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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Lixiana

Procedure no: EMEA/H/C/002629/P46/012

Roteas

Procedure no: EMEA/H/C/004339/P46/003

edoxaban

Note

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

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List of abbreviations

ABBREVIATION	DEFINITION
AE	Adverse event
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AUC	Area under the concentration-time curve
AUCinf	Area under the concentration-time curve from time 0 extrapolated to infinity
BID	Twice daily
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CL/F	Apparent systemic clearance (referred to as clearance from central compartment [CL] in the appended Population Pharmacokinetic Report)
CRF	Case Report Form (electronic or paper)
CSR	Clinical Study Report
CV	Coefficient of variation
CYP	Cytochrome P450
DSI	Daiichi Sankyo, Inc.
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
FXa	Activated factor X
GCP	Good Clinical Practice (refers to International Council for Harmonization and Code of Federal Regulations)
HPF	High power field
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous

LMWH	Low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
mo	Month
NR	Normal range
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PT	Prothrombin time
QD	Once daily
RBC	Red blood cell
RR	Reference range
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal
VAS	Visual analog scale
V/F	Apparent volume of distribution (referred to as central compartment volume [V1] in the appended Population Pharmacokinetic Report)
VTE	Venous thromboembolic event
WBC	White blood cell
yrs	Years

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1. Introduction

On 16 February 2021, the MAH submitted a completed paediatric study for edoxaban tosilate (Lixiana and its duplicate Roteas), in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

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

The Edoxaban Marketing Authorisation (Lixiana) was granted by the European Commission (EC) on 19 Jun 2015. In addition, Roteas was approved on 19 Apr 2017 as informed consent approval to Lixiana.

Edoxaban is currently approved in the EU as film-coated tablets for oral use for the following indications:

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

The recommended dose in adults with NVAF and venous thromboembolism (DVT and PE) is 60 mg of edoxaban once daily. A dose recommendation of 30 mg edoxaban once daily is addressed to adult patients with one or more of the following clinical factors: moderate or severe renal impairment (creatinine clearance [CrCl] 15 – 50 mL/min), low body weight (≤60 kg), and concomitant treatment with P-glycoprotein (P-gp) inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole). Edoxaban 15 mg is not indicated as monotherapy, as it may result in decreased efficacy. It is only indicated in the process of switching from edoxaban 30 mg to Vitamin K antagonist (VKA), together with an appropriate VKA dose.

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0028/2014 on the agreement of a paediatric investigation plan (PIP). According to the last PIP modification (EMEA-000788-PIP02-11-M11), the agreed PIP for edoxaban as film-coated tablet and age-appropriate oral dosage form for the prevention of arterial thromboembolism and the prevention and treatment of venous thromboembolism conditions, includes the following 3 clinical studies:

- For the acute treatment and secondary prevention of symptomatic recurrent venous thrombotic events (VTE) in paediatric patients at risk (paediatric population with confirmed VTE)

  - Supportive Phase 1 Study DU176b-A-U157 (hereafter referred to as Study U157; Study 13 in the PIP). Completed.

  - Pivotal Phase 3 Study DU176b-D-U312 (Hokusai VTE Pediatric Study, hereafter referred to as Study U312; Study 11 in the PIP). Ongoing.

- For the prevention of arterial thromboembolism in paediatric cardiac patients at risk of thrombotic events indication (paediatric population with cardiac diseases at risk of thromboembolic events) Phase 3 Study DU176b-C-U313 (ENNOBLE-ATE, hereafter referred to as Study U313; Study 10 in the PIP). Ongoing.

The number of enrolled subjects by age cohort in each of the 3 paediatric studies of the PIP is shown in Table 1. The Applicant plans to update the summary of product characteristics (SmPC) with results from these 3 studies in Quarter 4 of 2022.

Table 1: Enrolment by Age Cohort in Studies of the Paediatric Investigational Plan

Age Cohorts (age on the day of dosing)	**Number of Subjects[a]**		
	Study U157	**Study U312**	**Study U313**
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
1 to <2 years of age	NA	NA	9
6 months to <2 years of age	13	29	NA
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**

[a] Enrolment was closed for all studies.

In accordance with Article 46 of the regulation (EC) No. 1901/2006, Daiichi Sankyo Europe GmbH hereby submits to the EMA a final study report for the study number DU176b-A-U157, which is part of the PIP EMEA-000788-PIP02-11-M11 (PIP Study 13). In addition, the results of the population-based pharmacokinetic (PopPK) model to predict the dose in the single-dose Study U157 are included in Appendix 16.1.13 of the clinical study report. This modelling study refers to PIP Study 14.

The MAH stated that the study DU176b-A-U157 “A Phase 1, Open-label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients” is a stand alone study. As such, a line listing is not provided.

2.2. Information on the pharmaceutical formulation used in the study

Edoxaban (as tosilate) has been approved in the European Union for oral administration as film-coated tablets containing 15 mg, 30 mg or 60 mg of edoxaban. As stated in Section. 4.2. *Method of administration* of the approved SmPC: for patients who are unable to swallow whole tablets, edoxaban tablets may be crushed and mixed with water or apple puree and immediately administered orally (see Section 5.2). Alternatively, edoxaban tablets may be crushed and suspended in a small amount of water and immediately delivered through a gastric tube after which it should be flushed with water (see Section 5.2). Crushed edoxaban tablets are stable in water and apple puree for up to 4 hours.

In accordance with the CSR, the pharmaceutical formulations used in Study U157 were as follows:

- Edoxaban 15 mg or 30 mg oral tablets: for subjects in the 12 to <18 years age cohort.

- Edoxaban granules for oral suspension (60 mg reconstituted with water to provide a 6 mg/mL suspension for oral administration): for subjects <12 years.

Tablets used in Study U157 were the same as the tablets approved in the EU.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study DU176b-A-U157: "A Phase 1, Open-label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients".

2.3.2. Clinical study

Clinical study number DU176b-A-U157 (U157): "A Phase 1, Open-label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients"

Description

This was a Phase 1, open-label, non-randomized, multiple-center study to evaluate PK and PD (a dose-finding goal) and safety of edoxaban in paediatric patients (from 38 weeks gestational age to <18 years) with ongoing risk of thromboembolic events. Study U157 was a single-dose study with a sequential enrolment (from older to younger) and with 2 tested doses (a "low" dose to achieve exposures comparable to a 30 mg adult dose and a "high" dose to achieve exposures comparable to a 60 mg adult dose). The study included 5 paediatric age cohorts (12 to <18 years (yrs), 6 to <12 yrs, 2 to <6 yrs, 6 months (mo) to <2 yrs and 0 to <6 mo) with evaluation of 2 different doses within each age cohort (low and high dose). The pharmaceutical formulations used in Study U157 were edoxaban 15 mg or 30 mg oral tablets (for subjects in the 12 to <18 years age cohort) and edoxaban granules for oral suspension (60 mg reconstituted with water to provide a 6 mg/mL suspension for oral administration; for subjects <12 years).

Study duration was approximately 4 weeks for each patient, which included a screening period (within 21 days of dosing), a treatment period, and a follow-up visit conducted within 10 days after dosing. A patient was considered to have completed the study if he/she provided the last scheduled PK sample.

