CLINICAL STUDY PROTOCOL

A PHASE 3, OPEN-LABEL, RANDOMIZED, MULTI-CENTER, CONTROLLED TRIAL TO EVALUATE THE PHARMACOKINETICS AND PHARMACODYNAMICS OF EDOXABAN AND TO COMPARE THE EFFICACY AND SAFETY OF EDOXABAN WITH STANDARD OF CARE ANTICOAGULANT THERAPY IN PEDIATRIC SUBJECTS FROM BIRTH TO LESS THAN 18 YEARS OF AGE WITH CONFIRMED VENOUS THROMBOEMBOLISM (VTE)

DU176b-D-U312

IND NUMBER 63,266

EUDRACT NUMBER 2016-000991-49

VERSION 4.0, 08 JUN 2021

VERSION 3.0, 07 JUN 2019

VERSION 2.0, 19 JAN 2018

VERSION 1.0, 21 APR 2016

SPONSOR:	Daiichi Sankyo, Inc. 211 Mount Airy Road Basking Ridge, NJ 07920, USA

INVESTIGATOR AGREEMENT

A Phase 3, Open-Label, Randomized, Multi-Center, Controlled Trial to Evaluate the Pharmacokinetics and Pharmacodynamics of Edoxaban and to Compare the Efficacy and Safety of Edoxaban with Standard of Care Anticoagulant Therapy in Pediatric Subjects from Birth to Less Than 18 Years of Age with Confirmed Venous Thromboembolism (VTE)

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo Inc. representative listed below.

PPD

Print Name

PPD

Signature

Executive Director, Clinical Development (Specialty Medicine)

Title

8 Jun 2021

Date (DD MMM YYYY)

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a principal Investigator as provided by the sponsor.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

Print Name

Signature

Title

Date (DD MMM YYYY)

GLOBAL AMENDMENT, PROTOCOL VERSION 4.0

HIGH-LEVEL DESCRIPTION OF EACH CHANGE: RATIONALE AND LOCATION

Changes to the Protocol:

Please refer to the comparison document (tracked changes) of protocol Version 3.0 (dated 07 Jun 2019) versus protocol Version 4.0 (dated 08 Jun 2021) for actual in-text changes. The summary of changes below is a high-level summary of major changes in the clinical study protocol (Version 4.0) by section.

Table of High Level Changes to Protocol from Version 3.0 to Version 4.0

1	**In Cohort 5, subjects ≤28 days old are to be given a reduced dose of edoxaban at 0.4 mg/kg.** The following sections of the protocol were updated: • Table 5.1 Edoxaban Dose Recommended for All 5 Cohorts (12 to <18 years, 6 to <12 years, 2 to <6 years, 6 months to <2 years, and birth to <6 months)
2	**In Cohort 5, subjects may receive anticoagulation treatment for an intended duration of at least 6 to 12 weeks.** The following sections of the protocol were updated: • Protocol Synopsis • Section 2.1.1 Primary Objective • Section 2.1.2 Secondary Objectives • Section 3.2 Discussion of Study Design • Section 3.3 End of Study • Section 5.6.6 Follow-up Procedures • Section 6.3 Main Treatment Period • Section 6.3.1 Subjects randomized to the edoxaban treatment arm • Section 6.3.3 Monthly Visits (Months 1 and 2; Visits 3 and 4) for both arms • Section 6.3.4 End of Main Treatment Period Visit (Month 3 or at least 6 to 12 Weeks for Cohort 5, Visit 5) Procedures • Section 7.1 Primary Efficacy Endpoint(s) • Section 7.2 Secondary Efficacy Endpoint(s) • Section 9.2 Safety Endpoint Event(s) • Table 17.1: Schedule of Events

3	**For Cohort 5, the sample size on Day 5 will be between 5 and 12 for subjects on edoxaban treatment.** The following sections of the protocol were updated: • Protocol Synopsis • Section 3.2 Discussion of Study Design • Section 4.3.1 Stopping Rules for Age-based cohort during PK/PD assessment • Section 6.3.1 Subjects randomized to the edoxaban treatment arm • Section 8 Pharmacokinetic/Pharmacodynamic Assessments • Table 17.1: Schedule of Events
4	**In Cohort 5, renal function monitoring will be done on or around Day 5 (at the same time of PK sampling).** The following sections of the protocol were updated: • Section 6.3.1.1 Study Day 5 (+3 days) for Subjects Randomized to Edoxaban Only (Visit 2a) • Section 8 Pharmacokinetic/Pharmacodynamic Assessments • Table 17.1 Schedule of Events
5	**In Cohort 5, site staff will contact the parents by phone on approximately Day 2, Day 7, and every week thereafter until Month 1 (Visit 3) post discharge to inquire about AEs, SAEs, and bleeding events.** The following section of the protocol was updated: • Section 9.1 Adverse Event Collection and Reporting
6	**For subjects in Cohort 5, a radiologic VTE image will be taken at the end of the intended treatment period (at least 6-12 weeks) or at the discontinuation visit if anticoagulant treatment is received for <3 months.** The following sections of the protocol were updated: • Protocol Synopsis • Section 4.1 Inclusion Criteria • Section 6.3.1 Subjects randomized to the edoxaban treatment arm • Section 6.3.3 Monthly Visits (Months 1 and 2; Visits 3 and 4) for both arms • Section 7.1 Primary Efficacy Endpoint(s) • Table 17.1: Schedule of Events

PROTOCOL SYNOPSIS

EudraCT:	2016-000991-49
IND Number:	IND 63,266
Protocol Number:	DU176b-D-U312
Investigational Product:	Edoxaban (DU-176b)
Active Ingredient(s)/INN:	Edoxaban tosylate: *N*-(5-Chloropyridin-2-yl)-*N'*-[(1*S*,2*R*,4*S*)-4-(*N*,*N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-*c*]pyridine-2-carboxamido)cyclohexyl] oxamide mono(4-methylbenzenesulfonate) monohydrate
Study Title:	A Phase 3, open-label, randomized, multi-center, controlled trial to evaluate the pharmacokinetics and pharmacodynamics of edoxaban and to compare the efficacy and safety of edoxaban with standard of care anticoagulant therapy in pediatric subjects from birth to less than 18 years of age with confirmed venous thromboembolism (VTE)
Study Phase:	Phase 3
Study Acronym:	The Edoxaban Hokusai VTE PEDIATRICS Study
Indication Under Investigation:	Treatment and secondary prevention of VTE

Study Objectives:

Primary Objective:

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

Secondary Objectives:

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

	• To compare edoxaban against SOC with regard to occurrence of DVT, catheter-related thrombosis, PE, sinovenous thrombosis within and after the first 3-month treatment period (for Cohort 5, the intended duration of treatment is at least 6-12 weeks). • To compare edoxaban against SOC with regard to a composite combination of major and CRNM bleedings from first to the last dose + 30 days. • To characterize the multiple dose pharmacokinetics of edoxaban in pediatric subjects at Day 5 using population pharmacokinetic (PK) analysis (apparent systemic clearance [CL/F] and apparent volume of distribution [V/F]) and to assess the effect of covariates such as age, body weight, and renal function on the PK of edoxaban. • To evaluate the relationship between edoxaban exposure and safety (such as bleeding) and efficacy (thromboembolic events). • To characterize the effect of edoxaban on biomarkers of coagulation (ie, prothrombin time [PT], activated partial thromboplastin time [aPTT], and anti-activated factor X [anti-FXa]).
Study Design:	This is an event driven Phase 3, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group study in subjects with confirmed VTE. This study is designed to evaluate the PK and pharmacodynamics (PD) of edoxaban and to compare the efficacy and safety of edoxaban after at least 5 days of heparin (LMWH or SP Xa inhibitors or unfractionated heparin (UFH); with overlapping VKAs if needed) against SOC (LMWH, VKA, or SP Xa inhibitors) in pediatric subjects with confirmed VTE. The adjudication of the efficacy and safety endpoints will be conducted by a blinded adjudication committee. The study includes two periods: • The Main Treatment Period is defined as the time from randomization, until the end of Month 3 of treatment. The Main Treatment Period for subjects less than 6 months (Cohort 5) old is defined as the time from randomization until the end of anticoagulant therapy for at least 6 to12 weeks

  - Subjects who early discontinue the Main Treatment Period will be monthly followed according to the Schedule of Events (Table 17.1) through Month 3 visit (Visit 5) and 30 day Follow-Up Visit (Visit 9).
  - Subjects who complete the Main Treatment Period but do not continue into the Extension Period will be followed for 30 days after last dose of study drug (Visit 9).
  - If a subject discontinues study medication before Month 2, the follow up visit may be combined with the Month 3 Visit.

- The Extension Period is discretionary for the Investigator and will include treatment from the end of the Main Treatment Period (Month 3, Visit 5) up through the end of Month 12 (Visit 8).
  - Subjects who discontinue the treatment at any time after Month 3 will have a Month 12/Discontinuation Visit (Visit 8) performed with the subsequent 30-day follow-up (Visit 9).
  - Subjects who complete Extension Period treatment at Month 12 (Visit 8) will be followed for 30 days after last dose of study drug (Visit 9).
- Subjects who require anticoagulant treatment after discontinuation of the study treatment at any time will be transitioned to a therapy as determined by the Investigator.

The study will attempt to recruit at least 10% of the subjects diagnosed with pulmonary embolism.

About 274 subjects will be included in this randomized study (137 subjects in each treatment arm) which will be conducted at clinical sites located worldwide.

Randomization will be stratified by age cohorts and by region (US/Canada, Europe, Asia/Pacific, and Rest of the World).

After subjects are assessed for eligibility based on a newly diagnosed index VTE by imaging and per the inclusion/exclusion criteria, and have undergone bridging treatment of at least 5 days of heparin (LMWH or SP Xa inhibitors or UFH; with overlapping VKAs if needed) prior to

randomization, the subjects will be randomized in a 1:1 ratio into one of the two study arms:

- Edoxaban treatment arm: subjects will receive selected dose of Edoxaban

or

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

In the case of centrally sourced SOC treatment, Sponsor will only provide enoxaparin as LMWH, fondaparinux as SP Xa inhibitor, or warfarin as VKA.

The subjects will be recruited into 5 age cohorts:

- Ages 12 to <18 years
- Ages 6 to <12 years
- Ages 2 to <6 years
- Ages 6 months to <2 years
- Ages birth to <6 months

Sequential enrollment of age cohorts will be used for randomization. The order of enrollment will be from the oldest age cohort to te youngest age cohort. The first age cohort to be randomized will be from ages 12 to <18 years. Doses for all subsequent age cohorts will be made by separate notifications to the investigative sites, outside the content of this protocol, and after the Independent Data Monitoring Committee (IDMC) has approved the proposed edoxaban doses.

