# Office of Clinical Pharmacology Review

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| NDA Number | NDA 206316 S-019 |
| Link to EDR | \\CDSESUB1\evsprod\NDA206316\0213 |
| Submission Date | 19 Dec 2022 |
| Submission Type | Efficacy supplement (Standard) |
| Brand Name | SAVAYSA® |
| Generic Name | Edoxaban tosylate |
| Dosage Form and Strength | Strengths are expressed as the anhydrous free base (edoxaban)<br>• Film-coated immediate-release tablets: 15, 30 and 60 mg<br>• Granules for oral suspension 60 mg |
| Route of Administration | Oral |
| Approved Indication | • Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant<br>• To reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF) |
| Proposed Indication | Not seeking pediatric indication |
| Applicant | Daiichi Sankyo, Inc. |
| Associated IND | IND 063266 (Venous thromboembolism)<br>IND 077254 (Atrial fibrillation) |
| OCP Reviewers | Harisudhan Thanukrishnan, PhD;<br>Sudharshan Hariharan, PhD |

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# 1. EXECUTIVE SUMMARY

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

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

To support pediatric dosing, the Applicant developed edoxaban granules for oral suspension (60 mg). Patients younger than 12 years of age received edoxaban granules for oral suspension according to body weight, in the above Phase 1 study. The relative oral bioavailability of granules for oral suspension (10 mL of 6 mg/mL) versus tablets (2 x 30 mg) was assessed in healthy adult subjects (Study DU176b-A-U154). The exposure ($AUC_{last}$ and $AUC_{inf}$) was similar between both formulations but the $C_{max}$ of oral suspension was 13% lower than the tablets.

The second study (PMR 2852-2) was the pivotal registrational study (Study U312, Hokusai VTE Pediatric Study) titled "A Phase 3, Open-label, Randomized, Multicenter, Controlled Trial to Evaluate the Pharmacokinetics and Pharmacodynamics of Edoxaban and to Compare the Efficacy and Safety of Edoxaban with Standard-of-Care Anticoagulant Therapy in Pediatric Subjects from Birth to Less Than 18 Years of Age with Confirmed Venous Thromboembolism (VTE)" and the CSR was submitted in this supplement. The primary objective of the study was to demonstrate the non-inferiority of edoxaban to standard of care therapy in the treatment and secondary prevention of VTE in pediatric subjects during the first 3-month treatment period. The study also characterized multiple dose PK and PD in a subset of patients. Patients aged 12 to <18 years received fixed dose of 30 mg, 45 mg and 60 mg based on body

weight of < 30 kg, ≥ 30 to <60 kg and ≥60 kg, respectively. Patients in age cohorts ≥6 to <12 years, ≥2 to <6 years, ≥6 months to <2 years, and ≥0 to <6 months, received body weight-based doses of 1.2 mg/kg, 1.4 mg/kg, 1.5 mg/kg and 0.8 mg/kg, respectively. The observed mean pre-dose plasma concentrations of edoxaban in pediatric subjects were comparable across 5 age cohorts from birth to <18 years and were comparable with those in adult patients with VTE administered with edoxaban at 60 mg QD estimated by adult population PK modeling. Overall, the median simulated steady state $AUC_{0\text{-}24h,\ ss}$ values in pediatric patients across five age groups were 18% to 27% lower than that in adult VTE patients receiving 60 mg QD dose. However, the exposure in pediatric patients were within the range of exposures observed in adult VTE patients. The nature of the PK/PD relationship (PT, aPTT, and anti-FXa) in pediatric subjects were consistent with those in adult VTE patients administered edoxaban at 60 mg QD.

Study U312 did not demonstrate non-inferiority of edoxaban versus the standard-of-care (SOC) as the upper bound of the 95% CI (1.72) was above the prespecified non-inferiority margin of 1.5 (hazard ratio (edoxaban/SOC) is 1.01 with two-sided 95% CI (0.59 to 1.72). As per Applicant, the study was expected to observe 68 events, with an expected event rate of 24%, and the study was sized to have 274 patients. However, during the interim analysis, the Applicant observed 23 events among the 138 enrolled patients, resulting in an event rate of 16.7%. Based on this analysis, the sample size was recalculated to be 422, which would have led to approximately 68 events by the end of the study, assuming the observed event rate remained constant. However, despite the recommendation from the interim analysis, the Applicant terminated the study at a sample size of 286. At that point, they had observed 57 events, with an event rate of 20%. Consequently, the resulting analysis yielded a wide 95% confidence interval of 1.01 (0.59, 1.72), with the upper bound exceeding the non-inferiority margin of 1.5. Based on these results, the statistical review team concludes that the study was underpowered, i.e., it did not have an adequate sample size to confirm non-inferiority. This is in contrast to the adult study, which was confirmed based on a hazard ratio of 0.89 (95% CI 0.70, 1.13), where the upper bound of the 95% confidence interval was below the threshold of 1.5.

## 1.1 Conclusions

The Office of Clinical Pharmacology (OCP)/ Division of Cardiometabolic and Endocrine Pharmacology has reviewed the information contained in this supplement of NDA 206316. The Applicant has fulfilled PMR 2852-1 with completion of the single dose PK/PD study in pediatric patients. Based on this PK/PD study, the Applicant identified doses for pediatric patients across different age cohorts for evaluation in the efficacy trial. While selection of pediatric doses resulted in exposures in the range of adult exposures equivalent to 60 mg in patients with VTE, the simulated median steady-state $AUC_{0\text{-}24}$ was approximately 18 to 27% lower compared to adult exposures. The current pediatric efficacy trial failed due to inadequate sample size, however, if the Applicant were to conduct another trial, the pediatric dosing could be refined further to match adult exposures even closely.

## 1.2 Post-Marketing Requirements and Commitments

None

# 2. SUMMARY OF PEDIATRIC EFFICACY TRIAL AND PK/PD ASSESSMENT

- In this pediatric sNDA, the Applicant submitted the CSR for the Phase 3 pediatric study (DU176B-D-U312) following the requirement under pediatric PMR 2852-2.
- Previously, Applicant had also submitted two other study reports as below:
  1. Study DU176b-A-U157 (PMR study 2852-1) was a single dose Phase 1 study to evaluate pharmacokinetics and pharmacodynamics (PK/PD) of edoxaban in pediatric patients at risk for venous thromboembolism (VTE), to allow dose selection for the pediatric Phase 3 study. The final CSR was submitted on 01/28/2022 to the IND 063266 under SN0411.
  2. Study DU176b-A-U154 was an open label 3-way crossover Phase 1 study in healthy adult subjects to assess the Relative Bioavailability and Food Effect for edoxaban granules for oral suspension, to support dosing in pediatric patients. The final CSR for this study was submitted in paper format to IND 063266 on 02/07/2014 under SN1643 and a scanned copy was later added to this NDA under SN0220.

## 2.1 Phase 1 study (DU176b-A-U154) to assess relative bioavailability of granules for oral suspension compared to approved tablet formulation

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

Objectives: The study was conducted in healthy adult subjects to (1) describe the PK of the liquid suspension formulation of edoxaban with respect to the adult tablet formulation, both dosed at 60 mg under fasting conditions and (2) to assess how food affects the rate and extent of absorption of edoxaban from the oral suspension.

Study design:

The bioavailability of 60 mg dose of edoxaban was evaluated in 3 treatment periods:

1. Treatment A: Single oral dose of 2 × 30 mg tablets of edoxaban dosed under fasting conditions
2. Treatment B: Single oral dose of 10 mL of 6 mg/mL edoxaban oral suspension dosed under fasting conditions
3. Treatment C: Single oral dose of 10 mL of 6 mg/mL edoxaban oral suspension dosed after an FDA standard high-fat, high-calorie breakfast (approximately 800 to 1000 calories total with approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively)

A total of 24 healthy subjects were enrolled and randomized to 1 of 6 treatment sequences.

Table 1. Treatment sequences in Study U154

| Sequence | Period 1 | Washout | Period 2 | Washout | Period 3 |
|---|---|---|---|---|---|
| 1 (ABC) | Treatment A | ≥ 7 days | Treatment B | ≥ 7 days | Treatment C |
| 2 (BCA) | Treatment B | ≥ 7 days | Treatment C | ≥ 7 days | Treatment A |

| | | | | | |
|---|---|---|---|---|---|
| 3 (CAB) | Treatment C | ≥ 7 days | Treatment A | ≥ 7 days | Treatment B |
| 4 (ACB) | Treatment A | ≥ 7 days | Treatment C | ≥ 7 days | Treatment B |
| 5 (BAC) | Treatment B | ≥ 7 days | Treatment A | ≥ 7 days | Treatment C |
| 6 (CBA) | Treatment C | ≥ 7 days | Treatment B | ≥ 7 days | Treatment A |

For treatments A and B, subjects were required to fast overnight for 10 hours prior to and 4 hours following administration of edoxaban. For treatment C, edoxaban was administered 30 minutes after start of the high-fat diet. Meal was provided 4 hours after dosing for all treatments. Water was not permitted from 1 hour before to 2 hours after dosing with edoxaban (except for the 240 mL used for dosing). For each period, blood samples were collected 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 post dose.

The peak ($C_{max}$) and total exposures ($AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$) 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 $C_{max}$, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ with fixed effects for treatment sequence, period, and treatment, and subject nested with sequence fitted as a random effect. Similarity in bioavailability between two treatments was concluded if the 90% CI for the ratio of geometric least squares means between treatments was contained in the equivalence limits of 80% to 125% for AUCs and $C_{max}$.