Methods

Study participants

Inclusion criteria

Male and female paediatric patients who might require or currently were on anticoagulant therapy were eligible for enrolment, including:

- Patients who had a recently acquired or Investigator determined ongoing risk of thromboembolic events (eg, patients with thrombophilia, congenital heart disease, presence of a central venous catheter, and prior VTE).
- Patients who were completing their standard-of-care anticoagulant therapy. Edoxaban could have been initiated 12 hours after cessation of enoxaparin, dabigatran, or apixaban therapy (A-U136, A-U151, and A-E152) and 24 hours after cessation of rivaroxaban therapy (A-U151). Note that the

dose of edoxaban should have been at the time of the next scheduled standard-of-care anticoagulant administration:

  - At least 4 hours after last dose of unfractionated heparin.
  - At least 12 hours after last dose of twice daily (BID) low molecular weight heparin (LMWH).
  - At least 24 hours after last dose of once daily (QD) LMWH and synthetic pentasaccharide FXa inhibitors.
  - For patients who had been on a prior VKA (eg, warfarin [C-U122] and any other anticoagulants) therapy, international normalized ratio (INR) value should have been 2.5 prior to edoxaban dosing. If the patient's INR was >2.5, the patient's INR should have been monitored until it was 2.5.

- Patients who had been currently treated for VTE with at least 5 days of heparin may have interrupted their standard-of-care anticoagulant therapy for edoxaban administration. The timing of the dose of edoxaban should have been:
  - At least 12 hours from last dose of BID LMWH, with a restart of LMWH 24 hours after edoxaban dose.
  - At least 24 hours from last dose of QD LMWH, with a restart of LMWH 24 hours after edoxaban dose.
- Patients with cardiac conditions who may have required anticoagulant therapy.
- Patients with sickle cell disease who may have required anticoagulant therapy.

For any condition, anticoagulant treatment interruption or discontinuation did not take place if the patient was at increased risk and interruption or discontinuation were appropriate as per standard-of-care practices.

Patients had to satisfy all of the following criteria to be included in the study. Any temporal changes in the following criteria that may have prohibited patient consideration, but should have normalized for future eligibility, were reassessed for the patient's future participation in the study:

1. Patients/legal guardian(s) had to be able to provide written informed assent (patient, when applicable) and ICFs (signed by parent/legal guardian) prior to participating in the study.

2. Male or female patients 38 weeks gestation to 18 years of age on the day of dosing.

3. Patients 2 to <18 years of age had to have a body mass index (BMI) between the 5th and 95th percentile based on the 2000 Centers for Disease Control and Prevention (CDC) Growth Charts (the maximum number of patients in each dose group that had a BMI between the 85th and 95th percentile should have not been more than 2 patients). Patients <2 years of age had to have a body weight between the 5th and 90th percentile based on the 2000 CDC Growth Charts.

4. Female patients who have had menarche had to test negative for pregnancy, as per local practice, at screening and check-in.

5. Female patients who have had menarche and were sexually active, had to agree to use an effective contraception method, per local practice, for at least 30 days prior to edoxaban dose.

6. Patients/legal guardian(s) had to agree to food and drug restrictions during the study.

- Patients had to agree to abstain from and/or legal guardians had to agree not to give the patient cola, tea, coffee, chocolate, and other caffeinated drinks and food from 48 hours before dose administration to until after the last PK sample collection.

Mothers who were breastfeeding study patients, should have maintained this same dietary restriction for 24 hours prior to edoxaban dosing.

- Patients had to agree to abstain from and/or legal guardian(s) had to agree not to give the patient St. John's Wort and food/supplements and beverages containing grapefruit, grapefruit juice, and Seville oranges from 14 days before the first dose through to until after the last PK sample collection.
- Patients had to agree to abstain from cytochrome P450 (CYP) 3A4 inhibitors/inducers and P-gp inhibitors/inducers for 14 days prior to the edoxaban dose to until after the last PK sample collection.

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

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

Exclusion Criteria

Patients who met any of the following criteria were disqualified from entering the study. Any temporal changes in the following criteria that may have prohibited patient consideration, but should have normalized for future eligibility, were reassessed for the patient's future participation in the study:

1. Patients with abnormal coagulation tests during screening, as defined by local laboratory reference ranges (RRs), which were not explained by anticoagulant therapy or temporary concomitant affections.

2. Patients with stroke where anticoagulant therapy was contraindicated.

3. Patients with stage 2 hypertension defined as blood pressure confirmed >99th percentile +5 mmHg.

4. Patients with renal function less than 50% of normal for age and size as determined by the National Kidney Disease Education Program version of the Schwartz formula.

5. Actively bleeding, had a high risk of bleeding, or had a history of major bleeding.

6. Had a currently active gastrointestinal ulceration or a known history of peptic ulcer or gastrointestinal bleeding (including hematemesis, melena, or rectal bleeding including bleeding from haemorrhoids) within the previous 3 months.

7. Had known diabetic retinopathy.

8. Had thrombocytopenia at screening ($<20 \times 10^9$/L).

9. Patients with history of major trauma, or major or invasive procedures within the last month prior to screening. Otherwise, shorter time was permitted depending on the surgery and based on the Investigator's judgment of bleeding risk.

10. Patients with known malabsorption disorders (eg, cystic fibrosis or short bowel syndrome).

11. Hepatic disease which was associated with coagulopathy leading to a clinically relevant bleeding risk, alanine transaminase (ALT) >5 times the upper limit of normal (ULN), or total bilirubin >2 times the ULN with direct bilirubin >20% of the total.

12. Patient was currently enrolled in another investigational device or drug study or was receiving other investigational agents. Patients had to complete the prior clinical study at least 30 days prior to dosing.

13. Patients of childbearing potential (post-menarche) who were sexually active and were not using approved contraception, per local practice; who were pregnant (as based on test results); or were breastfeeding.

14. Females with history of abnormal menses, including history of menorrhagia (heavy menstrual bleeding), metrorrhagia, or polymenorrhea.

15. Patient had known hypersensitivity to the active ingredient or any of the excipients of any compounds of the investigational product (IP).

16. Positive drug or alcohol screen (excluding cotinine) at screening for patients 12 years of age or older, neonates (0 to 28 days old), and for patients who were being breastfed. Exception to this was if patients were on prescription drug(s). The window to potentially hold and/or resume the prescription drug needed to be determined by DSI based on the information of the prescription drug.

17. Patients who had received a transfusion or any blood products within 30 days prior to the first dose.

18. Patients with any condition that, as judged by the Investigator, would have placed the patient at increased risk of harm if he/she participated in the study or would have interfered with the conduct of the study or the interpretation of the data.

19. Patients with a history of thrombosis who were diagnosed with antiphospholipid syndrome and were triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies).

Treatments

Subjects received a single dose of edoxaban only. The treatment period consisted of predose procedures occurring on Day -1 or 1, dosing on Day 1, and post dose procedures occurring post dose on Days 1 and 2 (all cohorts) and Day 3 (all patients enrolled prior to version 5.0 of the Protocol could have had Day 3 PK samples obtained).

Edoxaban dosing regimens for the different age groups were selected to achieve exposures comparable to adult doses of 60 mg (recommended dose) and 30 mg (dose reduction based on clinical factors), referred to as a high dose and a low dose regimen. The doses given to each age cohort and dose group were adjusted based on emerging data. The doses (mg/kg) for patients younger than 6 years were based on patients' body weight, as presented in Table 2.

Table 2: Edoxaban Dose by Cohort

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

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

Objectives

Primary objective

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

PK analysis objectives were:

- To establish a preliminary edoxaban population PK (PopPK) model in paediatric patients aged 0 to <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 the ongoing Phase 3 Study DU176b-A-U312.

Secondary Objectives

The secondary objectives of this study were as follows:

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

Exploratory Objectives

No exploratory objectives were planned for this study.

Study Hypothesis

The study was not intended to test a hypothesis but rather to generate information that would allow dose selection (comparable to the exposure of efficacious doses in adults) for subsequent clinical efficacy/safety Phase 3 studies in paediatrics.