Subjects in edoxaban treatment arm (137 subjects):

Starting doses for each age cohort in the U312 study will be selected based on edoxaban exposure for age matched subjects and safety data from a supporting Phase 1 Study DU176b-A-U157 study (Single-dose PK/PD study in pediatric subjects at risk of VTE), and on population-based PK.

Edoxaban treatment will be dispensed to the subject on a monthly visit schedule. After Month 3, on a case-by-case basis, confirmed by the Sponsor, a 3-month dispense may occur to facilitate subject travel arrangements. The oldest cohort (12 to

<18 years of age) will receive tablets. All younger age cohorts (<12 years) will receive edoxaban granules for oral suspension and will be dosed on an mg/kg basis (see Section 5.1.1.1).

The enrollment into the first age cohort (12 to <18 years) of U312 study will begin when the edoxaban dose for this age cohort is selected from the supporting Phase 1 Study U157 (see Section 5.1.1.1). Approximately the first 12 subjects of each age cohort (total of 53 to 60 subjects) randomized to the edoxaban treatment arm (subject number is determined by evaluable blood specimens demonstrating edoxaban exposure) will participate in the multiple-dose PK/PD assessment on Day 5 (+3 days, Visit 2a) as follows:

- Ages 12 to <18 years (N≈12)
- Ages 6 to <12 years (N≈12)
- Ages 2 to <6 years (N≈12)
- Ages 6 months to <2 years (N≈12)
- Ages birth to <6 months (N≈5-12)

Two blood samples will be collected on the day of the fifth dose of edoxaban (Day 5+3 days, Visit 2a) for all age cohorts, participating in the edoxaban PK/PD analysis, including:

- PK Pre-dose sample for all participating subjects.
- PK Post-dose sample can be taken at either:
  - any time between 1.0 to 3 hours post-dose

  or

  - any time between 5 to 8 hours post-dose
- The PD sampling times on Day 5 for measurement of PT, aPTT and anti-FXa, will be taken at the same time as the PK samples.
- A PK analysis will be performed. If the analysis of the subjects confirms the edoxaban exposure predictions and based on emerging safety, the expanded enrollment in the same age cohort will be allowed to start. A notification will be sent to all Investigators that expansion of the age cohort is permitted after the PK analysis. In addition, a notification to the Investigator will indicate that Day 5 PK/PD edoxaban exposure evaluation will no

	longer be necessary for future subjects randomized to edoxaban in the corresponding age cohort. Enrollment in the next younger age cohorts in U312 study will begin upon the availability of: • PK analysis performed on participating subjects in the prior older age cohort in U312. • Safety data analysis on the subjects in the prior older age cohort in U312. • PK analysis of the subjects in the next younger age cohort in U157. • Safety data analysis on the subjects of the next younger age cohort in U157. PK and safety data will be reviewed by an Independent Data Monitoring Committee (IDMC; Section 15.9) who will approve the start of the next younger age cohort. In each age cohort if the estimated median AUC based on the observed PK data in a subset of subjects on Day 5 PK assessment is less than 1.5-fold the median AUC from the simulated subject population profiles (over-exposure and under-exposure), the enrollment of subjects in the corresponding age cohort will continue and enrollment in the next younger age cohort can begin.
Study Duration:	The total duration of the study is expected to be approximately 4.5 years. The total duration of study participation for any individual subject will be a minimum of 4 months (3-month Main Treatment Period and 30 days Follow-up) and maximum of 13 months (3-month Main Treatment Period, 9-month Extension Period and 30 days Follow-up). -For subjects <6 months old (Cohort 5) with the presence of documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy, the intended duration of treatment is for at least 6 to 12 weeks.
Study Centers and Location:	This study will be conducted in US/Canada, Europe, Asia/Pacific, and Rest of the World.

Subject Eligibility Criteria:

Inclusion Criteria:

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

1. Male or female pediatric subjects between birth (defined as 38 weeks gestational age) and less than 18 years of age at the time of consent.
2. Pediatric subjects with the presence of documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 90 days (list of VTE provided in Section 7.1).

   -Subjects <6 months old (Cohort 5) with the presence of documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 6 to12 weeks
3. Subjects must have received at least 5 days of heparin (LMWH or SP Xa inhibitors or UFH according to the edoxaban label for VTE treatment) therapy prior to randomization to treat the newly identified index VTE. In addition, prior to being randomized to edoxaban or SOC, subjects initially treated with VKA are recommended to have an INR ≤2.5.
4. Subject and/or parent(s)/legal guardian(s) or legally acceptable representative is informed and provides signed consent for the child to participate in the study with edoxaban treatment. Pediatric subjects with appropriate intellectual maturity will be required to sign an assent form in addition to the signed informed consent from the parent(s)/legal guardian(s) or any legally acceptable representative.
5. Female subjects who have menarche must test negative for pregnancy at Screening and must consent to avoid becoming pregnant by using an approved contraception method throughout the study (Appendix 17.3).

Exclusion Criteria:

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Subjects with active bleeding or high risk of bleeding contraindicating treatment with LMWH, SP Xa inhibitors, VKAs, or direct oral anticoagulants (DOACs; identified high risk of bleeding during prior experimental administration of DOACs).

2. Subjects who have been or are being treated with thrombolytic agents, thrombectomy or insertion of a caval filter for the newly identified index VTE.
3. Administration of antiplatelet therapy is contraindicated in both arms except for low dose aspirin defined as 1-5 mg/kg/day with maximum of 100 mg/day (see Appendix 17.4.1).
4. Administration of rifampin is prohibited during the study and subjects on concomitant use of rifampin are excluded.
5. a) Subjects with severe hepatic impairment or hepatic disease associated with coagulopathy (eg, acute hepatitis, chronic active hepatitis, and cirrhosis).

   b) Subjects with ALT >5 × the upper limit of normal (ULN) or total bilirubin >2 × ULN with direct bilirubin >20% of the total at Screening.

   c) Subjects with aPTT >50 seconds or international normalized ratio [INR] >2.0 not related to anticoagulation therapy).
6. Subjects with estimated glomerular filtration rate (eGFR) <30% of normal for age and size (see Appendix 17.7).
7. Subjects with stage 2 hypertension defined as blood pressure (BP) systolic and/or diastolic confirmed >99th percentile + 5 mmHg (see Appendix 17.8).
8. Subject with thrombocytopenia <50 × 10^9/L at Screening Visit. Subjects with a history of heparin-induced thrombocytopenia may be enrolled in the study at the Investigator's discretion.
9. Life expectancy less than the expected study treatment duration (3 months).
10. Subjects who are known to be pregnant or breastfeeding.
11. Subjects with any condition that, as judged by the Investigator, would place the subject at increased risk of harm if he/she participated in the study including contraindicated medications identified in Appendix 17.4.
12. Subjects who participated in another interventional clinical study or were treated with an experimental therapy with less than a 30-day wash-out period prior to identifying the qualifying index VTE.

	13. Hypersensitivity to the active ingredient or to any of the excipients of any components of the trial treatment. 14. Patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome who are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies).
Additional Requirements:	**Stopping Rules for Age-based cohort during PK/PD assessment:** • In each age cohort, if the estimated edoxaban median AUC based on the observed PK data in the approximately 12 subjects (5-12 subjects in Cohort 5) on Day 5 PK assessment is 50% higher or 50% lower than the median AUC from the simulated subject population profiles, dose reevaluations for Phase 3 subjects will be recommended to achieve the exposure comparable to adult 60 mg doses. The enrollment of subjects in the corresponding age cohort will be put on hold until reevaluation of the dose for this age cohort. **Stopping Rules for Study:** An IDMC may recommend termination of the study. Termination may be made for any of the following reasons: • Concern about significantly higher bleeding risk relative to one of the study arms, • Concern about drug-induced liver injury, • Any other safety concern based on benefit/risk evaluation.
Dosage Form, Dose and Route of Administration:	**<u>Pre-Randomization Treatment (Screening)</u>** Pre-randomization treatment will be provided by the Investigator or diagnosing clinic of the index VTE. Initial treatment using LMWH or SP Xa inhibitor or UFH for index VTE prior to randomization must be within the range of 5 to 15 days and up to 20 days with Sponsor approval. If VKA are administrated prior randomization, INR prior to randomization is recommended to be ≤2.5. After pre-randomization, study treatment should be administered on the same day of randomization (Day 1).

Subject will be randomized (Day 1) in a 1:1 ratio into one of the two study arms.

Randomization to Edoxaban Treatment Arm

Randomization will occur after at least 5 days of LMWH/UFH/SP Xa inhibitors (with overlapping VKA if needed), post diagnosis of VTE.

Edoxaban treatment will be dispensed to the subject on a monthly visit schedule. After Month 3, on a case-by-case basis, confirmed by the Sponsor, a 3-month dispense may occur to facilitate subject travel arrangements.

Randomization Day will be edoxaban Day 1. If the subject was on a VKA and randomized with INR ≥2.5, edoxaban treatment may be delayed until the INR is ≤2.5. The Day 5 PK/PD assessment will be adjusted to accommodate the delay in edoxaban dosing. For subjects participating in PK/PD assessment and receiving LMWH twice a day and who already received a morning dose on Day 1 prior to randomization, edoxaban can be started on the morning of Day 2 (12 hours ± 3 hours after last evening dose of LMWH).

Edoxaban will be started orally at the age/weight/renal function appropriate dose (see Section 5.1.1.1.1) for the Treatment Period (see Section 5.2.4.1). The following dosage forms will be provided for this study:

- Edoxaban 15 mg and 30 mg tablets for 12 to <18 years old subjects;
  - 60 mg dose will be dispensed with two 30 mg tablets
  - 45 mg dose will be dispensed with one 30 mg tablet plus one 15 mg tablet
  - 30 mg dose will be dispensed with one 30 mg tablet
- If a subject does not have the capacity to swallow tablets in the 12 to <18 year old group, the tablets may be crushed and served with applesauce or mixed with 2 to 3 ounces of water and immediately administered by mouth or through a gastric tube.
- Edoxaban granules for oral suspension 60 mg. It will be reconstituted in 8 mL water to provide a 6 mg/mL liquid suspension for subjects younger than 12 years old. Doses provided by the granulation formulation

will be dispensed with an oral dosing syringe according to the recommended doses for the age cohort.