Results:

The study was conducted between 09 Jun 2013 (first enrolled subject) and 10 Jul 2013 (last subject completion). Of the 24 subjects randomized into the study, 17 (71%) were men and 7 (29%) were women. The mean age at screening was 36.8 years. One subject withdrew consent after receiving only treatment C in period 1 and did not receive treatments A and B. The PK profiles of edoxaban after Treatments A, B, and C are compared in Figure 1 and Figure 2. The mean $C_{max}$ of edoxaban following administration of oral suspension was about 13% lower in comparison to tablets (212 ng/mL vs 246 ng/mL), but there were no obvious differences beyond the 4-h time point. The mean $t_{1/2}$ was similar across treatments and ranged from 10.7 to 11.6 h.

Figure 1. Mean (±SD) plasma edoxaban concentration-time profiles after single administrations of 60 mg tablet under fasting (Treatment A) and 60 mg oral suspension under fasting conditions (Treatment B) up to 52 hours and 8 hours (right panel)

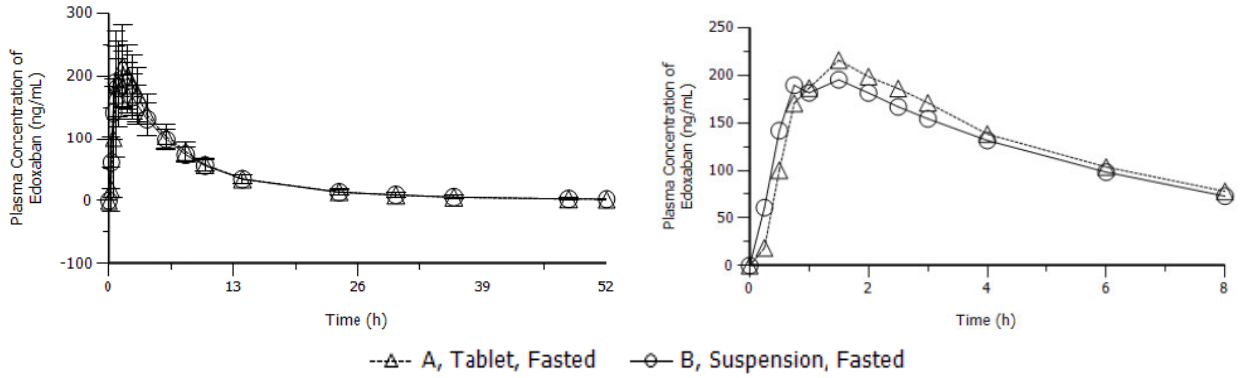
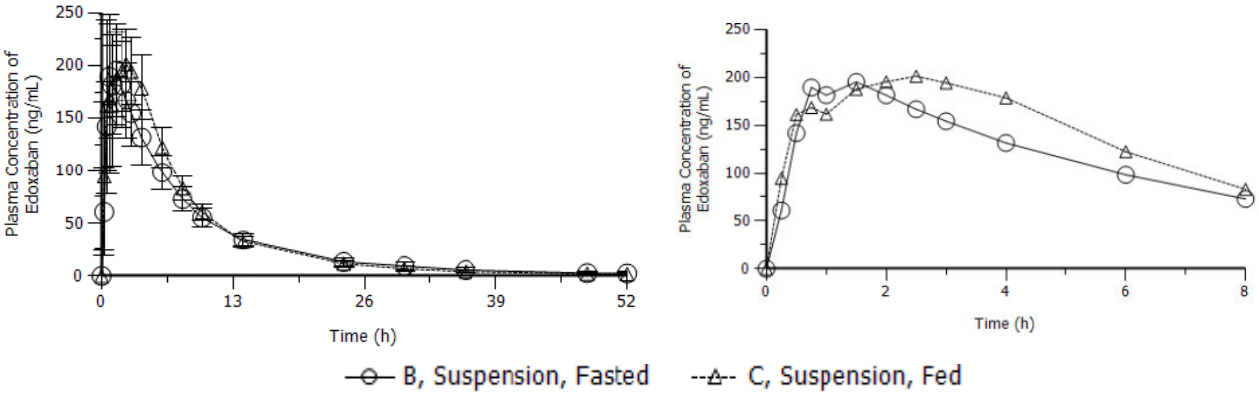


Figure 2. Mean (±SD) plasma edoxaban concentration-time profiles after single administrations of 60 mg oral suspension under fasting (Treatment B) and under fed (Treatment C) conditions up to 52 hours and 8 hours (right panel)




The oral bioavailability was similar across treatments with ratios of geometric mean ranging between 0.97 to 1.09.

Table 2. Statistical Analysis for bioequivalence between treatments in Study U154

| Relative Bioavailability: Comparison of 60 mg Edoxaban Oral Suspension Under Fasting Conditions (Treatment B) to 60 mg Edoxaban Tablet Under Fasting Conditions (Treatment A) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Ln (Geo LS Mean) | | Geo LS Mean | | Ratio (%) | 90% CI | |
| Variable | Suspension fasting | Tablet fasting | Suspension fasting | Tablet fasting | Suspension fasting/Tablet fasting | Lower | Upper |
| $C_{max}$ (ng/mL) | 5.3 | 5.5 | 205.1 | 236.1 | 86.9 | 73.0 | 103.4 |
| $AUC_{last}$ (ng·h/mL) | 7.5 | 7.5 | 1718.5 | 1788.2 | 96.1 | 90.3 | 102.3 |
| $AUC_{inf}$ (ng·h/mL) | 7.5 | 7.5 | 1755.5 | 1827.5 | 96.1 | 90.4 | 102.0 |
| Food effect: Comparison of 60 mg Edoxaban Oral Suspension Under Fed Conditions (Treatment C) to 60 mg Edoxaban Oral Suspension Under Fasting Conditions (Treatment B) | | | | | | | |
| | Suspension fed | Suspension fasting | Suspension fed | Suspension fasting | Suspension fed/Suspension fasting | Lower | Upper |
| $C_{max}$ (ng/mL) | 5.4 | 5.3 | 212.6 | 205.1 | 103.7 | 87.1 | 123.4 |
| $AUC_{last}$ (ng·h/mL) | 7.5 | 7.5 | 1854.4 | 1718.5 | 107.9 | 101.4 | 114.8 |
| $AUC_{inf}$ (ng·h/mL) | 7.5 | 7.5 | 1887.9 | 1755.5 | 107.5 | 101.2 | 114.2 |

Abbreviations: $AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{0\text{-}last}$ = area under the plasma concentration-time curve from time zero until the last measurable concentration; $C_{max}$ = maximum plasma concentration; CI = confidence interval; Ln (Geo LSMean) = Natural log of the geometric mean based on the least squares mean; Geo LSMean = geometric mean based on the least squares mean; Ratio (%) = Geo LSMean (Test)/Geo LSMean (Reference)

Source: Table 14.4.15 and Table 14.4.16 in Clinical Study Report DU176b-A-U154

Conclusion:

- Comparison of bioavailability between the oral suspension and oral tablets of edoxaban showed that the geometric mean ratios and the 90% CIs for $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were within the 80% to 125% range. The geometric mean value of edoxaban $C_{max}$ was approximately 13% lower for edoxaban 60 mg oral suspension in comparison to edoxaban 60 mg oral tablets; the 90% CI for $C_{max}$ was outside the 80% to 125% range. The median edoxaban $t_{max}$ was 1.5 h for both treatments.
- For edoxaban 60 mg oral suspension under fed vs. fasted conditions, the 90% CIs for $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were within the 80% to 125% range, indicating an absence of food effect on edoxaban exposure. The median edoxaban $t_{max}$ under fed conditions (2.5 h) was delayed by 1 h relative to that under fasting state (1.5 h).

## 2.2 Dose finding study in pediatrics (DU176b-A-U157)

Title: A Phase 1, open-label, single-dose, non-randomized study to evaluate pharmacokinetics and pharmacodynamics of edoxaban in pediatric patients

Objectives: The goal of this study was to identify pediatric doses that provide comparable exposure to adult efficacious doses to guide dose selection for Phase 3 studies in pediatric patients (ages 38 weeks gestation to < 18 years). The PK/PD of edoxaban following a single dose of oral edoxaban will be used to identify the appropriate doses in pediatric patients at risk for VTE.

Study design:

The study was designed to evaluate exposures of a low and high dose in each pediatric cohort, to guide dosing in the Phase 3 pediatric trial. The study evaluated two doses in pediatric patients and targeted to have similar edoxaban exposure as in the adult Phase 3 VTE study with low (30 mg) and high (60 mg) dose. A total of 60 patients were planned to be enrolled such that each age cohort had 12 evaluable patients with 6 patients within each dose group.