Outcomes/endpoints

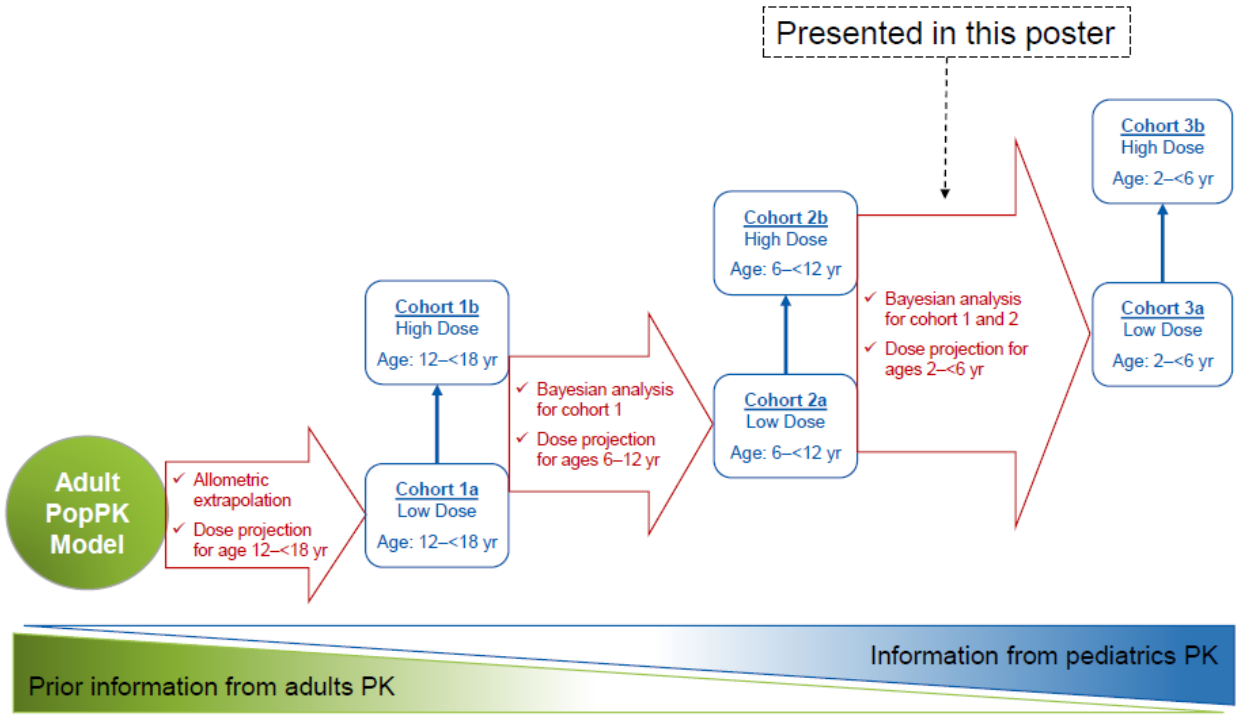
- *Pharmacokinetic/Pharmacodynamic Endpoints*

Drug concentrations and other pharmacokinetic endpoints

The PK endpoints included PopPK model-estimated PK parameters such as apparent systemic clearance (CL/F; also referred to as clearance from central compartment [CL]), apparent volume of distribution (V/F; also referred to as central compartment volume [V1]), and area under the concentration-time curve (AUC).

The current paediatric PopPK analysis used a Bayesian approach (software stan® with R package Torsten), incorporating the information from the PopPK model previously developed to describe edoxaban PK in adult subjects (Niebecker et al., 2015). Initially the adult PopPK model was modified to derive the PK model for paediatric 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.

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



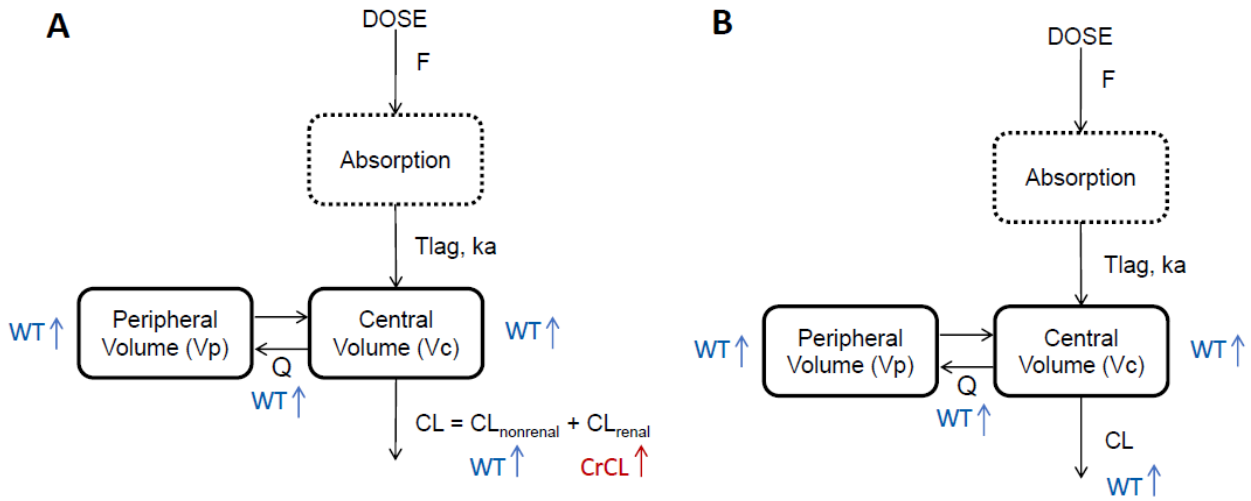
Source: Appendix 16.1.13

Model development for paediatric population

This preliminary PopPK analysis includes available PK data from the single-dose paediatric study DU176b-A-U157 and the ongoing multiple-dose paediatric study DU176b-A-U312 as of 03 Sep 2021. A final PopPK analysis will be conducted when both studies are completed. Bayesian estimation was conducted after each age cohort with available cumulative data from both paediatric studies and the dose projection was performed for the subsequent cohort in study DU176b-A-U157. Edoxaban exposure in the paediatric population was estimated using the individual PK parameters. The specific modeling/simulation procedure is briefly listed below:

• Step 1: Edoxaban adult PopPK model was modified by replacing the separate nonrenal and renal-clearance components with an overall clearance (CL) parameter to derive PK model for paediatrics (Figure 2). Differences in size was accounted for by allometry.

Figure 2: Transition from adult PK model (A) to the paediatric PK model (B)



CL, clearance from central compartment; CrCL, creatinine clearance; ka, oral absorption constant; PopPK, population pharmacokinetics; Q, compartmental clearance; Tlag, lag time; Vc, ventral compartment; Vp, peripheral compartment; WT, body weight.

Source: Appendix 16.1.13

The paediatric PopPK model was further modified to take into account ontogeny related to clearance mechanisms by incorporating maturation function that adjusts clearance by postmenstrual age (PMA) in weeks.

• Step 2: Edoxaban paediatric data from Studies DU176b-A-U157 and DU176b-A-U312 was fitted with the predefined model in Step 1 using a Bayesian approach.

• Step 3: The individual exposure (median and 90% CrI) was estimated using the post hoc parameter estimates. The exposures of the low and high dose group were compared with the exposure in the adult VTE subjects receiving 30 mg QD and 60 mg QD, respectively.