All subjects will receive once a day edoxaban tablet(s) of 15 mg and/or 30 mg strength if they are at least 12 years of age. Subjects younger than 12 years of age will receive edoxaban granules for oral suspension. In each cohort, doses will be selected to elicit target exposures comparable to those achieved from adult doses of 60 mg if no dose adjustment needed.

Dosing regimen for each age cohort will be determined from Phase 1 single dose Study U157 and population based PK.

The dose for the 12 to <18 years of age cohort was selected from the Study DU176b-A-U157 data that were available when this Study U312 was first designed (see Section 5.1.1.1.1). Based on subsequent IDMC review of Cohort 1 (12 to <18 years of age) data from this Study U312 and corresponding cohort data from Study U157, the proposed dose for 6 to <12 years and 2 to < 6 years cohort is proposed; for subjects < 2 years, the final dose for the cohort is based upon IDMC recommendation (see Section 5.1.1.1.2).

Subjects will be instructed to take edoxaban (tablets or granules) orally once a day, at the same time every day, with or without food. Tablets should be swallowed with a glass of water. Edoxaban dosage regimen will be reduced (see Table 5.1 the following reasons:

Body Weight (BW) <5th percentile of subject's age (see Appendix 17.9)

- The edoxaban dosage regimen will be reduced permanently for subjects with moderate renal impairment (eGFR) ≥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 (Appendix 17.7). If a subject experiences a change in renal function from normal to eGFR ≥30% to ≤50% after randomization, the measurement will be repeated within 1 week to 10 days after correction of the underlying factor's causing pre-azotemia. If the repeat measurement confirms the reduced eGFR, the edoxaban dose will be reduced permanently.

- Additionally, if a subject requires concomitant administration of a certain P-glycoprotein (P-gp) inhibitor (Appendix 17.4.6), the edoxaban dose will be reduced during P-gp administration and re-established to the original dose once P-gp inhibitor administration had concluded.
- Subject is ≤28 days old (corrected for gestation age of 38 weeks). This may change based on the IDMC recommendation.

Randomization to Standard of Care Treatment Arm

Standard of care treatment will be dispensed to the subject on a monthly visit schedule. After Month 3, on a case-by-case basis, confirmed by the Sponsor, a 3-month dispense may occur to facilitate subject travel arrangements.

Local SOC sourcing:

The SOC will be provided by the Investigator. Subject will be treated with LMWH, VKA, or SP Xa inhibitors according to the site SOC treatment regimen (see Section 5.1.1.2).

Central/Sponsor Sourcing:

However, if there are regulatory or site hurdles providing the SOC, the Sponsor will provide SOC as enoxaparin or fondaparinux or warfarin as follows:

- Enoxaparin – Subjects will be treated with enoxaparin alone or can be switched to warfarin anytime during the study treatment period.
  - Enoxaparin (LMWH) will be provided to the subjects as solution for subcutaneous (SC) injection in pre-filled syringes with 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1.0 mL concentration for injection, or as multiple dose vials (for subjects <10 kg) for injection where allowed per standard clinical practice.
- Fondaparinux – Subjects will be treated with fondaparinux alone or can be switched to warfarin anytime during the study treatment period.
  - Fondaparinux will be supplied as solution for SC injection in pre-filled syringes (2.5 mg/0.5 mL, 5.0 mg/0.4 mL, 7.5 mg/0.6 mL, 10.0 mg/0.8 mL, and where available 1.5 mg/0.3 mL).

	• Warfarin will be supplied as tablets (0.5 mg, 1.0 mg, and 3.0 mg). For subjects in whom clinicians prescribe warfarin, then warfarin will be started on Day 1. Heparin (enoxaparin or fondaparinux or UFH depending on the therapy received during pre-randomization period) will be discontinued when INR ≥2.0 and ≤3.0 for 2 consecutive measurements obtained at least 24 to 48 hours apart. The subject will continue warfarin for the remainder of the study treatment period.
Study Endpoints:	All safety and efficacy endpoints described below will be adjudicated in a blinded manner by the Clinical Events Committee (CEC). **Primary Efficacy Endpoint:** The primary efficacy endpoint is a composite endpoint consisting of the incidence of symptomatic recurrent venous thromboembolic disease, death as a result of VTE, and no change or extension of thrombotic burden (Section 7.1) during the first 3 months period. -For subjects in Cohort 5, (ie, <6 months old), the primary efficacy endpoint is a composite endpoint consisting of the incidence of symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden within 6 to12 weeks + 3 days. **Secondary Efficacy Endpoints:** The secondary efficacy endpoints include: • A composite endpoint consisting of symptomatic recurrent venous thromboembolic disease, death as a result of VTE, and no change or extension of thrombotic burden from randomization to the date of the last dose of study drug + 30 days . • The individual components of the primary efficacy endpoint during the first 3-month period (for Cohort 5, the intended duration of treatment is 6-12 weeks): – Symptomatic recurrent VTE – Death as a result of VTE – No change or extension of thrombotic burden • All-cause mortality from randomization to last dose + 30 days.

- The DVT, Catheter-related thrombosis, PE, sinovenous thrombosis events within and after the first 3-month treatment period (for Cohort 5, the intended duration of treatment is 6-12 weeks).

Net Clinical Outcome Endpoint:

- Composite of symptomatic recurrent VTE events, death as a result of VTE, and major and CRNM bleeding that occurred from the date of the first dose of study drug to the date of last dose of study drug + 30 days.

Safety Endpoints:

The safety endpoints are:

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

Pharmacokinetic and Pharmacodynamic Endpoints:

Approximately, the first 12 subjects of each age cohort (total of approximately 53 to 60 subjects) randomized to the edoxaban treatment arm will participate in the multiple-dose PK/PD assessment on Day 5

Pharmacokinetics:

- Using population PK analysis, the following PK parameters will be estimated: apparent systemic clearance (CL/F) and apparent volume of distribution (V/F) of edoxaban.

Pharmacodynamics:

- The following biomarkers of coagulation will be estimated: PT, aPTT, anti-FXa for edoxaban treatment arm.

Planned Sample Size:	This is an event driven trial and the total number of subjects randomized to treatment may be adjusted to ensure accumulation of 68 events in the mITT Analysis Set during the Main Treatment Period (Interim Analysis). Assuming that the edoxaban group will observe a 24% reduction of the event rate relative to SOC and a non-inferiority margin of 1.5, then the study with 68 total primary endpoint events will have approximately 80% of power to demonstrate non-inferiority with alpha=0.05 (two sided). Assuming that 28% of event rate in the SOC-treatment group, 274 subjects, 137 subjects per treatment group, will be the randomization target for the study.
Statistical Analyses:	**Analysis Sets:** Randomized Analysis Set will include all subjects who are randomized. Safety Analysis Set will include all subjects in the Randomized Analysis Set who received at least one dose of study drug actually taken. Modified intent-to-treat (mITT) Analysis Set will include all subjects in the Randomized Analysis Set who received at least one dose of randomized study drug. Per-protocol (PP) Set will include all subjects in the mITT Analysis Set who are sufficiently compliant with the protocol. Criteria of sufficiently compliant will be detailed in SAP. PK Analysis Set will include all subjects in the Safety Analysis Set who had at least one PK sample with measurable concentration. PD Analysis Set will include all subjects in the Safety Analysis Set who had at least one measurable PD sample. **Efficacy Analyses:** <u>Primary Efficacy Analyses:</u> The primary efficacy endpoint is a composite endpoint, including symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden based on imaging during the first 3-month treatment period (ie, primary efficacy events occurring from randomization through the end of the 3-month treatment period). For subjects in Cohort 5,(ie, <6 months old), the primary efficacy endpoint is a composite endpoint consisting of the incidence of symptomatic recurrent VTE, death as a result of

VTE, and no change or extension of thrombotic burden within 6 to 12 weeks + 3 days. The primary efficacy analysis will be based on mITT Analysis Set. Analyses will be based on the randomized treatment even if a subject inadvertently receives the incorrect study drug.

In this analysis, the time to the first event of the composite primary efficacy outcome will be analyzed using a Cox's proportional hazard regression model including treatment and age groups as covariates.

The edoxaban-to-comparator hazard ratio will be computed with 95% confidence interval [CI] (two-sided) based on this model.

Edoxaban will be considered non-inferior to comparator if the upper limit of the 95% CI is <1.5.

If non-inferiority of edoxaban is established, edoxaban will be tested for superiority to comparator. Edoxaban will be considered superior to comparator if the upper limit of the 95 % CI from above analysis is <1.0.

The same proportional hazard model used for primary efficacy analysis will be performed for PP Analysis Set and Randomized Analysis Set as sensitivity analyses.

<u>Secondary Efficacy Analyses:</u>

The following secondary efficacy endpoints will be analyzed:

- For the composite endpoint, including symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden from the randomization to the date of the last dose of study medication + 30 days, the proportional hazard model similar to primary efficacy analysis will be used based on mITT and PP Analysis Set
- Incidence of all-cause mortality from randomization to the date of the last dose of study drug + 30 days will also be summarized by treatment arm for the mITT Analysis Set
- The incidence of each component (symptomatic recurrent venous thromboembolic disease, death as result of VTE and no change or extension of thrombotic burden) of the composite primary endpoint occurred during the first 3 month treatment period (for Cohort 5, the intended duration of treatment is at least 6 to 12 weeks) will be

summarized by treatment arm for the mITT and PP Analysis Sets

- The occurrence of DVT, catheter-related thrombosis, sinovenous thrombosis, and PE during the first 3 month treatment period, after 3 month treatment period (for Cohort 5, the intended duration of treatment is 6 to12 weeks), as well as whole study period will be summarized by treatment arm for the mITT Analysis Set

Net Clinical Outcome Endpoint analyses:

- Incidence of net clinical outcome, defined as the composite of symptomatic recurrent VTE events, death as a result of VTE, and major and CRNM bleeding from the first dose to the last dose + 30 days, will be analyzed using the similar proportional hazard regression model will be summarized by treatment based on mITT and per- protocol (PP) Analysis Sets.

Safety Analyses:

Analysis of Safety Endpoint

An analysis will be performed for the composite of safety endpoints of major and CRNM bleeding events which occurred on-treatment from the first dose of study treatment to 3 month + 3 days, or to the last dose of the study treatment + 3 days, whichever occurred first. An event will be considered an "On-Treatment" event if it occurred while on randomized treatment or within 3 days of randomized study drug interruption or discontinuation.

The time to "On-Treatment" major or CRNM bleeding will be compared between treatment groups for subjects in the Safety Analysis Set, using a similar Cox's proportional hazard regression model as described in the primary efficacy analysis. Analyses will be based on the randomized treatment, unless a subject inadvertently receives the incorrect drug during the entire study, in which case, the subject will be grouped according the treatment actually received.