Age cohorts and dose groups:

- Cohort 1. 12 to < 18 years of age on the day of dosing
  - Cohort 1a: Low-dose group (6 patients)
  - Cohort 1b: High-dose group (6 patients)
- Cohort 2. 6 to < 12 years of age on the day of dosing
  - Cohort 2a: Low-dose group (6 patients)
  - Cohort 2b: High-dose group (6 patients)
- Cohort 3. 2 to < 6 years of age on the day of dosing
  - Cohort 3a: Low-dose group (6 patients)
  - Cohort 3b: High-dose group (6 patients)
- Cohort 4. 6 months to < 2 years of age on the day of dosing
  - Cohort 4a: Low-dose group (6 patients)
  - Cohort 4b: High-dose group (6 patients)
- Cohort 5. 38 weeks gestation to < 6 months of age on the day of dosing
  - Cohort 5a: Low-dose group (6 patients)
  - Cohort 5b: High-dose group (6 patients)

Enrollment began in the lower dose group of the oldest age cohort (to achieve exposures comparable to a 30 mg adult dose). After evaluation of PK and safety data from at least half the patients in the lower dose group, enrollment was initiated in the higher dose group (to achieve exposures comparable to a 60 mg adult dose) in the same cohort. If the observed exposures were higher than expected in the lower dose group and exceeded the projected 60 mg adult exposure, then a lower dose may be investigated in the proposed high dose group. Enrollment in the next younger age cohorts began after PK and safety data from at least 50% (N = 6) of patients in the preceding older dose group have been reviewed. The doses given to each age cohort and dose group were adjusted based on emerging data.

Patients were asked to fast for at least 4 hours before dosing and for an additional 2 hours after dosing. If this was not feasible because of the patient's age or other needs, (unflavored) milk, or an equivalent liquid substitute (but not fruit juices), was allowed until 1 hour before and starting at 1-hour post dose. Patients in the 12 to <18 years of age cohort were dosed with multiples of edoxaban tablets of 15 mg or 30 mg strength. Patients younger than 12 years of age received the edoxaban granules for oral suspension according to body weight (mg/kg).

Sampling time window:
The PD sampling for estimation of biomarkers of coagulation (prothrombin time [PT], activated partial thromboplastin time [aPTT], and anti-activated factor X [FXa]) was concurrent with PK sampling.

- In Cohort 1, seven sampling windows for PK were at: 0.25 to 1 hour, 1.5 to 3 hours, 3.5 to 6 hours, 6.5 to 8 hours, 8.5 to 14 hours, 24 to 36 hours, and 48 to 54 hours post dose. PD sampling was at 0.25 to 1 hour, 1.5 to 3 hours, 3.5 to 6 hours, 6.5 to 8 hours, and 24 to 36 hours post dose.
- In Cohorts 2 and 3, five sampling windows for PK were at: 0.25 to 1 hour, 1.5 to 3 hours, 4 to 8 hours, 9 to 14 hours, and 24 to 36 hours post dose. PD sampling was at 0.25 to 1 hour, 1.5 to 3 hours, 4 to 8 hours, 9 to 14 hours, and 24 to 36 hours post dose
- In Cohort 4, four sampling windows for PK were at: 0.5 to 2 hours, 3 to 8 hours, 9 to 14 hours, and 24 to 36 hours post dose. PD sampling were at screening and 0.5 to 2 hours post dose.
- In Cohort 5, three of the four possible sampling windows for PK were at: 0.5 to 2 hours (mandatory), 3 to 8 hours, 9 to 14 hours, and 24 to 36 hours. PD sampling were at screening and 0.5 to 2 hours post dose.

The plasma edoxaban concentrations were measured using a validated LC-MS/MS assay. The study prohibited the use of inhibitors or inducers of CYP3A4 or P-glycoprotein and the use of nonsteroidal anti-inflammatory drugs (such as ibuprofen) and anti-platelet agents (except low dose aspirin [1 to 5 mg/kg/day, maximum of 100 mg/day]) from 14 days prior to the edoxaban dose until after the last PK sample was collected.

Results:
A total of 66 patients were enrolled in Cohorts 1 to 5, as follows:

- Cohorts 1a/1b: 15 patients
- Cohorts 2a/2b: 13 patients
- Cohorts 3a/3b: 13 patients
- Cohorts 4a/4b: 13 patients
- Cohorts 5a/5b: 12 patients

The age and weight range of subjects randomized to each of the five age cohorts is shown in the table below.
Table 3. Baseline demographics of patients in Cohorts 1 to 5 in Study U157

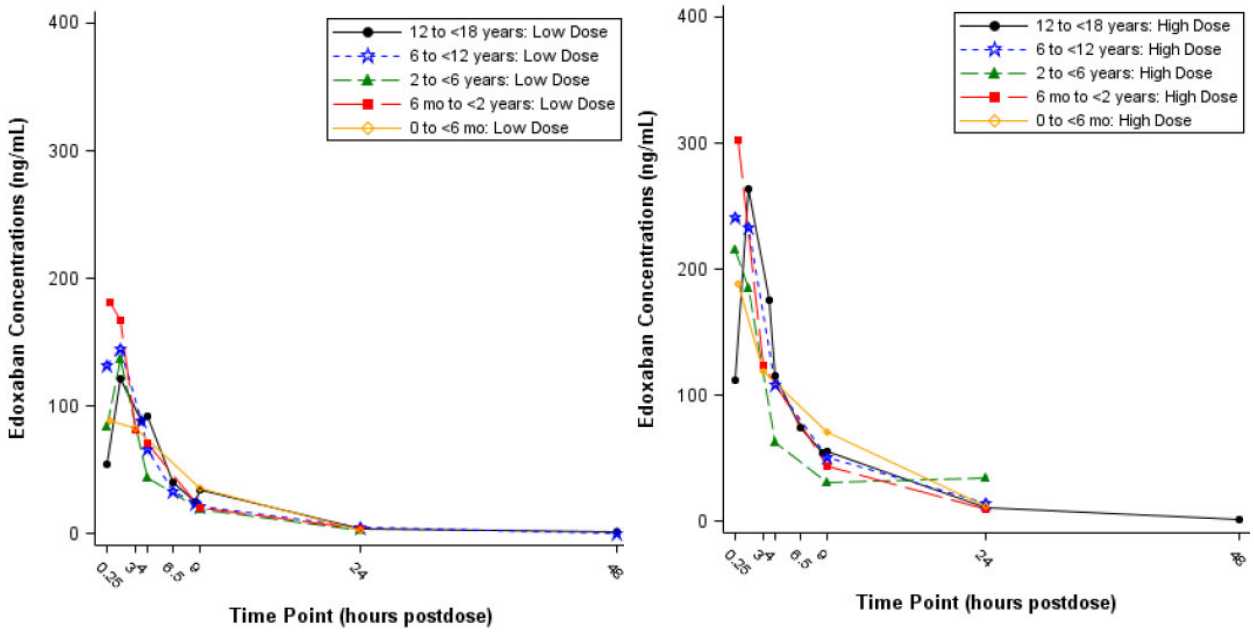
| Cohort | 12 to <18 years (N=15) | 6 to <12 years (N=13) | 2 to <6 years (N=13) | 0.5 to <2 years (N=13) | <0.5 years (N=12) | Overall (N=66) |
|---|---|---|---|---|---|---|
| Age (years) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Mean (SD) | 15.6 (1.2) | 9.5 (1.5) | 4.3 (1.5) | 1.1 (0.5) | 0.2 (0.2) | 6.5 (6.0) |
| Median (CV%) | 15.9 (7.8) | 9.8 (15.4) | 4.3 (32.8) | 0.8 (48.1) | 0.2 (92.9) | 5.2 (92.5) |
| [Min, Max] | [13.0, 17.5] | [6.4, 11.4] | [2.2, 5.9] | [0.6, 1.9] | [0, 0.4] | [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 (7.0) | 17.1 (3.7) | 9.06 (1.7) | 4.82 (1.7) | 27.2 (26.6) |
| Median (CV%) | 59.2 (41.1) | 27.9 (22.6) | 17.8 (21.4) | 8.90 (18.3) | 4.7 (35.0) | 18.2 (97.9) |
| [Min, Max] | [35.4, 157] | [22.0, 47.2] | [11.3, 23.5] | [7.0, 12.3] | [2.7, 6.6] | [2.7, 157] |