Appropriateness of the proposed paediatric dose

The model was also used to estimate individual paediatric subject exposures (area under the concentration time curve (AUC) from time 0 extrapolated to infinity, AUCinf) and compared to adult references (steady state AUC over the dosing interval) of 30 mg or 60 mg, depending on the dosage group, to assess whether the individual exposures are within the 90% confidence interval (CI) of the median target adult exposure. The appropriateness of the dose in an age cohort is assessed by comparing the median exposure in that dose group with the median adult exposure. If the median paediatric exposure was within the 0.5 to 1.5-fold of the adult VTE exposure at 60 mg QD dose, the paediatric dose was considered appropriate.

Pharmacodynamic Endpoints

The PD endpoints included observed, change from Baseline, and percent change from Baseline prothrombin time (PT), activated partial thromboplastin time (aPTT), and anti-FXa.

- *Efficacy Endpoints*

Not applicable.

- *Safety Endpoints*

Safety assessments included AEs; SAEs, TEAEs, and treatment-emergent SAEs (TESAEs); physical examination findings; vital signs; and standard haematology, clinical chemistry, and urinalysis laboratory tests.

Note: Urinalysis was performed with plastic bags with a sticky strip for neonates and infants with diapers.

- *Other Endpoints: Formulation Palatability*

Patients receiving the edoxaban granules for oral suspension formulation who were developmentally capable of providing an accurate response were asked to rate several aspects of palatability (including bitterness, sweetness, overall taste, and aroma) using a 100-millimeter visual analog scale (VAS). The VAS questionnaire was provided to the sites by Medpace.

Patients who were old enough scored the VAS themselves. For younger children, the parents provided this information, if possible. For the youngest children, there was free text input available to provide information on whether the patient spat it out or may not have liked the flavour, etc.

VAS and text responses were measured and/or recorded on the CRF.

Sample size

A total of 60 patients were to be enrolled, 12 evaluable patients per age cohort. Based on the assumptions of the inter-patient CV of 10.8% and 29.3% for CL/F and V/F, respectively, and the ratio of a younger age cohort to the reference age cohort (12 to <18 years) to be 1, a sample size of 12 evaluable patients per age cohort was to provide >95% power to assess that the 95% confidence interval (CI) for cohort to reference cohort ratio is contained within the 60% to 140% range for CL/F. This sample size was to provide about 76% power for the assessment of V/F. If emerging data suggested that the variability was much larger than anticipated, sample size could have been increased.

Randomisation and blinding (masking)

This was a non-randomized study. Blinding/masking methods were not applicable.

Statistical Methods

This was a Phase 1, open-label, single-dose, non-randomized, multiple-center study to evaluate PK and PD of edoxaban in paediatric patients. The analyses for this study were considered descriptive and exploratory. No visit windows were used for analyses.

In general, all data were summarized by age cohort and dose group, and all evaluable data were included in the analyses. For qualitative variables, the population size (N for sample size and n for available data) and the percentage/incidence (of available data) for each class of the variable are presented. Quantitative variables were summarized using descriptive statistics, including the population size (N for sample size and n for available data), mean, standard deviation (SD), median,

minimum, and maximum values. Coefficient of variation (CV), geometric mean, and geometric CV% were included for PK parameters.

Model-based approaches used for PK analysis are described in subsection *Drug Concentrations and Other Pharmacokinetic Endpoints.*

Interim Analyses and Data Monitoring

Emerging PK concentration-time data from completing patients were analyzed using model-based approaches on an ongoing basis and used to predict and optimize the doses required to obtain targeted exposures in upcoming age cohorts and dose groups.

Examination of Subgroups

The study included 5 paediatric age cohorts with evaluation of 2 different doses within each age cohort (low and high dose). In general, all data were summarized by age cohort and dose group, and all evaluable data were included in the analyses.

Analysis Sets

Pharmacokinetic Analysis Set

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

Pharmacodynamic Analysis Set

The PD Analysis Set comprised all patients who had received edoxaban as per Protocol and had at least 1 postdose PD measurement with known collection times and date/time of dose administration and Who did not have any clinically significant events or Protocol deviations that could have compromised the integrity of the PD results.

Safety Analysis Set

The Safety Analysis Set included all patients who had received edoxaban.

Results

Participant flow

A total of 66 patients was enrolled in the study, which were approximately evenly distributed among all age cohorts. In each age cohort, patients were approximately evenly distributed between both dosing groups. The dosing groups included 6 to 8 patients per group. All patients completed the last study visit.

Table 3 presents disposition of all patients who were enrolled in the study.

Table 3: Patient Disposition

Age	Cohorts 1a/1b		Cohorts 2a/2b		Cohorts 3a/3b		Cohorts 4a/4b		Cohort 5a/5b		
	12 to <18 yrs		6 to <12 yrs		2 to <6 yrs		6 mo to <2 yrs		0 to <6 mo		
Category	Low Dose (N=8) n (%)	High Dose (N=7) n (%)	Low Dose (N=7) n (%)	High Dose (N=6) n (%)	Low Dose (N=7) n (%)	High Dose (N=6) n (%)	Low Dose (N=7) n (%)	High Dose (N=6) n (%)	Low Dose (N=6) n (%)	High Dose (N=6) n (%)	Overall (N=66) n (%)
Enrolled											66
Safety Analysis Set[1]	8 (100.0)	7 (100.0)	7 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	66 (100.0)
PK Analysis Set[2]	8 (100.0)	7 (100.0)	7 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	66 (100.0)
PD Analysis Set[3]	8 (100.0)	7 (100.0)	7 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	66 (100.0)
Completed the last study visit	8 (100.0)	7 (100.0)	7 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	66 (100.0)
Withdrawal from the study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primary reason for withdrawal											
AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by patient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1. The Safety Analysis Set included all patients who received edoxaban.
2. The PK Analysis Set comprised all patients who received edoxaban as per Protocol and had at least 1 postdose PK measurement with known collection times and date/time of dose administration and who did not have any clinically significant events or Protocol deviations that may have compromised the integrity of the PK results.
3. The PD Analysis Set comprised all patients who received edoxaban as per Protocol and had at least 1 postdose PD measurement with known collection time and date/time of dose administration and who did not have any clinically significant events or Protocol deviations that may have compromised the integrity of the PD results.
AE = adverse event; mo = month(s); PD = pharmacodynamic(s); PK = pharmacokinetic(s); yrs = years.
Source: Post-text Table 14.1.1.1

Recruitment

A total of 66 patients, out of 100 patients screened, were enrolled during the study period (Date first patient enrolled: 05 November 2014; Date last patient completed: 16 September 2021).

This study was conducted at 32 clinical sites in the United States, Canada, France, India, Italy, Jordan, Lebanon, Spain, Turkey, and the United Kingdom.

Baseline data

For all age cohorts, the mean age of patients was similar in both dosing groups (approximately 15.9 years in the low dose and 15.3 years in the high dose groups for Cohorts 1a/1b, approximately 9.6 years in the low dose and 9.5 years in the high dose groups for Cohorts 2a/2b, approximately 4.3 years in both the low and high dose groups for Cohorts 3a/3b, approximately 1.2 years in the low dose and 1.0 year in the high dose groups for Cohorts 4a/4b, and 0.17 years in the low dose and 0.25 years in the high dose groups for Cohorts 5a/5b).

Given the small number of patients in each cohort, there was a balanced number of male and female patients in each dose group. In most cohorts and dose groups, the majority of patients were White, with the exception of the high dose treatment group of Cohort 3 (3b; half of the patients were White), low dose group of Cohort 4 (4a; approximately 43% of the patients were Asian), and both low and high dose groups of Cohort 5 (5a/5b; two-thirds of the patients in the low dose group [5a] and half of

the patients in the high dose group [5b] were Asian). In all cohorts, the majority or all of the patients were not Hispanic or Latino.