The incidence of bleeding events will also be summarized by treatment group for the Safety Analysis Set and on-treatment period.

Interim Analysis:

An interim assessment of incidence rate of the composite efficacy endpoint in both arms of the study will take place after first 140 subjects (about 50% of subjects) complete the first 3 months of treatment. This will allow for adjustment of number of subjects in the study if necessary.

Pharmacokinetic/Pharmacodynamic Analyses:

Pharmacokinetic and PD data collected on Day 5 (5^{th} edoxaban dose) from a subgroup of subjects dosed with edoxaban will be analyzed to confirm that the dose used in Phase 3 (based on single dose PK/PD pediatric data) is indeed providing the expected exposure.

Plasma concentration and biomarker data will be summarized by age, dose, and time point using descriptive statistics and will be included in the clinical study report for this study. The plasma concentration data will be pooled with data from other studies for a population PK analysis using nonlinear mixed effects modeling; the results will be provided in a separate report from the clinical study report for this study.

Exposure response relationships will be evaluated using Bayesian estimates of edoxaban exposure metrics (such as C_{av}, C_{max}, C_{trough}, and AUC) to explore relationships with safety and efficacy endpoints through a model based approach; the results will be provided in a separate report from the clinical study report for this study.

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ABBREVIATION	DEFINITION
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
AUC	Area under the concentration curve
BP	Blood pressure
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence interval
CMV	Cytomegalovirus
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CRF	Case report form
CRO	Contract Research Organization
CRNM	Clinically relevant non-major
CTA	Computed tomography angiogram
DOACs	Direct Oral Anticoagulants
DVT	Deep vein thrombosis
EBV	Epstein-Barr virus
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EIU	Exposure in utero
EOT	End of Treatment
ENT	Ears, nose, throat
FDA	Food and Drug Administration
FXa	activated Factor X
GCP	Good Clinical Practice (refers to ICH and CFR)
GI	Gastrointestinal

ABBREVIATION	DEFINITION
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INN	International Non-proprietary Name
INR	International normalized ratio
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
IV	Intravenous
IXRS	Interactive Web/Voice Response System
LE	Lower extremity
LFT	Liver function test
LMWH	Low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
NI	Non-inferiority
NSAIDs	Non-steroidal anti-inflammatory drugs
NVAF	Non-valvular atrial fibrillation
OTC	Over-the-counter
P-gp	P-glycoprotein
PD	Pharmacodynamic
PE	Pulmonary embolism
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per protocol
PROBE	Prospective, randomized, open-label, blinded endpoint evaluation
PT	Prothrombin time
aPTT	Activated partial thromboplastin time
PTS	Post-thrombotic syndrome
QD	Once a day
RFT	Renal function test

ABBREVIATION	DEFINITION
SAE	Serious adverse event
SAP	Statistical analysis plan
SAVER	Serious adverse events reporting
SC	Subcutaneous
SOC	Standard of care
SOP	Standard Operating Procedures
SP	Synthetic Pentasaccharide
SSC	Scientific and Standardization Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin level
TEAE	Treatment-emergent adverse event
UE	Upper extremity
UFH	Unfractionated heparin
ULN	Upper limit of normal
VKA	Vitamin K antagonist
V/Q	Nuclear ventilation/perfusion
VTE	Venous thromboembolism/venous thromboembolic
WBC	White blood cell

1. INTRODUCTION

1.1. Background

The clinical presentation of pediatric venous thromboembolic (VTE) disease includes many manifestations, such as catheter-related thrombosis, pulmonary embolism (PE), deep vein thrombosis (DVT), and sinovenous thrombosis. The majority of pediatric subjects (>95%) with VTE have at least 1 clinical risk factor.

Currently, the presence of a central venous catheter is the most important acquired trigger for the development of venous thromboembolic disease in pediatric subjects, contributing to >90% of all neonatal thrombi and more than half of all thrombi in the older children[1, 2 3, 4]. Several mechanisms play a role in the development of catheter related thrombosis, including vessel wall injury by the catheter or infused substances (especially parenteral nutrition), compromised blood flow, and thrombogenic effects of the catheter material[5]. Catheter-related thrombi develop in children with long-term venous access devices for diseases such as malignancy, intestinal failure, renal insufficiency, and cystic fibrosis and in children with short-term catheters on the intensive care unit or for cardiac catheterization[6, 7, 8]. Other important risk factors for pediatric thrombosis are congenital heart disease, surgery, immobilization, malignancy, nephrotic syndrome, sepsis, and estrogen treatment. The presence of congenital prothrombotic disorders contribute to the development of pediatric venous thrombosis, as well[9].

Increasing numbers of pediatric subjects with chronic diseases will require anticoagulation as the incidence of VTE events rises due to hypercoagulability and the use of central venous catheters[10].

Currently, the majority of pediatric thrombi are treated with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) followed by LMWH or vitamin K antagonists (VKAs) for a total of 3 to 6 months[11]. More recently, data exists for the use of fondaparinux in children[12, 13]. Subjects should receive LMWH, UFH, or fondaparinux for at least 5 days following diagnosis of VTE. Guidelines recommend starting VKA on the first treatment day because of slow onset of action. LMWH, UFH, or fondaparinux may be discontinued when the VKA has reached its therapeutic level, as indicated by an international normalized ratio (INR) ≥2.0 for 2 or more measurements at least 24 hours apart. Many pediatric subjects have severe underlying diseases which preclude early oral treatment and thus LMWH is continued.

In children, the outcome of venous thromboembolic disease has been reported in several studies. The REVIVE trial, a randomized controlled trial comparing LMWH with UFH and VKAs showed a direct mortality rate of 0% in both groups after 3 months[14]. In the Canadian outcome study mortality as result of thrombosis was 2.2%[15]. In the REVIVE trial, recurrent thrombosis occurred in 12.5% of the subjects in the UFH/VKA group and 5.6% in the LMWH group after 3 months of treatment.[14] The recurrence-free survival after 6 months was 93% in pediatric subjects of one center in the Netherlands[4]. Most subjects were treated with LMWH or UFH followed by VKAs. Merkel et al followed 27 subjects treated with LMWH. After a mean time of 2.3 years (range: 0.5 to 6.25 years), 55.6% of the subjects showed complete resolution with radiographic tests, 29.6% partial resolution, and 14.8% no resolution[16]. Newall et al studied radiographic outcome of 22 infants (<6 months old) and 73 children (≥6 months old) after 5 days to 4.2 years.

In infants and children, complete resolution occurred in 53% and 47%, partial resolution in 29% and 36%, and no resolution or extension in 18% and 17%, respectively[17].

Post-thrombotic syndrome (PTS) is a manifestation of chronic venous insufficiency following DVT. Children with PTS must endure chronic sequelae for many decades[18]. Goldenberg et al showed that PTS occurrence varied widely (<10% to 70%) depending on the scoring system; the calculated mean frequency of PTS was 26% (95% confidence interval [CI]: 23% to 28%) among a total of nearly 1000 subjects with upper extremity (UE)/lower extremity (LE) DVT. In the cross-sectional study[19], multiple logistic regression analysis revealed that lack of thrombus resolution was associated with a statistically significant 4 fold increase in odds of PTS. Therefore we propose to evaluate edoxaban on the reduction of thrombotic burden defined by "no change and extension" of the thrombus at the month 3 visit.

Edoxaban is an oral direct inhibitor of activated Factor X with predictable pharmacokinetics (PK) and pharmacodynamics (PD). As a result, anticoagulant effects are more likely to remain within the therapeutic range, thereby decreasing the likelihood of bleeding, and potentially removing the need for dose adjustment or frequent monitoring. These advantages may result in increased patient satisfaction and adherence compared with existing anticoagulants
Edoxaban has been approved for the following indications in the US:

- To reduce the risk of stroke and systemic embolism (SE) in subjects with nonvalvular atrial fibrillation (NVAF) with limitation of use in patients with CrCL >95 mL/min.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant.

In the EU and Japan, edoxaban has been approved for the following indications:

- Prevention of stroke and systemic embolism in adult subjects with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack (TIA) with no limitation of use.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

This study will evaluate the benefits and risks of edoxaban in pediatric subjects with thromboembolic disease.

1.2. Study Rationale

Currently available anticoagulants have significant limitations especially in the pediatric population. At the moment, the commonly used agents for long-term anticoagulation in children are LMWHs and VKAs. The important disadvantages of LMWH are subcutaneous (SC) administration and thrombocytopenia. Vitamin K antagonists (such as the coumarins: warfarin, acenocoumarol, or phenprocoumon) are indirect coagulation inhibitors, which act by blocking the vitamin K dependent liver synthesis of the plasma coagulation factors II, VII, IX, and X. These agents have been the only oral anticoagulants available for the last 50 years. The use of VKAs is complicated by several inherent problems including a delayed onset of antithrombotic action; a narrow therapeutic index that requires close laboratory monitoring using the INR; an

unpredictable and variable pharmacological response; and food and drug interactions requiring frequent dosage adjustment[20]. Furthermore, as no liquid formulation is available, oral administration of VKAs in tablet form is difficult in young children. Therefore, there exists a need for a safe, effective, and more easily managed oral antithrombotic agent for the treatment of pediatric subjects with thromboembolic disease.

1.3. Benefit/Risk

In pediatric subjects, the incidence of children developing recurrent VTE ranges from 3% in neonates to 8% in older children and as high as 21% in children reported with a first idiopathic VTE. The results of meta-analyses indicate that 11% of children with non-idiopathic thrombosis overall develop a second VTE. Hence, this study offers a platform by which the identification of subjects with non-idiopathic thrombosis or those with potential recurrence may be identified for therapeutic care.

In this U312 study, the risk is considered as minimal for subjects who already took anticoagulation therapy due to their health conditions. U312 is a study with a sequential enrollment (from older to younger) with tested doses from a Phase 1 study (U157). The established doses were mirrored to achieve exposures comparable to a 60 mg adult dose in the Hokusai VTE adult study where proven efficacy and safety were shown to be non-inferior and superior, respectively, to well-controlled warfarin.

In subjects with no history of thromboembolic events, the risk to receive anticoagulants is considered as a minor increase over minimal risk relative to the sequelae caused by a thromboembolic event. Bleeding risk is monitored based on established doses for edoxaban that were shown to be safe, and constant therapeutic monitoring of SOC is implemented for the alternative treatment in the study.