Source: Table 4 of population PK report of Study DU176b-A-U157

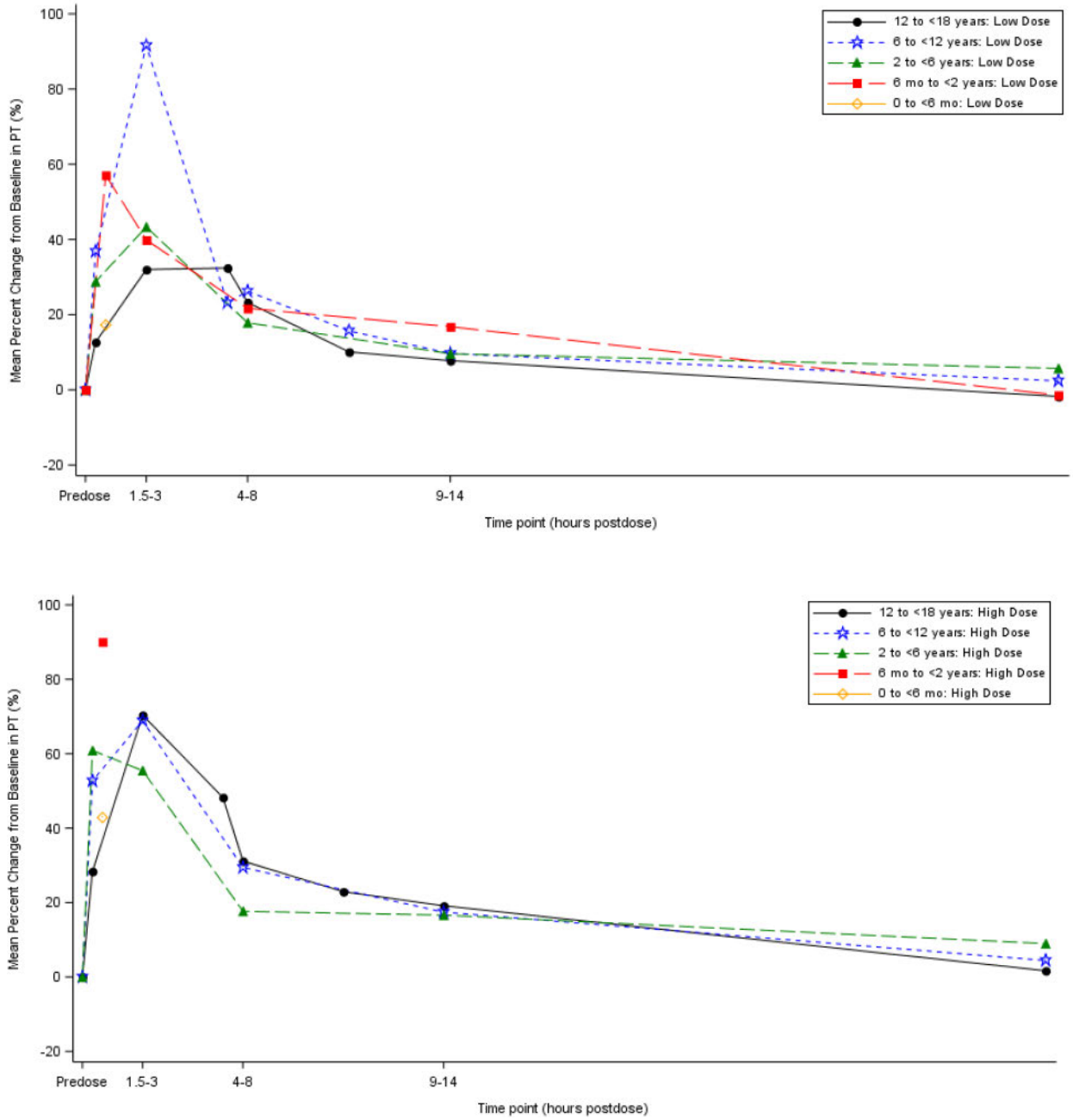
The selection of high and low doses for each age cohort is shown in Table 4. The plasma concentration-time profiles for different age cohorts were found to be similar within the respective low and high dose groups.

Figure 3. Mean plasma edoxaban concentration-time profiles after single dose administrations in pediatric cohorts of Study U157 (low dose= left panel; high dose= right panel)



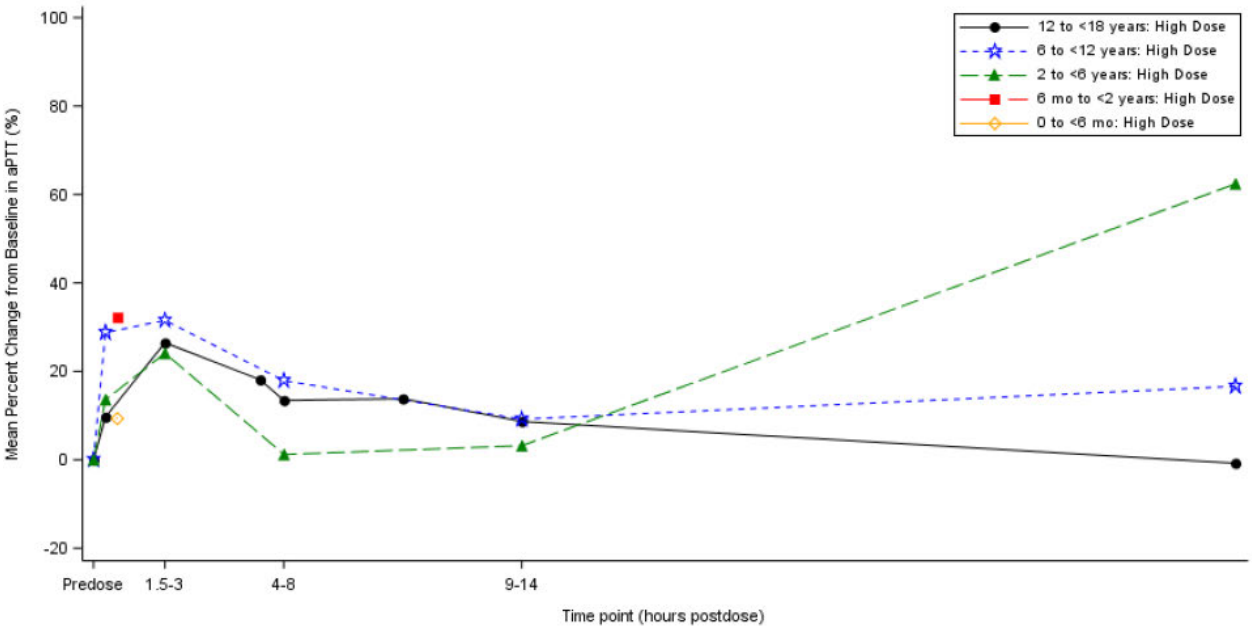

The mean PT, aPTT, and anti-FXa values increased following edoxaban administration with peak values observed approximately 1.5 to 3 hours post dose followed by a rapid decrease until 4 to 8 hours post-dose and slower decline after 8 hours. A trend for dose-dependent increase in the inhibitory effect of edoxaban on the PD markers PT, aPTT and anti-FXa was observed across all the age cohorts, as shown by the profiles for the mean percent change from baseline versus time, in Figure 4, Figure 5 and Figure 6.

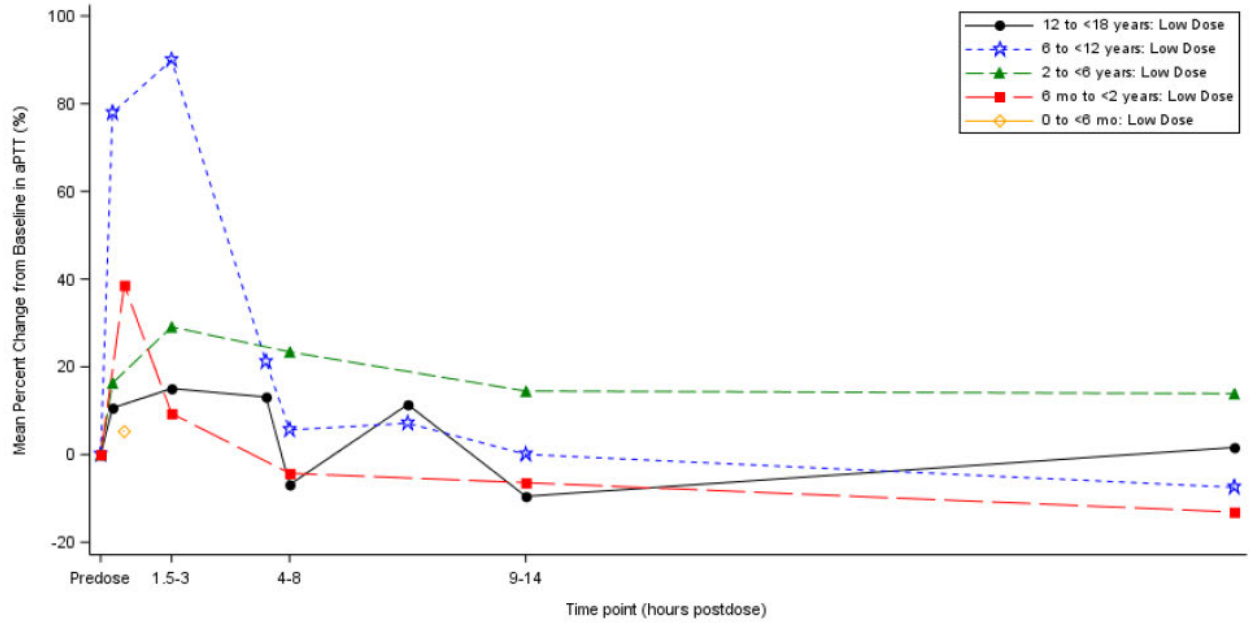
Figure 4. Mean percent change from baseline PT versus time profiles after single dose administrations in pediatric cohorts of Study U157 (low dose= top panel; high dose= bottom panel)