For all age cohorts, the median height, weight, and BMI at Baseline were similar in both dosing groups. The median BMI was approximately 21 kg/m2 in both low dose and high dose group for Cohorts 1a/1b, approximately 18 kg/m2 in the low dose group and 17 kg/m2 in the high dose group for Cohorts 2a/2b, approximately 15 kg/m2 in the low dose group and 16 kg/m2 in the high dose group for Cohorts 3a/3b, approximately 17 kg/m2 in both low dose and high dose groups for Cohorts 4a/4b, and approximately 14 kg/m2 in the low dose group and 15 kg/m2 in the high dose group for Cohorts 5a/5b.

Number analysed

The Safety Analysis Set included 66 subjects. All 66 (100.0%) subjects were included in the PK and PD analysis sets. All 66 (100.0%) subjects completed the last study visit. There were no withdrawals from the study due to an adverse event (AE), death, protocol violation, withdrawal by subject, or any other reasons.

A total of 66 subjects were enrolled in Cohorts 1 to 5, with low and high dose groups, as follows:

- Cohorts 1a and 1b: 15 subjects (low dose: 8 subjects; high dose: 7 subjects)
- Cohorts 2a and 2b: 13 subjects (low dose: 7 subjects; high dose: 6 subjects)
- Cohorts 3a and 3b: 13 subjects (low dose: 7 subjects; high dose: 6 subjects)
- Cohorts 4a and 4b: 13 subjects (low dose: 7 subjects; high dose: 6 subjects)
- Cohorts 5a and 5b: 12 subjects (low dose: 6 subjects; high dose: 6 subjects)

Pharmacokinetics and Pharmacodynamics results

Pharmacokinetics

The emerging PK concentration-time data from completing subjects from Studies U157 and DU176b-A-U312 were analysed using model-based PopPK approaches in an ongoing basis and used to predict and optimize the doses required to obtain targeted exposures in subsequent age cohorts and dose groups (high dose group after the PK data in the low dose group).

The paediatric dataset used in the PopPK analysis included data from 59 subjects from the single-dose paediatric study (U157) and data from 55 subjects from the multiple-dose paediatric study (DU176b-A-U312), with a total of 405 concentration samples from these 114 paediatric subjects. A total of 106 concentration samples were available after multiple doses of edoxaban and 299 concentration samples after a single dose.

Table 4 presents the number of samples in each age cohort by study. Table 5 presents the summary of the continuous covariates of interest.

Table 4: 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

Source: Appendix 16.1.13

Table 5: 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]

Source: Appendix 16.1.13

Population Pharmacokinetic (PopPK) Analysis

The edoxaban paediatric PK was best described by a 2-compartment model with linear CL/F, and 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.

The covariate effect of age was incorporated to account for PK in the youngest patients. The population median CL/F and V/F were estimated to be 42.9 L/h and 198 L, respectively. For more information regarding the final population PK parameters, please see Table 6.

Table 6: 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 model was also used to estimate individual paediatric subject exposures (AUC from time 0 extrapolated to infinity [AUCinf]) and compared to adult references (steady-state AUC over the dosing interval) of 30 mg or 60 mg, depending on the dosage group, to assess whether the individual exposures were within the 90% confidence interval (CI) of the median target adult exposure. The appropriateness of the dose in an age cohort was assessed by comparing the median exposure in that dose group with the median adult exposure. If the median paediatric exposure was within the 0.5- to 1.5-fold of the adult VTE exposure at the 60-mg QD dose, the paediatric dose was considered appropriate.

The individual estimates of AUCinf in all subjects in Cohorts 1 to 4 were within the 90% CI of the adult steady-state exposures. In Cohort 5 (birth to <6 months), exposure in 1 of the 6 dosed subjects was outside the 90% CI of the adult exposure. This was the only subject who was <28 days old and received the 0.8-mg/kg dose (the paediatric dose predicted to give exposure similar to adult 60 mg QD). Across all cohorts, the median exposure was within the 0.5- to 1.5-fold of the adult VTE exposure at the corresponding dose strength (30 mg QD for low dose and 60 mg QD for high dose).

The nominal doses (for low and high dose groups, respectively), as determined in the PopPK analysis, were 30 mg and 60 mg for Cohort 1, 24 mg and 45 mg for Cohort 2, 0.7 mg/kg and 1.4 mg/kg for Cohort 3, 0.75 mg/kg and 1.5 mg/kg for Cohort 4, and 0.4 mg/kg and 0.8 mg/kg for Cohort 5.

Mean Plasma Concentrations of Edoxaban

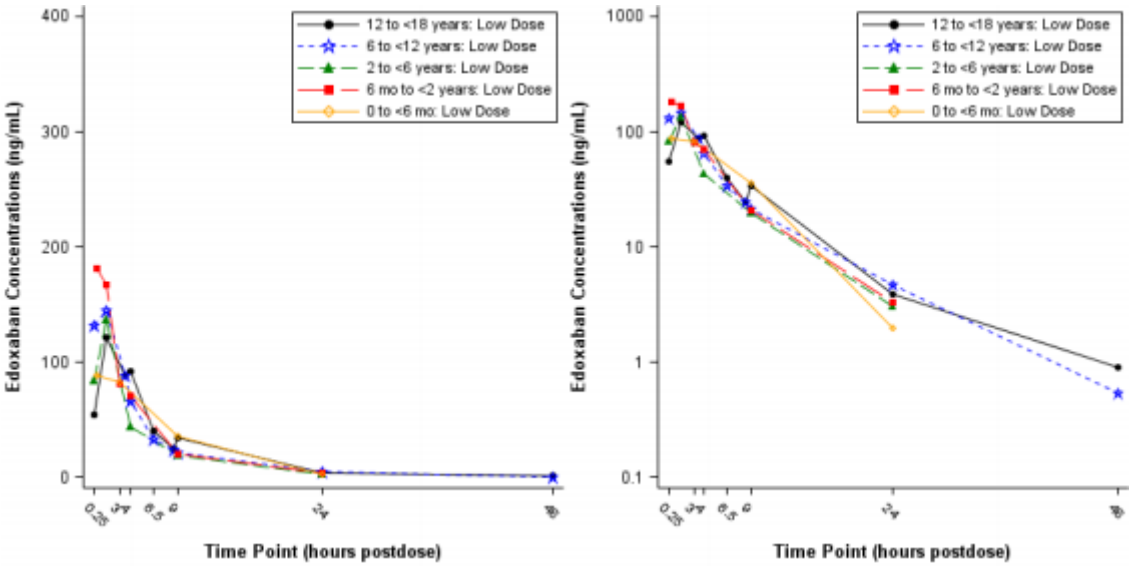
The plasma concentration-time profiles for different age cohorts were found to be visually similar. Edoxaban was absorbed rapidly after oral administration in all age cohorts in both the high dose and low dose groups. The highest plasma concentrations of edoxaban and edoxaban's metabolite D21-2393 were observed within 0.5 to 3 hours after oral administration for both high dose and low dose groups in all age cohorts.

The high dose of edoxaban produced higher exposure compared to low dose in all age cohorts. Rapid clearance after achieving peak concentration was observed for both the high and low dose groups in all age cohorts.

Figure 3 and Figure 4 present plasma concentrations of edoxaban versus time on linear and semi-logarithmic scales for low dose and high dose groups, respectively, for the PK Analysis Set.