In the U312 study, risk was estimated based on experience with similar treatments and procedures in the pediatric population and from the well-known edoxaban effects in adults (Hokusai-VTE Study). The benefit to participate in the U312 study can be considered as direct for subjects with health conditions exposing them to occurrence and/or recurrence of a thromboembolic event. Furthermore, the traditional anticoagulant drugs (warfarin, UFH, and LMWH) have a number of limitations including issues regarding laboratory monitoring, food and drug interactions (warfarin), and a narrow therapeutic window. Most of the parenteral anti-coagulants are used more for short-term use in the hospital. VKAs such as warfarin have been used widely as oral anti-coagulants for long-term out-patient treatment. Although warfarin is widely used as an oral antithrombotic agent for prophylaxis and treatment of thromboembolism, there are clinical limitations to using the drug. Physicians need to prescribe warfarin very carefully in terms of interactions with food and other drugs. Monitoring warfarin effects on coagulation time (PT and INR) is critical for minimizing the risk of bleeding complications. Furthermore, there is considerable person-to-person variation in lag time between starting warfarin and the onset of appropriate anti-coagulation activity.

Safer and more effective oral antithrombotic agents are needed for prophylaxis and treatment of VTE. Edoxaban, an oral selective inhibitor of FXa, and might be a candidate to meet this need because of more predictable PK without the necessity for laboratory monitoring and dosage adjustments; fewer drug/food interactions; and a favorable benefit to risk profile as demonstrated in prior Phase 3 studies in adults.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to demonstrate the non-inferiority of edoxaban to standard of care (SOC; including low molecular weight heparin (LMWH), vitamin K antagonist (VKA), or synthetic pentasaccharide (SP) Xa inhibitors) in the treatment and secondary prevention of VTE in pediatric subjects with regard to the composite efficacy endpoint (ie, symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden) during the first 3-month treatment period (for Cohort 5, the intended duration of treatment is 6 to12 weeks).

2.1.2. Secondary Objectives

- To compare edoxaban against SOC with regard to the combination of major and clinically relevant non-major (CRNM) bleedings occurring during treatment or within 3 days of completing or interrupting or stopping study treatment during the first 3- month treatment period (for Cohort 5, the intended duration of treatment is at least 6 to 12 weeks).
- To compare edoxaban against SOC with regard to a combination of major and CRNM bleedings and symptomatic recurrent VTE, and death as result of VTE which occur from first to the last dose + 30 days.
- To compare edoxaban against SOC with regard to all bleedings which occur from first to the last dose + 30 days.
- To compare edoxaban against SOC with regard to the composite efficacy endpoint as described in the primary objective from randomization to the last dose + 30 days.
- To compare edoxaban against SOC with regard to all-cause mortality from randomization to the last dose + 30 days.
- To compare edoxaban against SOC with regard to the individual components of the composite efficacy endpoints as described in the primary objective during the first 3-month treatment period (for Cohort 5, the intended duration of treatment is at least 6 to 12 weeks).
- To compare edoxaban against SOC with regard to occurrence of DVT, catheter-related thrombosis, PE, sinovenous thrombosis within and after the first 3-month treatment period (for Cohort 5, the intended duration of treatment is at least 6 to 12 weeks).
- To compare edoxaban against SOC with regard to a composite combination of major and CRNM bleedings from first to the last dose + 30 days.
- To characterize the multiple dose pharmacokinetics of edoxaban in pediatric subjects at Day 5 using population pharmacokinetic (PK) analysis (apparent systemic clearance [CL/F] and apparent volume of distribution [V/F]) and to assess the effect of covariates such as age, body weight, and renal function on the PK of edoxaban.

- To evaluate the relationship between edoxaban exposure and safety (such as bleeding) and efficacy (thromboembolic events).
- To characterize the effect of edoxaban on biomarkers of coagulation (ie, PT, aPTT, and FXa).

2.1.3. Exploratory Objectives

Not applicable.

2.2. Study Hypothesis

This study is designed to test the hypothesis that the administration of edoxaban after at least 5 days of heparin (LMWH or SP Xa inhibitors or UFH; with overlapping VKAs if needed) is non-inferior to SOC (SOC; including LMWH, SP Xa inhibitors and/or VKA) in treating and preventing the composite of symptomatic recurrent VTE, death as result of VTE, and no change or progression in thrombotic burden after 3 months of therapy.

3. STUDY DESIGN

3.1. Overall Design

This is an event driven Phase 3, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group study in subjects with confirmed venous thromboembolism (VTE). A schematic representation of the study design is provided in Figure 3.1. The parallel enrollment strategy schema in U157, U312 and between U157 and U312 is provided in Figure 3.2.

Figure 3.1: Study Design

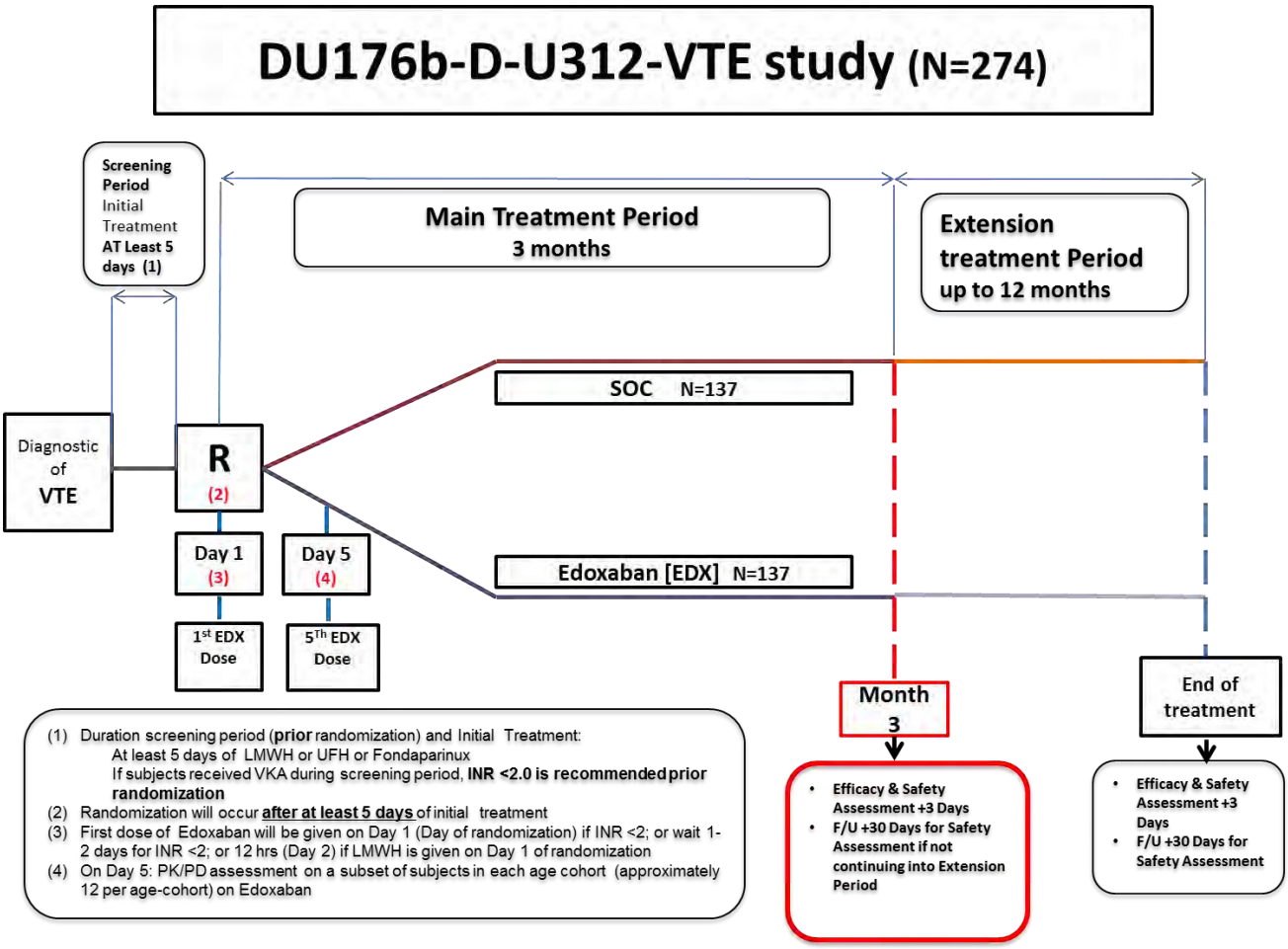
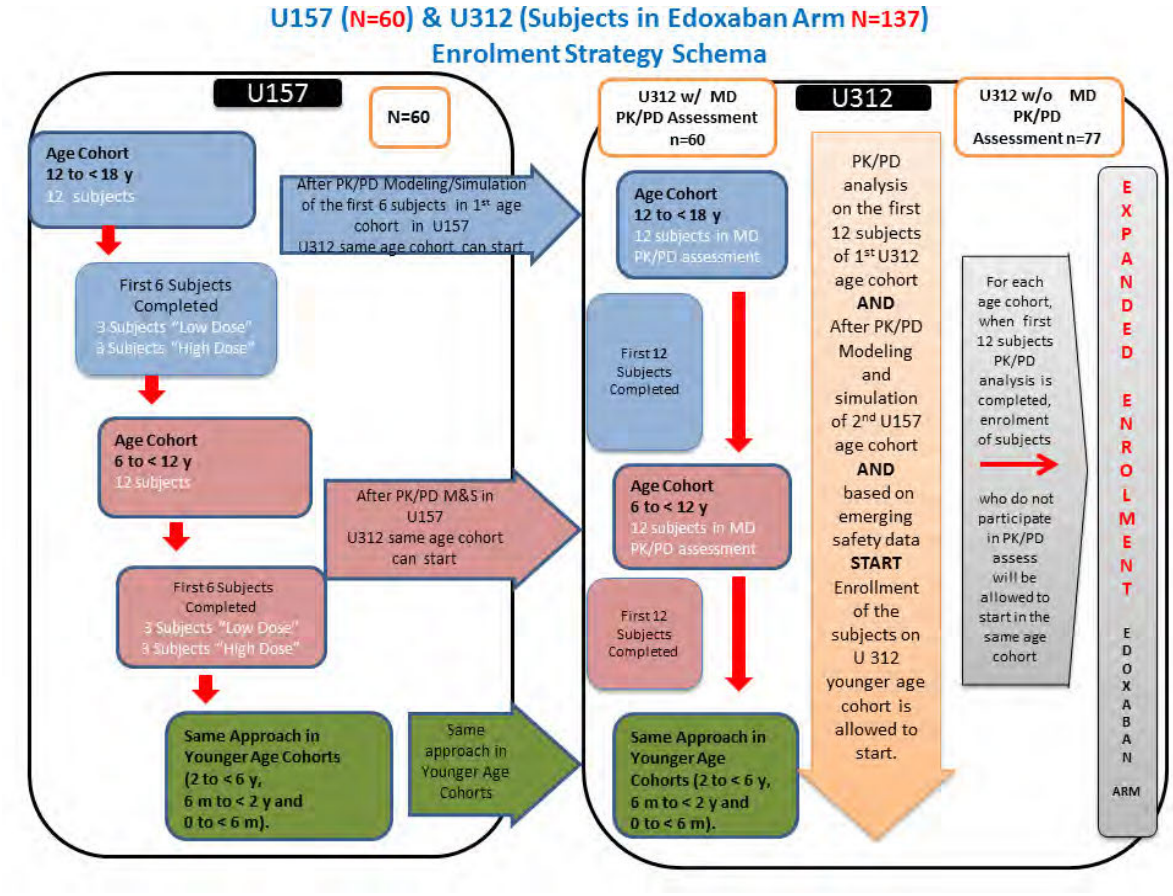


Figure 3.2: Enrollment Strategy Schema in U157, U312 and Between U157 and U312 Study



3.2. Discussion of Study Design

This study is designed to evaluate the PK and PD of edoxaban and to compare the efficacy and safety of edoxaban with SOC in pediatric subjects with confirmed VTE.