Source: Figure 14.4.4.5, 14.4.4.6 in Clinical Study Report DU176b-A-U157

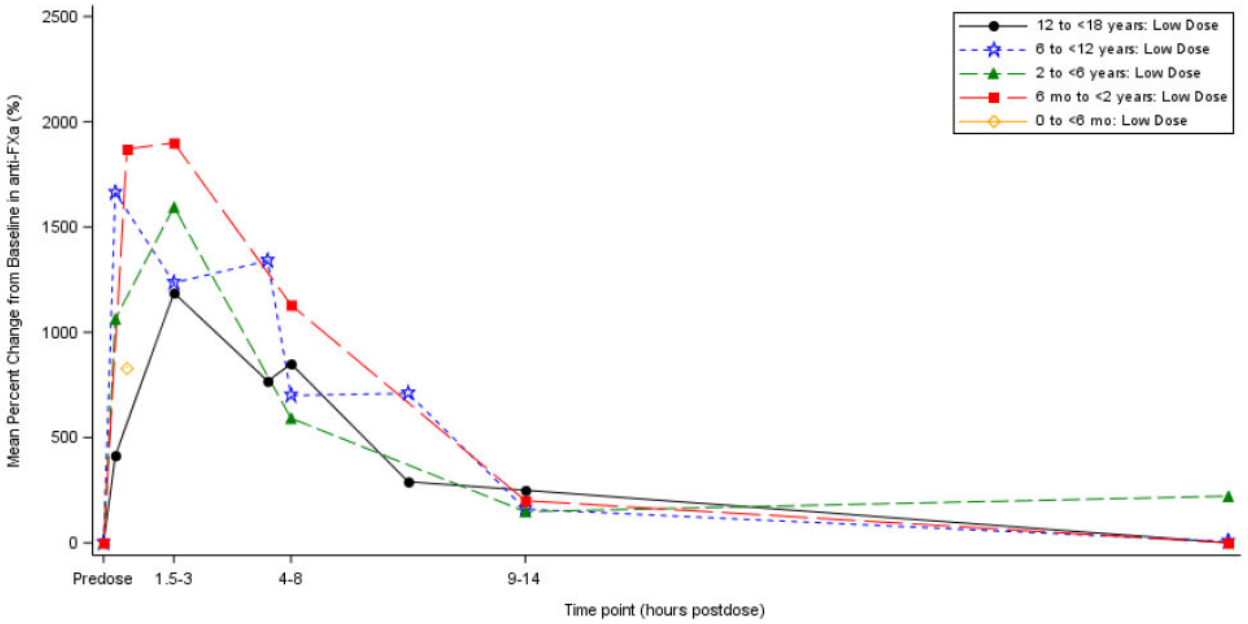
Figure 5. Mean percent change from baseline aPTT versus time profiles after single dose administrations in pediatric cohorts of Study U157 (low dose= top panel; high dose= bottom panel)

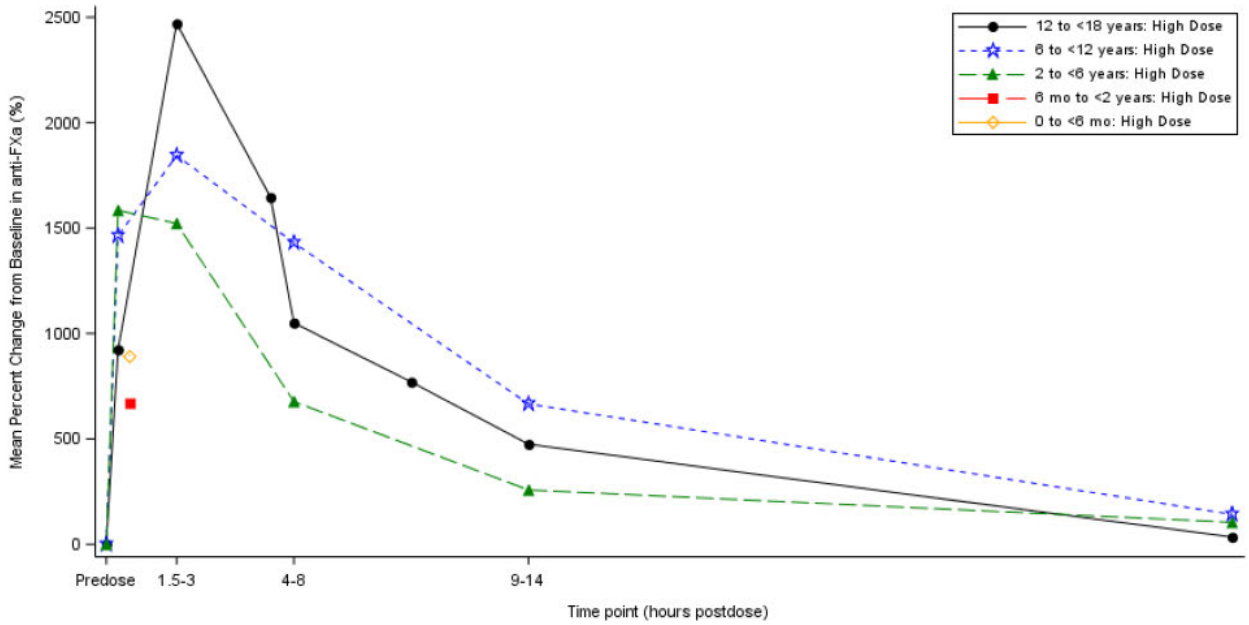



Source: Figure 14.4.4.11, 14.4.4.12 in Clinical Study Report DU176b-A-U157

Figure 6. Mean percent change from baseline anti-FXa versus time profiles after single dose administrations in pediatric cohorts of Study U157 (low dose= top panel; high dose= bottom panel)




Source: Figure 14.4.4.5, 14.4.4.6 in Clinical Study Report DU176b-A-U157

Population model for dose selection and calculation of exposure ($AUC_{inf}$):

The population PK model (PopPK) model was previously developed to describe edoxaban PK in adult patients. The edoxaban pediatric PK data (from Studies DU176b-A-U157 and DU176b-A-U312) was best described by a 2-compartment model with linear CL/F and with allometric body weight exponents (0.75

for clearance and 1 for volume). 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 estimated edoxaban concentrations and 90% credible interval (CrI) were well aligned with the observed concentrations. Bayesian estimation was conducted after each age cohort with available cumulative data from both the above pediatric studies and the dose projection was performed for the subsequent cohort in Study DU176b-A-U157.

The model was also used to estimate individual pediatric subject exposures (Area under the concentration time curve (AUC) from time 0 extrapolated to infinity, $AUC_{inf}$) 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 pediatric exposure was within the 0.5 to 1.5-fold of the adult VTE exposure at 60 mg QD dose, the pediatric dose was considered appropriate.

Table 4. Edoxaban doses selected across age cohorts in Study U157

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

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).

Table 5. Median exposures in Cohorts 1 to 5 in Study U157

| Cohort | Nominal Dose | Median Estimated $AUC_{inf}$ (ng.h/mL) | |
|---|---|---|---|
| | | Low dose | High Dose |
| 1 | Low Dose: 30 mg<br>High Dose: 60 mg | 861 | 1778 |

| | | | |
|---|---|---|---|
| 2 | Low Dose: 24 mg<br>High Dose: 45 mg | 963 | 1998 |
| 3 | Low Dose: 0.7 mg/kg<br>High Dose: 1.4 mg/kg | 746 | 1295 |
| 4 | Low Dose: 0.75 mg/kg<br>High Dose: 1.5 mg/kg | 865 | 1735 |
| 5 | Low Dose: 0.4 mg/kg<br>High Dose: 0.8 mg/kg | 900 | 1709 |

Adult reference median exposures for 30 mg and 60 mg QD doses were approximately 1000 and 1600 ng.h/mL, respectively; Source: Table 6 of population PK report of Study DU176b-A-U157

Conclusion:

The higher dose groups in pediatric cohorts resulted in exposures within the range of exposures after an efficacious dose of 60 mg QD in adult VTE patients.

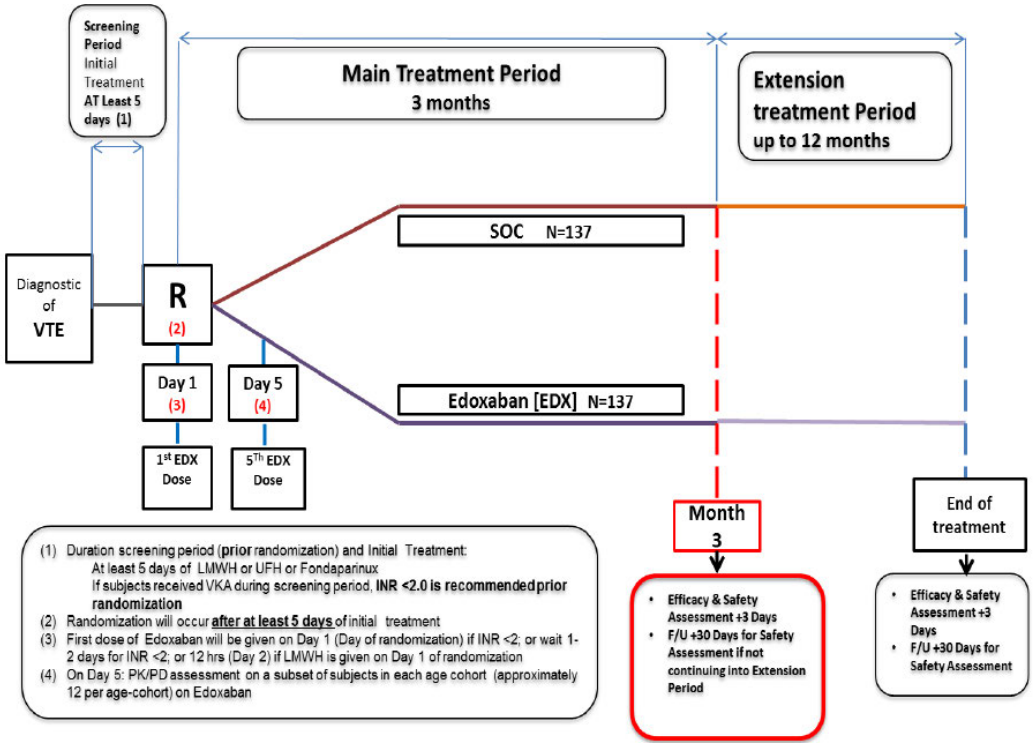
## 2.3 Pediatric efficacy trial (DU176b-D-U312)

Title: A Phase 3, Open-Label, Randomized, Multicenter, Controlled Trial to Evaluate the PK (Pharmacokinetics) and PD (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)

Objectives: The primary objective was to evaluate whether edoxaban after at least 5 days of heparin (UFH, LMWH, or fondaparinux, with overlapping Vitamin K antagonists (VKAs) if given (such as the coumarins: warfarin, acenocoumarol, or phenprocoumon) is noninferior to the standard of care (SOC) (LMWH, VKA, or SP Xa inhibitors) in the treatment of VTE in pediatric patients with regard to the composite efficacy end point, including symptomatic recurrent VTE, death as a result of VTE, and no change or extension in thrombotic burden, during the first 3-month treatment period.