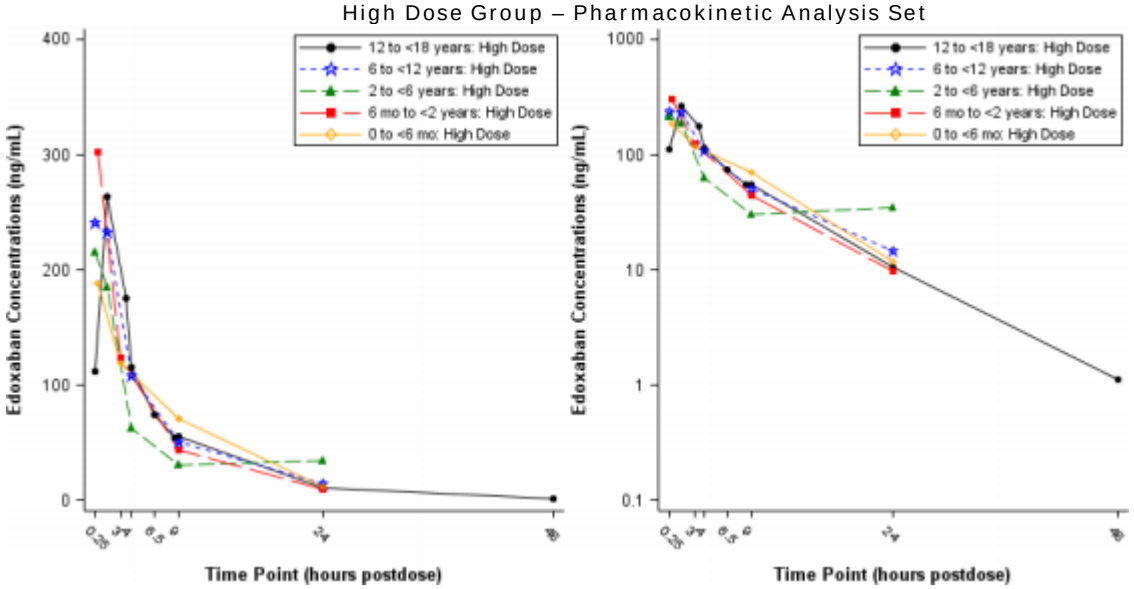
Figure 5 and Figure 6 present plasma concentrations of D21-2393 versus time on linear and semi-logarithmic scales for low dose and high dose groups, respectively, for the PK Analysis Set.

Figure 3: Plasma Concentrations of Edoxaban Versus Time on Linear and Semi-Logarithmic Scales – Low Dose Group – Pharmacokinetic Analysis Set



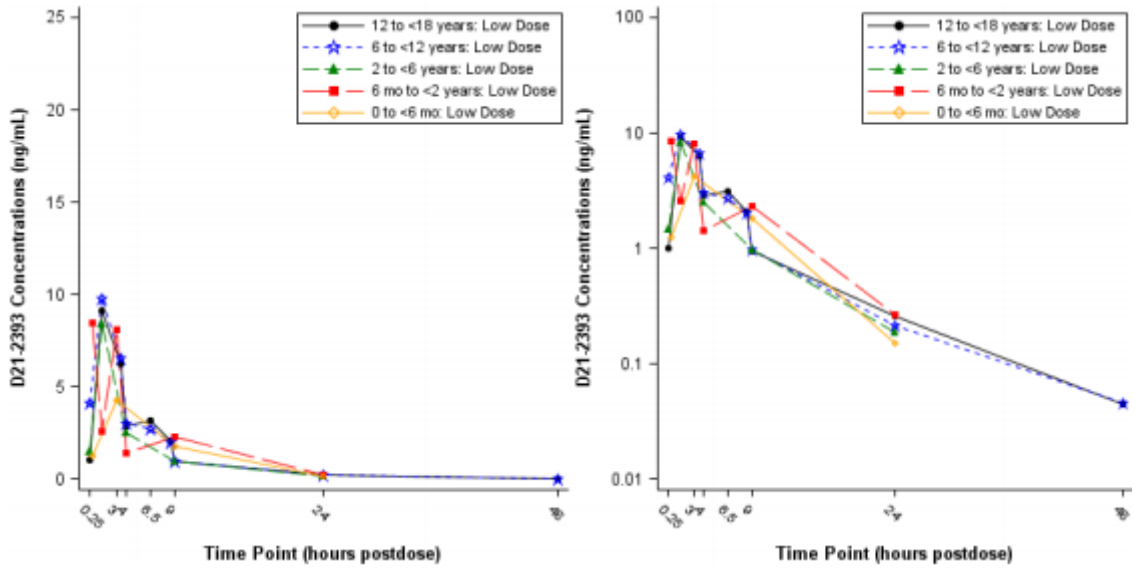
Note: Doses of edoxaban for each cohort are presented in Table 2.
The sampling time points were 0.25 to 1 hr, 0.5 to 2 hrs, 1.5 to 3 hrs, 3 to 8 hrs, 3.5 to 6 hrs, 4 to 8 hrs, 6.5 to 8 hrs, 8.5 to 14 hrs, 9 to 14 hrs, 24 to 36 hrs, and 48 to 56 hrs, respectively. The start time of each time window was used as the scheduled time point in the plot.
Hr(s) = hour(s); mo = months.
Source: Post-text Figure 14.4.1.2

Figure 4: Plasma Concentrations of Edoxaban Versus Time on Linear and Semi-Logarithmic Scales – High Dose Group – Pharmacokinetic Analysis Set



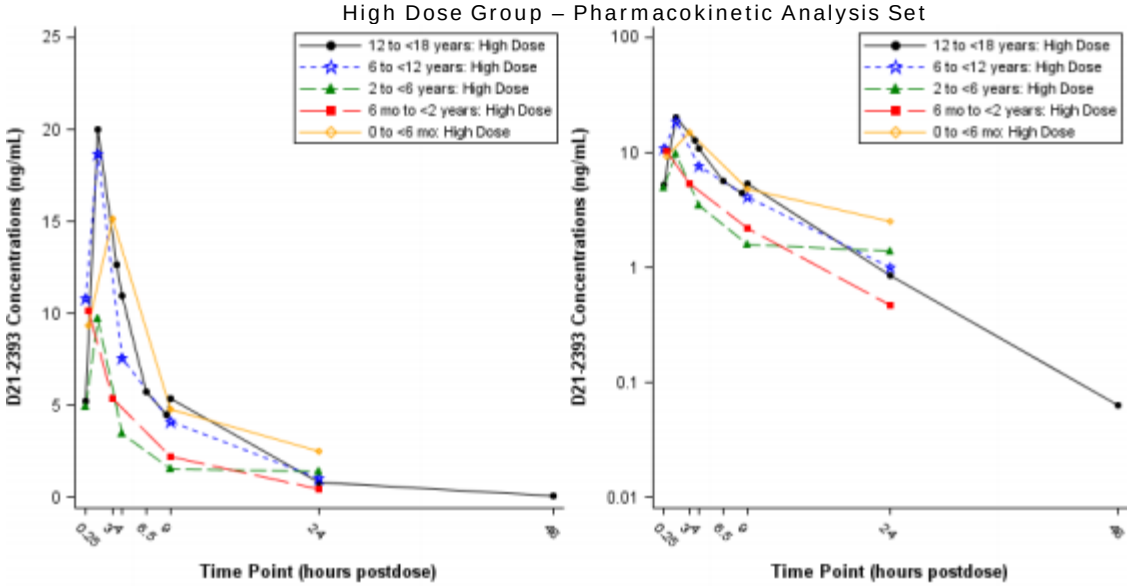
Note: Doses of edoxaban for each cohort are presented in Table 2.
The sampling time points were 0.25 to 1 hr, 0.5 to 2 hrs, 1.5 to 3 hrs, 3 to 8 hrs, 3.5 to 6 hrs, 4 to 8 hrs, 6.5 to 8 hrs, 8.5 to 14 hrs, 9 to 14 hrs, 24 to 36 hrs, and 48 to 56 hrs, respectively. The start time of each time window was used as the scheduled time point in the plot.
Hr(s) = hour(s); mo = months.
Source: Post-text Figure 14.4.1.1