The adjudication of the efficacy and safety endpoints will be conducted by a blinded adjudication committee.

The study includes two periods:

- The Main Treatment Period is defined as the time from randomization, until the end of Month 3 of treatment. The Main Treatment Period for subjects <6 months old (Cohort 5) is defined as the time from randomization until the end of anticoagulant therapy for at least 6 to 12 weeks.
  - Subjects who early discontinue the Main Treatment Period will be monthly followed according to the Schedule of Events (Table 17.1) through Month 3 visit (Visit 5), or earlier (unscheduled interim visit at 6 weeks) for subjects in Cohort 5, and 30-day Follow-Up Visit (Visit 9).

  - Subjects who complete the Main Treatment Period but do not continue into the Extension Period will be followed for 30 days after last dose of study drug (Visit 9).

- The Extension Period is discretionary for the Investigator and will include treatment from the end of the Main Treatment Period (Month 3, Visit 5) up through the end of Month 12 (Visit 8).
  - Subjects who discontinue the treatment at any time after Month 3 will have a Month 12/Discontinuation Visit (Visit 8) performed with the subsequent 30 day follow-up (Visit 9).
  - Subjects who complete Extension Period treatment at Month 12 (Visit 8) will be followed for 30 days after last dose of study drug (Visit 9).
- Subjects who require anticoagulant treatment after discontinuation of the study treatment at any time will be transitioned to a therapy as determined by the Investigator.

The study will attempt to recruit at least 10% of the subjects diagnosed with pulmonary embolism.

About 274 subjects will be included in this randomized study (137 subjects in each treatment arm) which will be conducted at clinical sites located worldwide.

Randomization will be stratified by age cohorts and by region (US/Canada, Europe, Asia/Pacific, and Rest of the World). The total duration of the study is expected to be approximately 4.5 years.

After subjects are assessed for eligibility based on a newly diagnosed index VTE by imaging and per the inclusion/exclusion criteria, and have undergone bridging treatment for at least 5 days of heparin (LMWH or SP Xa inhibitors or UFH; with overlapping VKAs if needed) prior to randomization, the subjects will be randomized in a 1:1 ratio into one of the two treatment arms:

- Edoxaban treatment arm: subjects will receive selected dose of edoxaban

  or

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

In the case of centrally sourced SOC treatment, the Sponsor will only provide enoxaparin as LMWH, fondaparinux as SP Xa inhibitor, or warfarin as VKA as mentioned previously.

The subjects will be recruited into 5 age cohorts:

- Ages 12 to <18 years
- Ages 6 to <12 years
- Ages 2 to <6 years
- Ages 6 months to <2 years
- Ages birth to <6 months

Sequential enrollment of age cohorts will be used for randomization. The order of enrollment will be from the oldest age cohort to the youngest age cohort. The first age cohort to be randomized will be from ages 12 to <18 years. Doses for all subsequent age cohorts will be made by separate notifications to the investigative sites, outside the content of this protocol, and after the IDMC has approved the proposed edoxaban doses. In addition, a notification will indicate that Day 5 PK/PD edoxaban exposure evaluation will no longer be necessary for future subjects randomized to edoxaban in the corresponding age cohort.

Subjects in edoxaban treatment arm (137 subjects):

Starting doses for each age cohort in U312 study will be 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.

Edoxaban treatment will be dispensed to the subject on a monthly visit schedule. After Month 3, a 3-month dispense may be provided based on the Sponsor's approval to match the study visit schedule. The oldest cohort (12 to <18 years of age) will receive tablets. All younger age cohorts (<12 years) will receive edoxaban granules for oral suspension (see Section 5.1.1.1) and will be dosed on an mg/kg basis.

The enrollment into the first age cohort (12 to <18 years) of U312 study will begin when edoxaban dose for this age cohort is selected from a supporting Phase 1 Study U157 (see Section 5.1.1.1). The first 12 subjects of each age cohort (total of 53 to 60 subjects) randomized to the edoxaban treatment arm will participate in the multiple-dose PK/PD assessment on Day 5 (+3 days, Visit 2a) as follows:

- Ages 12 to <18 years (N≈12)
- Ages 6 to <12 years (N≈12)
- Ages 2 to <6 years (N≈12)
- Ages 6 months to <2 years (N≈12)
- Ages birth to <6 months (N≈5-12)

Two blood samples will be collected on the day of the fifth dose of edoxaban (Day 5+3 days, Visit 2a) for all age cohorts, including:

- Pre-dose sample for all approximately 12 subjects.
- Post-dose sample can be taken at either:
  - any time between 1.0 to 3 hours post-dose

or

- any time between 5 to 8 hours post-dose

- The PD sampling times on Day 5 for measurement of PT, aPTT and anti-FXa, will be taken at the same time as the PK samples.
- A PK analysis will be performed on the subset of subjects in U312 study. If the analysis confirms the exposure predictions and based on emerging safety, the expanded enrollment in the same age cohort will be allowed to start. A notification will be sent to all Investigators that Day 5 visit is no longer necessary and expansion of the age cohort is permitted after the PK analysis.

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

- PK analysis performed on subjects in the prior older age cohort in U312.
- Safety data analysis on subjects in the prior older age cohort in U312.
- PK analysis of the subjects in the next younger age cohort in U157.
- Safety data analysis on the subjects of the next younger age cohort in U157.

PK and safety data will be reviewed by Independent Data Monitoring Committee (IDMC) (Section 15.9) who will approve the start of the next younger age cohort.

In each age cohort, if the estimated median AUC based on the observed PK data in a subset of subjects on Day 5 PK assessment is less than 1.5-fold the median AUC from the simulated subject population profiles (over-exposure and under-exposure), the enrollment of subjects in the corresponding age cohort will continue and enrollment in the next younger age cohort can begin.

3.3. End of Study

This event driven study will continue until approximately 68 primary efficacy endpoints are achieved during the first 3-month treatment period. Events occur across both treatment groups for the mITT analysis set (the mITT analysis set includes all symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden) during the first 3-month treatment period anytime from randomization through the final Month 3 visit (for Cohort 5, the intended duration of treatment is 6-12 weeks) in all randomized subjects who receive at least one dose of randomized study drug). The number of cumulative events will be closely monitored and further randomization of subjects will be stopped when the required number of events is projected to be reached (End of Randomization date). Based on the End of Randomization date a global End of Treatment (EOT) date will be established that ensures a minimum of 3 months of treatment for the last subject(s) randomized to study. All subjects must permanently discontinue study treatment on or before the EOT date. A final Follow-Up Visit date will be set one month following the EOT date. All subjects must complete their follow-up safety visit and permanently discontinue study on or before the Follow-Up Visit date. All subjects that discontinue treatment at Month 3 or earlier (for Cohort 5, the intended duration of treatment is 6 to12 weeks) based on EOT will be placed on SOC at Investigator discretion. All suspected recurrent events will be evaluated by the CEC. Adjudicated results will be the basis for the final analyses.

4. STUDY POPULATION

4.1. Inclusion Criteria

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

1. Male or female pediatric subjects between birth (defined as 38 weeks gestational age) and less than 18 years of age at the time of consent.
2. Pediatric subjects with the presence of documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 90 days (list of VTE provided in Section 7.1).

   -Subjects <6 months old (Cohort 5) with the presence of documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 6 to 12 weeks.
3. Subjects must have received at least 5 days of heparin (LMWH or SP Xa inhibitors or UFH according to the edoxaban label for VTE treatment) therapy prior to randomization to treat the newly identified index VTE. In addition, prior to being randomized to edoxaban or SOC, subjects initially treated with VKA are recommended to have an INR ≤2.5.
4. Subject and/or parent(s)/legal guardian(s) or legally acceptable representative is informed and provides signed consent for the child to participate in the study with edoxaban treatment. Pediatric subjects with appropriate intellectual maturity will be required to sign an assent form in addition to the signed informed consent from the parent(s)/legal guardian(s) or any legally acceptable representative.
5. Female subjects who have menarche must test negative for pregnancy at Screening and must consent to avoid becoming pregnant by using an approved contraception method throughout the study Appendix 17.3.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Subjects with active bleeding or high risk of bleeding contraindicating treatment with LMWH, SP Xa inhibitors, VKAs, or direct oral anticoagulants (DOACs; identified high risk of bleeding during prior experimental administration of DOACs).
2. Subjects who have been or are being treated with thrombolytic agents, thrombectomy or insertion of a caval filter for the newly identified index VTE.
3. Administration of antiplatelet therapy is contraindicated in both arms except for low dose aspirin defined as 1-5 mg/kg/day with maximum of 100 mg/day (see Appendix 17.4.1).
4. Administration of rifampin is prohibited during the study and subjects on concomitant use of rifampin are excluded.
5. a) Subjects with severe hepatic impairment or hepatic disease associated with coagulopathy (eg, acute hepatitis, chronic active hepatitis, and cirrhosis).

b) Subjects with ALT >5 × the upper limit of normal (ULN) or total bilirubin >2 × ULN with direct bilirubin >20% of the total at Screening.

c) Subjects with aPTT >50 seconds or international normalized ratio [INR] >2.0 not related to anticoagulation therapy).