Study design:
This study was an event driven, prospective, blinded endpoint evaluation parallel group study in pediatric subjects with confirmed VTE. The main treatment study period was defined as from randomization until the end of month 3 of treatment, which was mandatory for each randomized subject. The extension treatment period was optional, and it was from the end of the main treatment period up through the end of month 12.

Figure 7. Study Design of Phase 3 pediatric trial

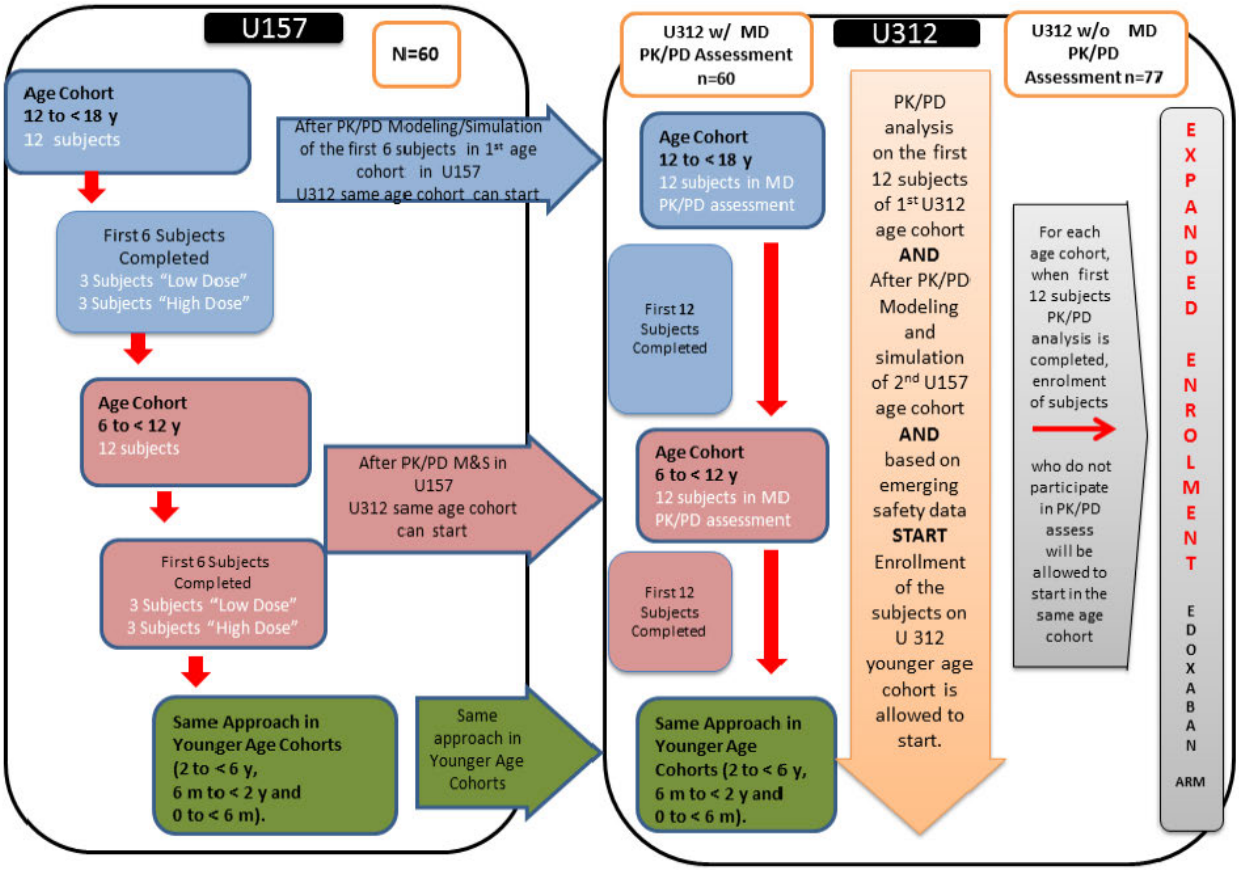



EDX = edoxaban; F/U = follow-up; INR = international normalized ratio; LMWH = low-molecular weight heparin; PD = pharmacodynamic; PK = pharmacokinetic; R = randomization; SOC = standard of care; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism;
Source: Figure 6.1 Clinical Study Report DU176B-D-U312

Based on the adult trials with edoxaban and literature review, an incidence of composite primary efficacy endpoint of 28% in the control arm was expected during the main study period. Based on these estimates, a sample size of 274 subjects (137 each arm) were planned to be randomized to accrue 68 primary efficacy events during the main treatment period.

Dose selection:
Sequential enrollment of age cohorts was used for randomization as well as dose selection for each subsequent younger age cohort. Starting doses for each age cohort in this study was selected based on edoxaban exposure for age-matched subjects and safety data from U157 study (Single-dose PK/PD study in pediatric subjects at risk of VTE) and on population -based PK. A parallel enrollment was used between studies U157 and U312 as shown in the figure.

Figure 8. Parallel enrollment strategy in Phase 1 (U157) and Phase 3 (U312) pediatric trials




Source: Figure 6.2 Clinical Study Report DU176B-D-U312

In Study U312, a subset of patients (first 12 subjects of each age Cohorts 1 to 4 and the first 8 subjects in Cohort 5 randomized to the edoxaban) participated in the multiple-dose PK/PD assessment on Day 5. Based on the Day 5 PK data in this subset of patients, if the estimated median area under the concentration-versus-time curve (AUC) was within (neither less than or higher than) 1.5-fold of the median AUC from the simulated subject population profiles, the enrollment of subjects in the corresponding age cohort continued and enrollment in the next younger age cohort was allowed to begin. Patients participating in the multiple dose PK/PD on Day 5 were on fasting from 1 h prior to and

at least 2 h after dosing of edoxaban. There were 2 PK/PD sampling times on Day 5, which were pre dose and anytime between 0.5 to 3 h after dosing or anytime between 5 to 8 h after dosing. A laboratory-developed test PK assay was performed for edoxaban exposure verification. The PD markers of coagulation included prothrombin time (PT), activated partial thromboplastin time (aPTT), and anti-FXa, levels.

Enrollment in the next younger age cohorts in U312 study began upon the availability of:

- PK analysis and safety data analysis performed on Day 5 participant subjects in the prior older age cohort in U312
- PK analysis and safety data analysis of the subjects in the next younger age cohort in U157

Based on supporting data from Study U157, the first cohort (12 to <18 years) was initiated with a fixed dose (45 and 60 mg for body weight of 30 to <60 and ≥60 kg, respectively), as simulations indicated that the doses would result in similar exposure in adult VTE patients who received edoxaban 60 mg once a day (QD). For the subsequent younger age cohorts (<12 years) a body weight-based dosing (mg/kg) was found appropriate and edoxaban granules for oral suspension was used for dosing.

Table 6. Doses of edoxaban recommended for all five age cohorts in Study 312

| Age | Dose | Dose Reduction [a] |
|---|---|---|
| 12 to <18 years (At date of consent) | 60 mg QD (≥60 kg) | 45 mg QD |
| | 45 mg QD (≥30 and <60 kg) | 30 mg QD |
| | 30 mg QD (<Fifth percentile for age) | NA |
| 6 to <12 years (At date of consent) | 1.2 mg/kg; maximum dose of 45 mg | 0.8 mg/kg; maximum dose of 45 mg |
| 2 to <6 years (At date of consent) | 1.4 mg/kg; maximum dose of 45 mg | 0.7 mg/kg; maximum dose of 24 mg |
| 6 months to <2 years (At date of consent) | 1.5 mg/kg; maximum dose of 45 mg | 0.75 mg/kg; maximum dose of 24 mg |
| >28 days to <6 months (At date of consent) | 0.8 mg/kg; maximum dose of 12 mg | 0.4 mg/kg; maximum dose of 6 mg |
| 38 weeks gestation to ≤28 days (At date of consent) | 0.4 mg/kg; maximum dose of 6 mg | 0.4 mg/kg; maximum dose of 6 mg |