Figure 5: Plasma Concentrations for D21-2393 Versus Time on Linear and Semi-Logarithmic Scales – Low Dose Group – Pharmacokinetic Analysis Set



Note: Doses of edoxaban for each cohort are presented in Table 2.
The sampling time points were 0.25 to 1 hr, 0.5 to 2 hrs, 1.5 to 3 hrs, 3 to 8 hrs, 3.5 to 6 hrs, 4 to 8 hrs, 6.5 to 8 hrs, 8.5 to 14 hrs, 9 to 14 hrs, 24 to 36 hrs, and 48 to 56 hrs, respectively. The start time of each time window was used as the scheduled time point in the plot.
Hr(s) = hour(s); mo = months.
Source: Post-text Figure 14.4.1.4

Figure 6: Plasma Concentrations for D21-2393 Versus Time on Linear and Semi-Logarithmic Scales – High Dose Group – Pharmacokinetic Analysis Set



Note: Doses of edoxaban for each cohort are presented in Table 2.
The sampling time points were 0.25 to 1 hr, 0.5 to 2 hrs, 1.5 to 3 hrs, 3 to 8 hrs, 3.5 to 6 hrs, 4 to 8 hrs, 6.5 to 8 hrs, 8.5 to 14 hrs, 9 to 14 hrs, 24 to 36 hrs, and 48 to 56 hrs, respectively. The start time of each time window was used as the scheduled time point in the plot.
Hr(s) = hour(s); mo = months.
Source: Post-text Figure 14.4.1.3

The simulated estimated individual plasma edoxaban area under the concentration-time curve (AUC) for subjects in each cohort demonstrated that the proposed dose regimens in the paediatric population resulted in similar exposures to those observed in adults with VTE who were administered edoxaban at 60 mg QD.

Pharmacodynamics

The PD blood samples were collected for the estimation of biomarkers of coagulation (prothrombin time [PT], activated partial thromboplastin time [aPTT], and anti-FXa).

Mean PT, aPTT, and anti-FXa values increased following edoxaban administration, with peak values observed approximately 1.5 to 3 hours post-dose followed by a rapid decrease until 4 to 8 hours post-dose and a slower decline after 8 hours. The curves of mean PT, aPTT, and anti-FXa versus time were similar for the high dose and low dose groups in all age cohorts.

The following PD correlations were observed: an approximately linear relationship between antiFXa and PT with limited dose response increase, an approximately flat relationship between antiFXa and aPTT without dose response, and an approximately linear relationship between antiFXa and edoxaban concentration with dose response increase.

Efficacy results

Not applicable.

Safety results

Analysis Set for Safety

The Safety Analysis Set included 66 subjects overall, approximately evenly distributed among all age cohorts and between dosing groups within each age cohort. The dosing groups included 6 to 8 subjects per group.

All 66 (100.0%) subjects were included in the PK and PD analysis sets. All 66 (100.0%) subjects completed the last study visit. There were no withdrawals from the study due to an adverse event (AE), death, protocol violation, withdrawal by subject, or any other reasons.

Extend of Exposure

All subjects received 1 dose of the study drug under the supervision of clinical study personnel.

Treatment-Emergent Adverse Events

Brief Summary of Treatment-Emergent Adverse Events

Overall, 15 (22.7%) subjects experienced TEAEs, of whom the majority were mild in severity, resolved without any sequelae, and did not require any medical intervention. No severe TEAEs were observed. 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 experienced drug-related TEAEs, of which all were mild in severity.

No deaths were reported during the study. No subjects in the Safety Analysis Set experienced TESAEs or study drug-related serious adverse events (SAEs) during the study, and no subjects discontinued study drug due to a TEAE.

In addition, 2 subjects experienced 3 SAEs in the screening phase and did not receive the study drug; therefore these SAEs were not treatment emergent. Both subjects had a medical history of sickle cell disease.

Common Treatment-Emergent Adverse Events

Overall, 15 (22.7%) subjects (4 subjects in Cohorts 1a and 1b, 6 subjects in Cohorts 2a and 2b, 1 subject in Cohorts 3a and 3b, 4 subjects in Cohorts 4a and 4b, and no subjects in Cohorts 5a and 5b) experienced any TEAE.

By system organ class (SOC), the most frequently reported TEAEs were gastrointestinal disorders (4 [6.1%] subjects overall: 2 subjects in the low dose group of Cohort 2 [2a] and 1 subject each in the low dose groups of Cohort 1[1a] and Cohort 4 [4a]); skin and subcutaneous tissue disorders (3 [4.5%] subjects overall: 1 subject each in the high dose groups of Cohort 2 [2b] and Cohort 4 [4b] and 1 subject in the low dose group of Cohort 4 [4a]); and respiratory, thoracic, and mediastinal disorders (3 [4.5%] subjects overall: 2 subjects in the low dose group of Cohort 4 [4a] and 1 subject in the low dose group of Cohort 2 [2a]). All other TEAEs by SOC were experienced by 2 subjects overall.

Relationship of Treatment-Emergent Adverse Events to Study Drug or Procedures

Overall, 5 (7.6%) subjects (2 subjects in Cohorts 2a/2b; 1 subject each in Cohorts 1a and 1b, 3a and 3b, and 4a and 4b; and no subjects in Cohorts 5a and 5b) experienced study drug-related TEAEs, of which all were mild in severity.

In Cohort 1, 1 subject in the high dose group experienced PT prolonged (SOC: investigations). In Cohort 2, 1 subject in the low dose group experienced haematochezia (SOC: gastrointestinal

disorders), and 1 subject in the high dose group experienced aPTT prolonged (SOC: investigations). In Cohort 3, 1 subject in the low dose group experienced psychomotor hyperactivity (SOC: nervous system disorders). In Cohort 4, 1 subject in the high dose group experienced rash (SOC: skin and subcutaneous tissue disorders). In Cohort 5, no subjects experienced any study drug-related TEAEs.

Deaths, Serious Adverse Events, Discontinuations Due to Adverse Events, and Other Clinically Relevant Adverse Events

No deaths occurred during the study.

No SAEs occurred during the study.

There were no AEs leading to discontinuation of study drug.

There were no AEs of special interest during the study.

Clinical Laboratory Evaluations

Chemistry:

No clinically meaningful changes in chemistry laboratory evaluations were observed during the study.

Haematology:

No clinically meaningful changes in haematology laboratory evaluations were observed during the study.

Coagulation:

In the 12 to <18 years age cohort, 1 subject treated with high dose of edoxaban (Cohort 1b) had PT prolonged (without bleeding) that was considered 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) that was considered related to edoxaban. Otherwise, no clinically significant changes in coagulation biomarkers were observed.

Individual Clinically Relevant Abnormalities:

No individual clinically meaningful abnormalities were noted during the study.

Vital Signs

No clinically meaningful changes in vital signs were observed during the study.

Palatability results

The mean (SD) overall palatability score ranged from 53.6 (35.78) millimeters in the low dose group of Cohort 2 to 83.3 (20.41) millimeters in the high dose group of Cohort 3.

The overall palatability score, the overall taste score, the sweetness score, and the aroma score were higher in the high dose groups compared to the low dose groups for Cohorts 2, 3, and 5.