6. Subjects with estimated glomerular filtration rate (eGFR) <30% of normal for age and size (see Appendix 17.7).
7. Subjects with stage 2 hypertension defined as blood pressure (BP) systolic and/or diastolic confirmed >99th percentile + 5 mmHg (see Appendix 17.8).
8. Subject with thrombocytopenia <50 × 10^9/L at Screening Visit. Subjects with a history of heparin-induced thrombocytopenia may be enrolled in the study at the Investigator's discretion.
9. Life expectancy less than the expected study treatment duration (3 months).
10. Subjects who are known to be pregnant or breastfeeding.
11. Subjects with any condition that, as judged by the Investigator, would place the subject at increased risk of harm if he/she participated in the study including contraindicated medications identified in Appendix 17.4.
12. Subjects who participated in another interventional clinical study or were treated with an experimental therapy with less than a 30 day wash-out period prior to identifying the qualifying index VTE.
13. Hypersensitivity to the active ingredient or to any of the excipients of any components of the trial treatment.
14. Patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome who are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies).

4.3. Additional Requirements

4.3.1. Stopping Rules for Age-based cohort during PK/PD assessment:

- In each age cohort if the estimated edoxaban median AUC based on the observed PK data in the approximately 12 subjects (between 5 and 12 subjects in Cohort 5) on Day 5 PK assessment is 50% higher or 50% lower than the median AUC from the simulated patient population profiles, dose reevaluations for Phase 3 subjects will be recommended to achieve the exposure comparable to adult 60 mg doses. The enrollment of subjects in the corresponding age cohort will be put on hold until reevaluation of the dose for this age cohort.

4.3.2. Stopping Rules for Study:

An IDMC may recommend termination of the study. Termination may be made for any of the following reasons:

- Concern about significantly higher bleeding risk relative to one of the study arms,
- Concern about drug-induced liver injury,
- Any other safety concern based on benefit/risk evaluation.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)

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

Study treatment should be administered on the same day as randomization (Day 1). Subjects randomized to edoxaban and previously treated with VKA, can initiate edoxaban treatment only after the INR is ≤2.5; or 12 hours after last dose of LMWH.

The Day 5 PK/PD assessment will be adjusted accordingly to have 5 doses of edoxaban prior to assessment. For subjects participating in PK/PD assessment and receiving LMWH twice a day and who already received a morning dose on Day 1 prior to randomization, edoxaban can be started on the morning of Day 2 (12 hours ± 3 hours after last evening dose of LMWH).

Initial treatment with heparin (with overlapping VKAs if needed) for index VTE prior to randomization must be within the range of at least 5 - 15 days and up to 20 days with Sponsor approval. In addition, prior to being randomized to edoxaban or SOC, subjects initially treated with VKA should have an INR ≤2.5.

5.1.1.1. Edoxaban Treatment Arm

Edoxaban treatment will be dispensed to the subject on a monthly visit schedule. After Month 3 the distribution of edoxaban may be for a 3-month period to align with the visit schedule, with the Sponsor's approval. Edoxaban will be started orally at the age/weight/renal function appropriate dose (depending on the results of the ongoing U157 study) for the Treatment Period.

5.1.1.1.1. Edoxaban dose recommended for 12 to <18 years old pediatric subjects

Edoxaban treatment will be dispensed to the subject on a monthly visit schedule (see caveat above). The oldest cohort (12 to <18 years old) will receive tablets (15 and/or 30 mg strength, see Table 5.1). (Doses for all subsequent age cohorts will be by notification to the investigative sites.) Subjects will be instructed to take edoxaban (tablets) orally once a day, at the same time every day, with or without food. Tablets should be swallowed with a glass of water.

Only on Day 5 (+3), the approximately first 12 subjects participating in PK/PD assessment should be fasting one hour prior to intake of edoxaban dose and a maximum of 2 hours after taking edoxaban dose.

Table 5.1: Edoxaban Dose Recommended For All 5 Cohorts (12 to <18 years, 6 to <12 years, 2 to <6 years, 6 months to <2 years, and birth to <6 months)

Age	Body Weight	Dose (Tablet)	Dose (Suspension) (6 mg/mL concentration)[c,e]	Dose Reduction[a]
12 to <18 years[b] (At date of consent)	≥60 kg	60 mg QD	NA	45 mg QD
	≥30 and <60 kg	45 mg QD	NA	30 mg QD
	<5th Percentile for Age[c]	30 mg QD	NA	NA
6 to <12 years (At date of consent)	<60 kg Dosed based on mg/kg[d]	NA	1.2 mg/kg with a maximum dose of 45 mg	0.8 mg/kg, with a maximum dose of 45 mg
2 to <6 years (At date of consent)	Dosed based on mg/kg	NA	1.4 mg/kg with a maximum dose of 45 mg	0.7 mg/kg, with a maximum dose of 24 mg
6 months to <2 years (At date of consent)	Dosed based on mg/kg	NA	1.5 mg/kg with a maximum dose of 45 mg	0.75 mg/kg with a maximum dose of 24 mg
>28 days to <6 months (At date of consent)	Dosed based on mg/kg	NA	0.8 mg/kg with a maximum dose of 12 mg/kg	0.4 mg/kg, with a maximum dose of 6 mg/kg
38 weeks gestation to ≤28 days (At date of consent)	Dosed based on mg/kg	NA	To be determined by the IDMC	0.4 [f] mg/kg,with a maximum dose of 6 mg/kg

Abbreviations: eGFR = estimated glomerular filtration rate; IDMC = Independent Data Monitoring Committee; NA = not applicable; P-gp = P-glycoprotein; QD = once a day

[a] Conditions for dose reduction:

If a subject requires concomitant administration of P-gp inhibitor (Appendix 17.4.6), the edoxaban dose will be reduced during P-gp administration and re-established to the original dose once P-gp inhibitor administration had concluded.

Edoxaban dosage regimen will be reduced permanently for subjects with moderate renal impairment 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). Refer to Appendix 17.7 for eGFR values below which dose reduction should be implemented.

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

[b] Dose reduction due to body weight applies only for fixed doses in subjects 12 to <18 years of age:

If body weight increases or decreases from the categories of weight defined at consent, the subject will be dose adjusted. Subjects who are ≥60 kg of body weight at consent and drop below that body weight will receive 45 mg dose at any subsequent visit. Subjects who are ≥30 and <60 kg at consent and increase their weight to ≥60 kg will increase their dose to 60 mg.

[c] Edoxaban dosage regimen will be reduced permanently for subject with body weight <5th percentile for age. Refer to Appendix 17.9.

[d] Edoxaban granulation will be diluted with 8 mL water to provide a concentration of 6 mg/mL dosing suspension. If body weight increases or decreases from the categories of weight defined at consent, the subject will be dose adjusted. Subjects who are ≥60 kg of body weight at consent and drop below that body weight will receive 45 mg dose at any subsequent visit. Subjects ≥30 and <60 kg at consent increasing their weight to ≥60 kg will increase their dose to 60 mg.

Note: Dose is based upon weight at corresponding visit.

[e] Edoxaban granules are for subjects <12 years of age only. Subjects 12 to <18 years of age should use crushed edoxaban tablets. For those subjects cannot swallow whole tablets, edoxaban tablets may be crushed and mixed with 2 to 3 ounces of water and immediately administered by mouth or through a gastric tube. The crushed tablets may also be mixed into applesauce and immediately administered..

[f] The IDMC may meet and conclude that subjects ≤28 days old no longer require a dose reduction and may recommend a revised dose based on the availability and re-review of PK data.

5.1.1.1.2. Edoxaban dose recommended for <12 years old pediatric subjects

Subjects of age <2 years will have dose recommendations based on the PK and safety data from same age cohort in U157 study and subjects evaluated for edoxaban exposure in the previous older cohort in U312 study. The PK and safety data will be reviewed by the IDMC (Section 15.9) who will approve the start of the next younger age cohort. Based on the IDMC review of Cohort 1 data from DU176b-D-U312 and corresponding cohort data from study DU176b-A-U157, the proposed dose that was safe and effective for VTE treatment was 1.2 mg/kg body weight for Cohort 2 (6 to <12 years) (Table 5.1), 1.4 mg/kg body weight for Cohort 3 (2 to <6 years), 1.5 mg/kg, for Cohort 4 (6 months to <2 years), 0.8mg/kg for Cohort 5 (>28 days to <6 months), and will be determined by the IDMC for Cohort 5 (38 weeks gestation to ≤28 days).

Doses for all subsequent age cohorts will be made by separate notifications to the investigative sites, outside the content of this protocol, and after the IDMC has approved the proposed edoxaban doses. An official notification will be sent when select age cohorts can begin randomization to either SOC or edoxaban treatment. In addition, a notification will indicate that Day 5 PK/PD edoxaban exposure evaluation will no longer be necessary for future subjects randomized to edoxaban in the corresponding age cohort.

Subjects of age <12 years will receive edoxaban granules for oral suspension (60 mg) and will be dosed on an mg/kg basis. Check the body weight prior to dosing and adjust dosage accordingly. Frequency of dosage changing is up to the Investigator's discretion, but the maximum dose would not exceed 45 mg once a day (QD).

5.1.1.2. Standard of Care Treatment Arm

SOC treatment will be dispensed to the subject on a monthly visit schedule. After Month 3, the distribution of SOC may be for a 3-month period to align with the visit schedule, with the Sponsor's approval. Subjects will receive SOC anticoagulant according to the site's SOC treatment, as follows (alone or combination):

- LMWH (alone or followed with VKA)
- SP Xa inhibitors (alone or followed with VKA)
- Vitamin K antagonist (VKA)

In case of centrally sourced SOC treatment, the Sponsor will only provide enoxaparin as LMWH, fondaparinux as SP Xa inhibitor, or warfarin as VKA with limited presentations. The subject will be treated with enoxaparin or fondaparinux or warfarin/heparin, with the following suggestion:

- Enoxaparin – Subjects will be treated with enoxaparin alone or can be switched to warfarin anytime during the study treatment period. Single dose (pre-filled syringe) or as multiple dose vials (for subjects <10 kg) for injection where allowed per standard clinical practice will be provided to the subject. Initial treatment age-dependent dose of enoxaparin:
  - Age <2 months: 1.5 mg/kg dose twice a day
  - Age ≥2 months: 1.0 mg/kg dose twice a day
- Fondaparinux – Subjects will be treated with fondaparinux alone or can be switched to warfarin anytime during the study treatment period.
  - Dosing of 0.1 mg/kg/day (0.05 mg/kg/day for subjects with renal disease).
  - If the appropriate required dose cannot be administered with the pre-filled syringes, the site should consider using alternative SOC treatment options.
- Warfarin will be started on Day 1. Heparin will be discontinued when INR ≥2.0 and ≤3.0 for 2 consecutive measurements obtained at least 24 to 48 hours apart. The subject will continue warfarin treatment for the remainder of the study treatment period.
  - Additional information on dosing and dose adjustment (Appendix 17.2)

5.1.2. Method of Treatment Allocation

Eligible subjects will be stratified by

1. Age (12 to <18 years of age; 6 to <12 years of age; 2 to <6 years of age; 6 months of age to <2 years of age; birth to <6 months of age)
2. Regions (ie US/Canada, Europe, Asia/Pacific and Rest of the World). Additional regions may be included if needed)

An independent biostatistician will generate the randomization schedule in accordance with the operating procedure for allocating study drug.