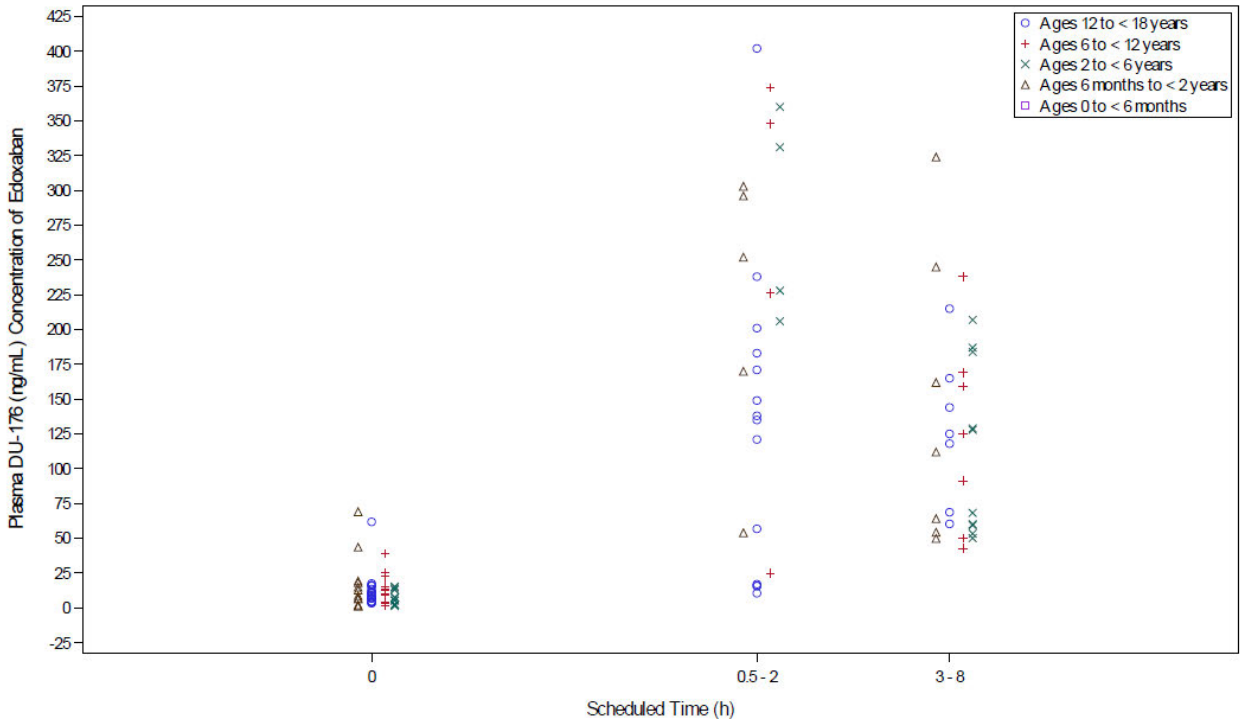
[a] Conditions for dose reduction: If a subject required concomitant administration of P-gp inhibitor, edoxaban dose was reduced during P-gp administration and reestablished to the original dose once P-gp inhibitor administration had concluded; Edoxaban dosage regimen was reduced permanently for subjects with moderate renal impairment (≥30% to ≤50% of normal) for the subject's age and size at randomization as determined by the age-appropriate formula: Cockcroft-Gault equation for pediatric subjects ≥12 years of age and modified Schwartz equation for pediatric subjects <12 years of age). Source: Table 6.1 Clinical Study Report DU176B-D-U312

Results:

The median body weight of the patients in Study 312 was 47 kg (range 2.6 to 183 kg). Majority of enrolled patients (58%) were in 12 to < 18-year cohort and the enrollment in the sequential younger

cohorts were a total of 15 %, 11%, 10% and 6%, respectively. Overall, the mean pre dose plasma concentrations of edoxaban in pediatric subjects across the 5 age cohorts (7.1 to 17 ng/mL) were comparable with those in adult VTE subjects administered with edoxaban at 60 mg QD estimated by adult population PK modeling (16.4 ± 6.3 ng/mL).

Figure 9. Scatter plot of plasma concentrations of edoxaban by time point and age group




Source: Figure 14.4.1.3 in Section 14.4 PK/PD/Biomarker data of Clinical Study Report DU176B-D-U312

The mean 0.5- to 3-hour post dose plasma concentrations in subjects aged 12 to <18 years receiving 60 mg QD dose (140 ± 125 ng/mL) or 45 mg QD dose (145 ± 85 ng/mL) were lower than the observed mean 1 to 3 hours post dose plasma concentration (236 ± 127 ng/mL) in adult VTE subjects administered with edoxaban at 60 mg QD in Study DU176B-D-U305. The mean 0.5-to-3-hour concentrations in all other pediatric cohorts were comparable to the mean 1 to 3 hours post dose plasma concentration in adult VTE subjects.

A population PK model was previously developed using edoxaban PK in adult subjects. Pediatric PK data from single dose study DU176b-A-U157 and multiple dose study DU176b-A-U312 were included in the analysis. The pediatric PK parameters were either fixed as appropriate, based on allometric scaling or ontology, or estimated based on the pediatric PK dataset. The model was used to estimate individual pediatric subject steady state exposures (area under the concentration time curve (AUC) from time 0 to 24 hours at steady state, $AUC_{0\text{-}24h,\ ss}$) and compared to adult references (steady state AUC, $AUC_{0\text{-}24h,\ ss}$) over the dosing interval of 60 mg QD.

The population PK model-estimated individual exposures ($C_{max}$ and $AUC_{0\text{-}24h,\ ss}$) are shown in Table 7. The median $C_{max,ss}$ values in younger patients (0 to <12 years) were 40-50% higher than that in adult patients, while the median $AUC_{0\text{-}24h,ss}$ values in 0 to <6 months, 6 months to <2 years, and 6 to <12 years cohorts

were comparable to that observed in adult patients. The median $AUC_{0\text{-}24h,\ ss}$ values in 2 to <6 years and 12 to <18 years cohorts were 18% and 26% respectively, lower than that observed in adult patients.

Table 7. Population PK model-estimated exposure measures ($C_{max}$ and $AUC_{0\text{-}24h,\ ss}$) for pediatric patients in Study DU176b-D-U312 and Study DU176b-C-U313 by age cohort compared with adult patients

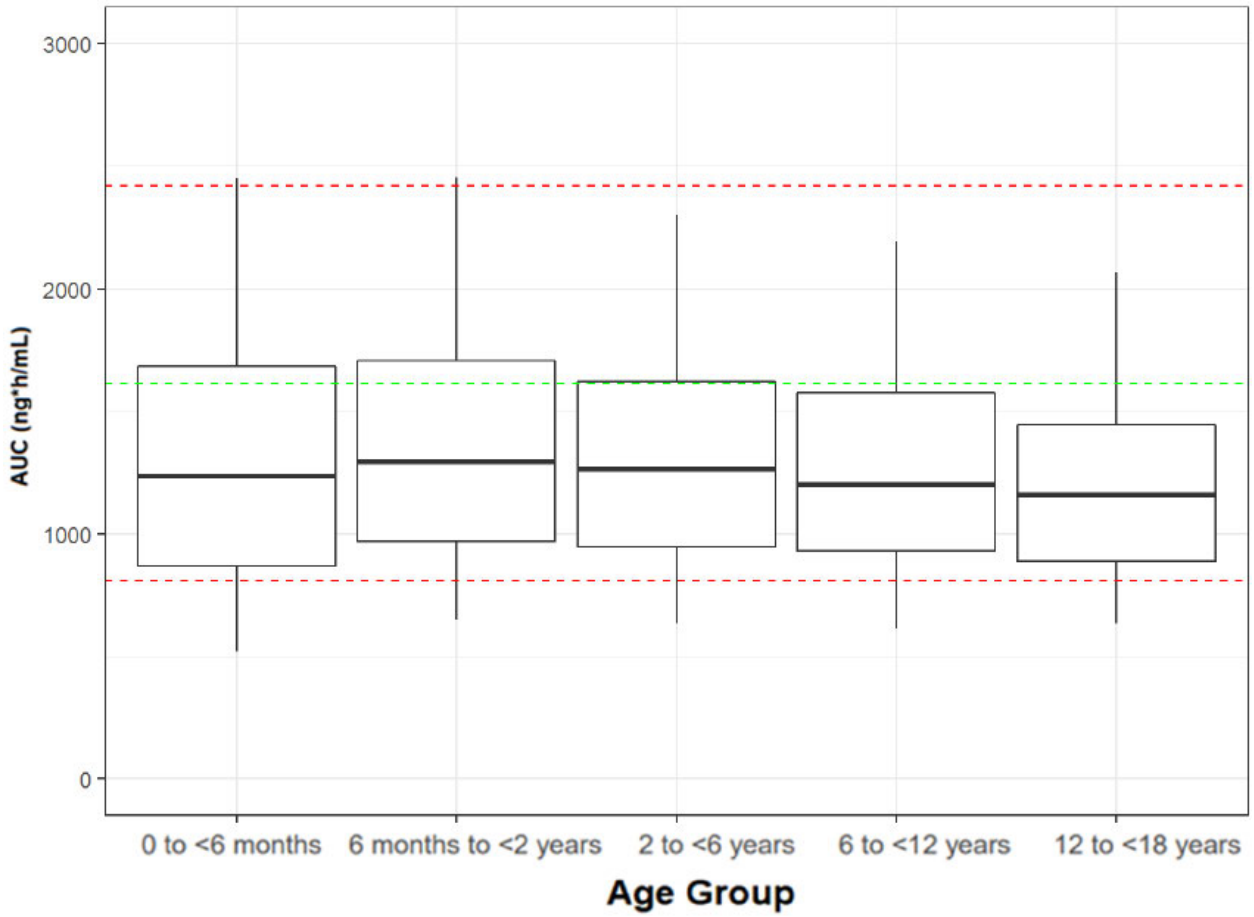
| | 0 to <6 months (N=9) | 6 months to <2 years (N=19) | 2 to <6 years (N=36) | 6 to <12 years (N=38) | 12 to <18 years (N=39) | Pediatric overall (N=141) | Adult VTE patients (N=8976) |
|---|---|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | | | | | | | |
| Mean (SD) | 282 (70.4) | 314 (90.4) | 274 (85.8) | 295 (58.6) | 191 (39.5) | 262 (81.4) | 205 (54.0) |
| Median [Min, Max] | 283 [154, 399] | 299 [161, 532] | 295 [16.4, 402] | 294 [139, 433] | 189 [105, 299] | 265 [16.4, 532] | 203 [52.6, 618] |
| GeoMean (Geo CV%) | 273 (27.9%) | 301 (30.0%) | 244 (72.0%) | 289 (21.6%) | 187 (21.9%) | 246 (44.3%) | 198 (27.2%) |
| $AUC_{0\text{-}24h,\ ss}$ (ng*h/mL) | | | | | | | |
| Mean (SD) | 1710 (713) | 1700 (919) | 1290 (611) | 1550 (622) | 1210 (363) | 1420 (637) | 1573 (361) |
| Median [Min, Max] | 1640 [640, 3140] | 1600 [679, 3960] | 1270 [58.2, 3100] | 1510 [629, 3990] | 1150 [613, 2490] | 1320 [58.2, 3990] | 1556 [607, 3141] |
| GeoMean (Geo CV%) | 1570 (47.1%) | 1480 (57.5%) | 1090 (85.2%) | 1450 (38.9%) | 1170 (28.7%) | 1450 (38.9%) | 1531 (24.0%) |