The bitterness score was higher in the high dose groups compared to the low dose groups for Cohorts 3 and 5.

2.3.3. Discussion on clinical aspects

This Article 46 procedure of Regulation (EC) No1901/2006, concerns the submission of a stand-alone paediatric study for edoxaban tosilate (Lixiana and its duplicate Roteas), which is Study DU176b-A-

U157 (U157) “A Phase 1, Open-label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients”. This study is part of the PIP EMEA-000788-PIP02-11-M11 (PIP Study 13). In addition, the results of the population-based pharmacokinetic (PopPK) model to predict the dose in the single-dose Study U157 are included in Appendix 16.1.13 of the clinical study report. This modelling study refers to PIP Study 14.

Study U157 was a Phase 1, open-label, non-randomized, multiple-center study to evaluate PK and PD (a dose-finding goal) and safety of edoxaban in paediatric patients (from 38 weeks gestational age to <18 years) with ongoing risk of thromboembolic events. The enrolment was sequential (from older to younger) and 2 doses were tested (a “low” dose to achieve exposures comparable to a 30 mg adult dose and a “high” dose to achieve exposures comparable to a 60 mg adult dose). The study included 5 paediatric age cohorts (12 to <18 yrs [Cohort 1], 6 to <12 yrs [Cohort 2], 2 to <6 yrs [Cohort 3], 6 mo to <2 yrs [Cohort 4] and 0 to <6 mo [Cohort 5]) with evaluation of 2 different doses within each age cohort (low [subcohort a] and high dose [subcohort b]). The pharmaceutical formulations used in Study U157 were edoxaban 15 mg or 30 mg oral tablets (for subjects in the 12 to <18 years age cohort) and edoxaban granules for oral suspension (60 mg reconstituted with water to provide a 6 mg/mL suspension for oral administration; for subjects <12 years). The study design appears adequate for a Phase 1 study which is not intended to test a hypothesis but rather to generate information that would allow dose selection (comparable to the exposure of efficacious doses in adults) for subsequent clinical efficacy/safety Phase 3 studies in paediatrics.

The primary objective of this study was to characterize the pharmacokinetic (PK) of edoxaban in paediatric patients who might require or currently were on anticoagulant therapy, following its single-dose oral administration. It was pursued by establishing a preliminary edoxaban paediatric population PK (PopPK) model as well as conducting PK simulations and proposing dose regimens for each subsequent dose cohort and also for the same age cohort (0 to <18 years) in the ongoing multiple-dose Phase 3 Study DU176b-A-U312. No efficacy endpoints were planned in the hereby submitted study. Measurements used in this study are considered acceptable as they are standard for a Phase 1 dose-finding study for subsequent clinical efficacy/safety Phase 3 edoxaban studies in paediatrics.

A total of 66 patients, out of 100 patients screened, were enrolled during the study period (from 05 November 2014 to 16 September 2021). This study was conducted at 32 clinical sites in the United States, Canada, France, India, Italy, Jordan, Lebanon, Spain, Turkey, and the United Kingdom.

Paediatric patients who received edoxaban (n=66) were approximately evenly distributed among all age cohorts (15 subjects in Cohort 1, 13 subjects in Cohort 2, 13 subjects in Cohort 3, 13 subjects in Cohort 4 and 12 subjects in Cohort 5). The dosing groups included 6 patients (subcohorts 2b, 3b, 4b, 5a and 5b), 7 patients (subcohorts 1b, 2a, 3a and 4a) or 8 patients (subcohort 1a) per group. The edoxaban paediatric PK was best described by a 2-compartment model with allometric body weight exponents (0.75 for clearances and 1 for volumes). The plasma concentration-time profiles for different age cohorts were found to be similar. The high dose of edoxaban produced higher exposure compared to low dose for all age cohorts. The curves of mean PT, aPTT, and anti-FXa versus time were also similar for the high dose and low dose groups in all age cohorts. Approximately linear relationships were observed between antiFXa and PT with limited dose response increase and between antiFXa and edoxaban concentration with dose response increase. An approximately flat relationship between antiFXa and aPTT without dose response was observed. The hereby submitted PK/PD results should be interpreted with caution as the Phase 3 studies are currently ongoing. A final pooled analysis of all of the paediatric PopPK and the corresponding report will be generated once the studies are completed.

With regards to safety, edoxaban was well tolerated when administered orally in a single low dose or single high dose to paediatric patients from 38 weeks gestation (0 months) to <18 years of age. Four patients in Cohorts 1a/1b, 6 patients in Cohorts 2a/2b, 1 patient in Cohorts 3a/3b, and 4 patients in

Cohorts 4a/4b experienced TEAEs, of which the majority were mild, resolved without any sequelae, and did not require any medical intervention. Given the small number of patients in each group, the number of TEAEs in the low and high dose groups in each cohort was comparable. No severe TEAEs were observed. One patient in Cohorts 1a/1b, 2 patients in Cohorts 2a/2b, 1 patient in Cohorts 3a/3b, and 1 patient in Cohorts 4a/4b experienced drug-related TEAEs, of which all were mild. No patients in Cohorts 5a/5b experienced any TEAEs. In the 12 to <18 years age cohort, 1 patient 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 patient 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 patients experienced TESAEs or study drug-related SAEs during the study, and there were no TEAEs leading to discontinuation of study drug. Two patients experienced 3 SAEs in the screening phase and did not receive the study drug. No clinically meaningful changes in chemistry or hematology laboratory evaluations, or vital signs were observed.

Overall, the safety profile of edoxaban observed in the paediatric study DU176b-A-U157 was consistent with the already known safety profile of edoxaban in adults with NVAF and venous thromboembolism.

3. Rapporteur's overall conclusion and recommendation

In accordance with Article 46 of the regulation (EC) No. 1901/2006, Daiichi Sankyo Europe GmbH hereby submits to the EMA a final study report for the study number DU176b-A-U157, which is part of the PIP EMEA-000788-PIP02-11-M11 (PIP Study 13). In addition, the results of the population-based pharmacokinetic (PopPK) model to predict the dose in the single-dose Study U157 are included in Appendix 16.1.13 of the clinical study report. This modelling study refers to PIP Study 14.

Study DU176b-A-U157 was a Phase 1, open-label, non-randomized, multiple-center study to evaluate PK and PD (a dose-finding goal) and safety of edoxaban in 66 paediatric patients (from 38 weeks gestational age to <18 years) with ongoing risk of thromboembolic events.

A PopPK model was developed describing the PK of edoxaban in the paediatric subjects (birth to <18 years of age). Model-estimated edoxaban AUCinf for all cohorts of study DU176b-A-U157 demonstrated that the proposed dosing regimens in the paediatric population would be expected to result in exposures that are aligned with those in adult VTE patients administered edoxaban at 60 mg QD. A final pooled analysis of all of the paediatric PopPK and the corresponding report are expected to be generated once the studies are completed.

Overall, the safety profile of edoxaban observed in the paediatric study DU176b-A-U157 was consistent with the already known safety profile of edoxaban in adults with NVAF and VTE.

☒ Fulfilled:

No regulatory action required.

☐ Not fulfilled:

References

- Niebecker R, Jönsson S, Karlsson MO, Miller R, Nyberg J, Krekels EH, Simonsson US. Population pharmacokinetics of edoxaban in patients with symptomatic deep-vein thrombosis and/or pulmonary embolism--the Hokusai-VTE phase 3 study. Br J Clin Pharmacol. 2015 Dec;80(6):1374-87. doi: 10.1111/bcp.12727. Epub 2015 Sep 30. PMID: 26218447; PMCID: PMC4693489.
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