational study showed that cumulative incidence of coronary artery thrombosis with LMWH was $5.7\% \pm 3.0\%$, with warfarin was $6.7\% \pm 3.7\%$, and with no anticoagulation was $20.6 \pm 3.0\%$ ($P < 0.001$) at 2.5 years after the start of thromboprophylaxis (Manlhoit et al., 2020). Thus, incidence of coronary artery thrombosis in the GCA patients in the extension study falls within these parameters.

The paediatric study, Study DU176b-C-U313, was an open-label, randomised, parallel-group, observational study to evaluate the safety and efficacy of edoxaban as a prophylaxis treatment in children with cardiac diseases at risk of TE. The Study U313 paediatric study results should be considered with respect to study limitations. Due to the rarity of heart disease in children compared to adult populations, the study was not adequately powered for efficacy. For the same reasons, the study cohort was heterogeneous and patients with varying types of heart disease were included. Although enrolment was stratified for specific diagnoses to maintain similarity between treatment groups in the main period, subgroups were too small for reliable independent analyses. Furthermore, thrombosis risk varies substantially among these subgroups.

The adult study, DU176b-C-U301 (Study U301) entitled "ENGAGE AF-TIMI 48," was a Phase 3, randomised, double-blind, double-dummy, parallel-group, multicentre, multinational study for the evaluation of the efficacy and safety of edoxaban versus warfarin in subjects with atrial fibrillation effective anticoagulation with FXa next generation in atrial fibrillation. The primary objective was to compare edoxaban to warfarin with regard to the composite primary endpoint of stroke and SEE. A secondary objective was the comparison of edoxaban to warfarin with regard to MACE, a composite of non-fatal MI, nonfatal stroke, nonfatal SEE, and death due to cardiovascular cause or bleeding, as well as each component separately.

Myocardial Infarction

In the Study U301 mITT analysis set Overall Study Period, fewer subjects in the edoxaban 60 mg group experienced an MI than the warfarin group (0.70% per year and 0.75% per year, respectively), with a HR of 0.94 (95% CI: 0.741, 1.190). For the mITT Analysis Set On-Treatment Period, the HR for MI was 0.84 (95% CI: 0.635, 1.120) for the edoxaban 60 mg group compared with the warfarin group (Table 2).

Table 2: Key Components of the Secondary Efficacy Endpoints in Study U301 (ENGAGE AF-TIMI 48)

First Event	Edoxaban 60 mg (30 mg Dose Adjusted)		Warfarin		Edoxaban 60 mg (30 mg Dose Adjusted) vs Warfarin	
	No. of Events	Event Rate (%/year) ^a	No. of Events	Event Rate (%/year) ^a	HR (95% CI)	P Value
ITT Analysis Set – Overall Study Period						
Number of subjects in	7035		7036			
MI	133	0.70	141	0.75	0.94 (0.741, 1.190)	0.6016
Fatal	18	0.09	17	0.09	1.05 (0.544, 2.046)	0.8751
Non-fatal	117	0.62	125	0.66	0.93 (0.724, 1.199)	0.5812
mITT Analysis Set – On-Treatment Period						
Number of subjects	7012		7012			
MI	88	0.57	105	0.68	0.84 (0.635, 1.120)	0.2398
Fatal	10	0.06	11	0.07	0.92 (0.390, 2.160)	0.8434
Non-fatal	78	0.50	94	0.60	0.84 (0.619, 1.128)	0.2398

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; MI = myocardial infarction; mITT = modified intent-to-treat; N = number of subjects; No. = number

^a The event rate (%/year) is calculated as the number of events / subject-year exposure.

Note: A subject can appear in multiple rows of this table (eg, MI and death).

Source: DU176b-C-U301 CSR Table 14.2.2.6, Table 14.2.2.8

Overall, the median age for the study population in Study U301 was 72 years, and the average CHADS2 score was 2.8, with prior medical history of stroke, hypertension, congestive heart failure, Type 2 diabetes mellitus, stroke, and hyperlipidaemia. The secondary efficacy endpoints demonstrated that subjects in the edoxaban 60 mg group had a reduced risk of experiencing the MACE events (HR 0.89, 95% CI: 0.806, 0.972) compared with subjects in the warfarin group. The MI events in adults could be attributed to aggravating factors such as history of hypertension, congestive heart failure, Type 2 diabetes mellitus, stroke, ischaemic heart disease, coronary heart disease, and hyperlipidaemia. In children, MI is related to the cardiac conditions including genetic disorders or illness such as Kawasaki disease leading to coronary aneurysm or Fontan's surgery.

REFERENCES

Manlhiot C, Newburger JW, Low T, et al. Low-molecular-weight heparin vs warfarin for thromboprophylaxis in children with coronary artery aneurysms after Kawasaki disease: a pragmatic registry trial. *Can J Cardiol*. 2020;36(10):1598-607.

Assessment of the WSA's response

The applicant has provided extensive narratives of two children with Kawasaki disease experiencing MI during the extension phase of study DU176b-C-U313, an open-label, randomised, parallel-group, observational study to evaluate the safety and efficacy of edoxaban as a prophylaxis treatment in children with cardiac diseases at risk of thromboembolism (TE).

This study was unique as a substantial portion of the cohort were at risk for arterial thrombosis within giant coronary aneurysms (GCAs). These GCAs are themselves relatively rare in the Kawasaki disease (4% to 8%) population treated during the acute episodes with intravenous gamma globulin.

Development of intimal hyperplasia primarily at the proximal and distal ends of the GCA exacerbates abnormal fluid haemodynamics, which promotes clotting. Thus, patients with GCA carry the highest risk classification for development of coronary artery thrombosis and myocardial ischemia and or infarction. The applicant states that the two patients with Kawasaki disease who experienced MI during the extension phase had concomitant GCA. Both patients were at very high risk developed treatment-emergent TE episodes both with MI during the extension study. There was no comparative SOC group during the extension phase. However, an observational study showed that cumulative incidence of coronary artery thrombosis with LMWH was $5.7\% \pm 3.0\%$, with warfarin was $6.7\% \pm 3.7\%$, and with no anticoagulation was $20.6 \pm 3.0\%$ ($P < 0.001$) at 2.5 years after the start of thromboprophylaxis (Manlhoit, et al, 2020). Thus, incidence of coronary artery thrombosis in the GCA patients treated with edoxaban in the extension phase of study U313 falls within these parameters, and no signal of increased risk of MI with edoxaban is apparent in children.

The adult study, DU176b-C-U301 (Study U301) entitled "ENGAGE AF-TIMI 48," (n=) included MACE events as secondary endpoints, and the subjects on the edoxaban 60 mg group had a reduced risk of experiencing the MACE events than those on the warfarin group (HR 0.89, 95% CI: 0.806, 0.972) compared with subjects in the warfarin group. Therefore, no signal of increased risk of MI with edoxaban is apparent also in adults.

Conclusion

Issue solved.

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

RMP aspects

N/A