The summary is based on the model-estimated $AUC_{0\text{-}24h,\ ss}$ and $C_{max,ss}$ of 141 pediatric patients enrolled in DU176b-D-U312 and DU176b-C-U313 studies and with available PK data; GeoMean = geometric mean; Geo CV% = geometric coefficient of variation; Source: Table 1.1 of Response to Information request on 03 May 2023 under SN0220 of NDA 206316

To evaluate the age-, weight-, and eGFR-based doses, simulations were conducted with a virtual population (approximately 1000 subjects per age cohort) generated by sampling for each age-, body weight-, and eGFR group. The simulations were performed using the final PopPK model and following the proposed clinical doses and the simulated $AUC_{0\text{-}24h,ss}$ of the five age cohorts were compared with 0.5-fold and 1.5-fold median $AUC_{0\text{-}24h,ss}$ of adult VTE patients receiving 60 mg QD dose.

Across the five pediatric age groups, the simulated median exposures were lower (by 19% to 28%) than the adult exposures, however, the median and interquartile range of pediatric exposures ($AUC_{0\text{-}24h,\ ss}$) were still within the range of adult reference exposures (0.5- to 1.5-fold of median $AUC_{0\text{-}24h,\ ss}$ of adult VTE patients receiving 60 mg QD dose). The median adult reference exposure was 1613 ng*h/mL and the median values for cohorts of 0 to <6 months, 6 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years were 1250, 1310, 1270, 1210, and 1160 ng*h/mL, respectively.

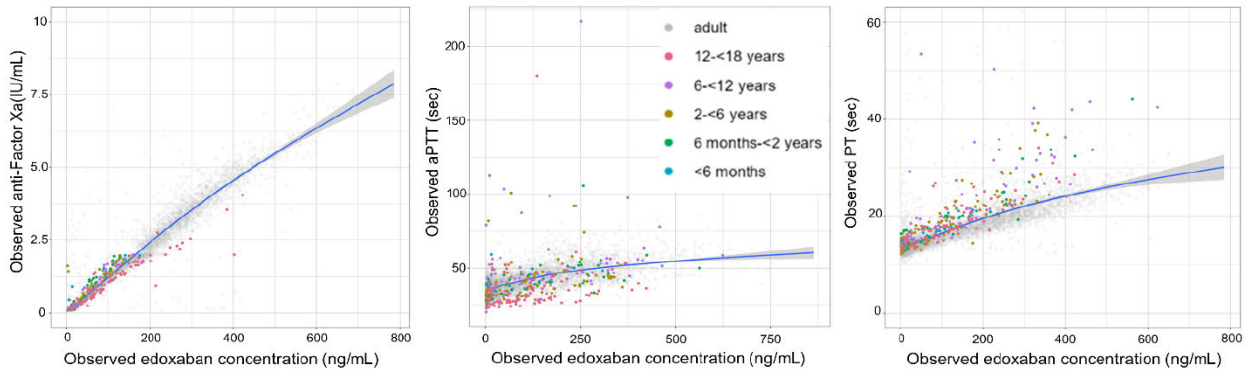
Figure 10. Simulated post hoc $AUC_{0\text{-}24\ h,\ ss}$ of edoxaban in the five pediatric age cohorts using a virtual population (~1000 subjects per age cohort)




Note: Green dotted line shows Population PK model-estimated median $AUC_{0\text{-}24,\ ss}$ (1613 ng*h/mL) in adult VTE patients receiving edoxaban 60 mg QD. Red dotted lines show 0.5- and 1.5-fold of median $AUC_{0\text{-}24,\ ss}$ (806.5 and 2419.5 ng*h/mL) in adult VTE patients receiving edoxaban 60 mg QD. Boxplot represents $5^{th}$, $25^{th}$, median, $75^{th}$, and $95^{th}$ percentiles of simulated $AUC_{0\text{-}24h,\ ss}$ in the five pediatric cohorts;
Source: Figure 1.1 of Response to Information request on 03 May 2023 under SN0220 of NDA 206316

The visual comparison showed that the nature of the PK/PD relationship for the PD markers (PT, aPTT, and anti-FXa) in pediatric subjects were also consistent with observations in adult VTE subjects administered with 60 mg QD of edoxaban.

Figure 11. Comparison of pharmacodynamic biomarkers (anti-Factor Xa, aPTT, and PT) vs. observed edoxaban concentration in adults and children




Source: Figure 1.2 of Response to Information request on 03 May 2023 under SN0220 of NDA 206316

*Reviewer's note:*

From the primary endpoint perspective, the Phase 3 study failed to demonstrate non-inferiority of edoxaban over the standard-of-care, as the predefined upper boundary of the 95% CI margin of 1.5 was exceeded. A total of 31 and 26 events occurred in the edoxaban and SOC groups, respectively, resulting in a total of 57 events. However, as the study expected to accrue 68 primary events in total, the lower-than-expected number of events has contributed to the failure to meet the pre-specified non-inferiority margin. Overall, the dose selection in pediatric patients was considered reasonable as pediatric exposures were within the range of adult exposures following 60 mg dose in patients with VTE. That said, the median simulated steady state $AUC_{0\text{-}24}$ of edoxaban across various pediatric age groups was modestly lower (ranging from 18% to 27%) in comparison to adult VTE exposures. While the current pediatric efficacy trial failed due to inadequate sample size, if the Applicant were to conduct another trial, the pediatric dosing could be refined further to match adult exposures even closely.

## 2.4 Summary of Bioanalytical Method Validation and Performance

Study DU176b-A-U157:

The plasma concentrations of edoxaban in Study DU176b-A-U157 were quantified using the validated LC-MS/MS method (Validation Report 140524PVRM_DEN_R1). Lithium heparinized plasma aliquots (20 µL) were processed using solid phase extraction and edoxaban-D6 was used as the internal standard. The assay had a lower limit of quantification of 0.764 ng/mL and the upper limit of quantitation was 382 ng/mL. The concentrations used for quality control (QC) samples were 2.29, 45.8, 153 and 306 ng/mL.

The cumulative and individual bias and precision for calibration curves and QC samples during study sample analyses (done in 29 batches) were within (≤15%) acceptable limits.

| | Accuracy (% bias) | Precision (% CV) |
|---|---|---|
| Performance of calibration standards | -1.0% to 0.8% | 1.9% to 3.6% |
| Performance of Analytical QCs | -2.2% to 0.4% | 5.8% to 9.8% |

All study samples were quantified within 703 days and less than the time limits for storage stability that were employed during validation (793 days at -20°C). Incurred sample reproducibility data were generated by re-analysis of 45 samples of which 43 (96%) were within the limits (±20% of the original for at least 67% of cases).

Study DU176b-D-U312:

The plasma concentrations of edoxaban in Study DU176b-D-U312 were quantified using the validated LC-MS/MS method (Validation Report 140524PVRM_DEN_R1). Lithium heparinized plasma aliquots (20 µL) were processed using solid phase extraction and edoxaban-D6 was used as the internal standard. The assay had a lower limit of quantification of 0.764 ng/mL and the upper limit of quantitation was 382 ng/mL. The concentrations used for quality control (QC) samples were 2.29, 45.8, 153 and 306 ng/mL.

The cumulative and individual bias and precision for calibration curves and QC samples during study sample analyses (done in 19 batches) were within (≤15%) acceptable limits.

| | Accuracy (% bias) | Precision (% CV) |
|---|---|---|
| Performance of calibration standards | -0.7% to 0.8% | 2.2% to 4.6% |
| Performance of Analytical QCs | -3.1% to 0.4% | 5.2% to 16.6%* |

*Overall precision was biased due to individual outlier replicates, however, within run acceptance criteria were met for each QC

All study samples were quantified within 289 days and less than the time limits for storage stability that were employed during validation (793 days at -20°C). Incurred sample reproducibility data were generated by re-analysis of 43 samples of which 37 (86%) were within the limits (±20% of the original for at least 67% of cases).

Results of accuracy, precision, stability, and incurred sample reanalysis using the same validated method were within acceptable limits during the quantification of edoxaban in clinical samples from both the clinical studies above. Hence, the PK results from studies DU176b-A-U157 and DU176b-D-U312 are considered acceptable.

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