At randomization, the Investigator provides the IXRS with the study center number; the subject's presenting diagnosis (symptomatic VTE) and date of birth. Dose reduction stratification will take into account for:

- eGFR is 30-50% of normal for age and size (Appendix 17.7).
- Whether the subject is receiving concomitant treatment with P-gp inhibitors (Appendix 17.4.6).
- For all subject: whether body weight <5th percentile of subject's age (see Appendix 17.9).

The IXRS will assign the unique subject identification number, allocate the treatment group assignment for the subject and provide the appropriate drug supply kit number(s), for edoxaban and centrally sourced SOC.

A fax or e-mail will be sent by the IXRS to provide the appropriate drug supply kit number(s). The fax or e-mail will also provide a calendar with dates of subsequent prescheduled visits and drug resupply.

5.1.3. Blinding

Not applicable.

5.1.4. Emergency Unblinding Procedure

Not applicable.

5.2. Study Drug(s)

5.2.1. Description

The investigational medicinal products (IMP) for this study are edoxaban (DU-176b) and SOC anticoagulants (LMWH, SP Xa inhibitor and VKA).

Edoxaban will be supplied as a one month treatment interval as tablets (15 and/or 30 mg strength) or granules for oral suspension 60 mg. Subjects will be instructed to take edoxaban (tablets or granules) orally once a day, at the same time every day, with or without food. Tablets should be swallowed with a glass of water.

- 60 mg dose will be dispensed with two 30 mg tablets
- 45 mg dose will be dispensed with one 30 mg tablet plus one 15 mg tablet
- 30 mg dose will be dispensed with one 30 mg tablet

The SOC drugs will be supplied as a one month treatment interval sourced locally by the Investigator or centrally by the Sponsor.

If local sourcing is used, the Investigator is allowed to utilize LMWH, VKA, or SP Xa inhibitors according to the site SOC treatment (no strength restrictions).

If central sourcing is used only enoxaparin as LMWH, fondaparinux as SP Xa inhibitor, and warfarin as VKA will be provided by the Sponsor at fixed doses.

The Sponsor will provide SOC treatment as follows:

- Enoxaparin (LMWH) will be provided to the subjects as solution for SC injection in pre-filled syringes with 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1.0 mL concentration for injection, or as multiple dose vials (for subjects <10 kg) for injection where allowed per standard clinical practice. Guidance on dosing and dispensing is provided in Appendix 17.2.
- Fondaparinux (SP Xa inhibitor) will be supplied as solution for SC injection in pre-filled syringes (2.5 mg/0.5 mL, 5.0 mg/0.4 mL, 7.5 mg/0.6 mL, 10.0 mg/0.8 mL and

where available 1.5 mg/0.3 mL). Guidance on dosing and dispensing is provided in Appendix 17.2.

- Warfarin (VKA) will be supplied as tablets (0.5 mg, 1.0 mg, and 3.0 mg). Various doses will be available for INR maintenance in the therapeutic range of ≥2.0 and ≤3.0. Guidance on dosing and dispensing is provided in Appendix 17.2.

5.2.2. Labeling and Packaging

Investigational products will be provided in adequate quantity for study conduct and labeled in an open-label format. Investigational product labels will include all information required by federal and local regulations.

Edoxaban 15, 30 mg tablets will be supplied by Sponsor in an open-label format. The edoxaban granules for oral suspension 60 mg will be provided in glass bottles, as per visit schedule, for single dose application.

Centrally sourced SOC will be presented in its commercial presentation with clinical study over label. It will include information required by federal and local regulations.

5.2.3. Preparation

No special preparation will be required for the tablet formulation. However, if a subject does not have the capacity to swallow tablets in the 12 to <18 year old group, the tablets may be crushed and served with applesauce or mixed with 2 to 3 ounces of water and immediately administered by mouth or through a gastric tube.

The edoxaban granules for oral suspension 60 mg will be provided in amber glass bottles (wide neck) with white polypropylene caps. The edoxaban granules for oral suspension 60 mg formulation will be reconstituted with 8 mL of water to provide a 6 mg/mL liquid suspension. Doses provided by the granulation formulation will be dispensed with an oral dosing syringe according to the recommended doses for the age cohort. Instructions for reconstitution and syringes will be provided to the Investigator/designee.

No special preparation will be required for centrally sourced SOC. Instructions for daily use will be provided to the Investigator/designee.

5.2.4. Administration

Study drug will be dispensed to the subject on a monthly visit schedule. Note in Table 17.1, each monthly dispense visit is not indicated because no additional procedures are expected at that visit. After Month 3 the distribution of SOC may be for a 3-month period to align with the visit schedule, with the Sponsor's approval.

The study drugs will be shipped to the study sites, and the Investigator/designee will be responsible for dispensing the study drugs. The Investigator/designee will provide the subjects with product in sufficient quantity, plus overage, via IXRS dispensing, for Edoxaban and centrally sourced SOC until the next scheduled visit. The Investigator/designee will also instruct the subject on reporting study drug administration and accountability. Subjects who miss one dose of study drug will be instructed to take the next dose as their drug administration schedule.

5.2.4.1. Instruct the subject to begin taking edoxaban

LMWH / SP Xa inhibitors / UFH (with overlapping VKAs if needed) treatment during Pre-randomization must be discontinued at Randomization day (Day 1). Edoxaban dosing should begin when INR is ≤2.5 for warfarin-treated subjects. For subjects participating in PK/PD assessment and receiving LMWH twice a day and who already received morning dose on Day 1 prior to randomization, edoxaban can be started on the morning of Day 2 (12 hours ± 3 hours after last evening dose of LMWH).

1. A subject who was on LMWH twice a day regimen will start edoxaban dosing 12 ± 3 hours after the last LMWH dose
2. A subject who was LMWH QD regimen or on SP Xa inhibitors (once daily) will start edoxaban dosing 24 ± 3 hours after the last LMWH or SP Xa inhibitor dose
3. A subject who was on an UFH regimen will start edoxaban dosing 4 ± 1 hour after the last UFH dose
4. A subject who had received VKA during the Screening period, VKA should be stopped 24 hours prior to randomization (INR should be ≤2.5 in the absence of VKA therapeutic effect). Subject can take edoxaban on the day of randomization.

5.2.4.2. Instruct the subject randomized to SOC treatment

Subjects randomized to SOC treatment arm will receive SOC anticoagulant according to the study site's SOC treatment as follows (alone or combination):

- LMWH (alone or followed with VKA)
- SP Xa inhibitors (alone or followed with VKA)
- Vitamin K antagonist (VKA)

If Investigators choose to use centrally sourced SOC treatment from Sponsor, the subject will be treated as follows:

- For subjects randomized to enoxaparin: for neonates or children receiving either once- or twice-daily therapeutic enoxaparin the drug should be monitored to a target anti-FXa level of 0.5 to 1.0 units/mL in a sample taken at 4 hours post-dose for therapeutic levels. Monthly monitoring of anti-FXa levels is recommended. More frequent anti-FXa levels can be recommended as per Investigator's decision.
- For subjects randomized to fondaparinux: dosing of 0.1 mg/kg/day (0.05 mg/kg/day for subjects with renal disease). Monitoring fondaparinux levels (0.5- 1 mg/L) can be recommended as per Investigator's decision.
- For subjects randomized to warfarin: the dose should be titrated to achieve a target INR of 2.5 (≥2.0 and ≤3.0). Visits will be at the discretion of the Investigator and captured as unscheduled visits for data collection. Adjustment of the maintenance dose of VKA will be dependent on INR monitoring as follows:
  - INR = 2.0 to 3.0, no change in dose
  - INR = 1.1 to 1.4, increase dose by 20%

- INR = 1.5 to 1.9, increase dose by 10%
- INR = 3.1 to 3.5, decrease dose by 10%
- INR >3.5, hold VKA until INR is <3.5, then decrease dose by 20% when restarted.

To initiate SOC post screening, it is recommended to test infants and children every 4 weeks once a stable dose of VKA has been achieved. However, depending on the site's clinical practice and PI's discretion, the subjects can be tested at the physician's discretion and/or according to local practice. More frequent INR testing is recommended in infants and children receiving VKA with any change in diet or medication or when an illness occurs. An unscheduled visit will need to be performed to document the discretionary INR measurement and potential VKA dosage change as an unscheduled visit day.

If a therapeutic INR (≥2.0 on 2 separate measurements at least 24-48 hours apart or a single supratherapeutic INR >3.0) is not achieved within 12 days (by Day 12) after starting LMWH and warfarin, the Investigator may be contacted by a study physician for discussion and guidance.

Guidance on dosing and dispensing is provided in Appendix 17.2.

5.2.5. Storage

Edoxaban tablets and granules for oral suspension must be stored at 20° to 25°C (68° to 77°F) with excursions permitted to 15° to 30°C (59° to 86°F).

SOC treatments must be stored as per labeled storage conditions.

All drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions. If storage conditions go outside of allowable excursions, Sponsor/Contract Research Organization (CRO) must be contacted. The excursions will be discussed with the Sponsor and CRO to determine what action is necessary.

Recordings of storage temperature (eg, via the uses of a maximum/minimum thermometer) must be made. Temperature measurements will be recorded on a temperature log excluding weekends and holidays.

5.2.6. Drug Accountability

For Sponsor provided edoxaban or SOC upon receipt, the Investigator/designee will confirm the amount and condition of the drug, confirm the appropriate local language in the label, drug expiration date, confirm Temperature monitor readings and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be returned as instructed on the form. The original will be retained at the study center. In addition, the Investigator/designee shall contact Sponsor as soon as possible if there is a problem with the shipment and quarantine the shipment until resolution is obtained from the Sponsor.

For both locally sourced SOC and Sponsor provided study therapy a Drug Accountability Record will be used for the products. It may be provided by the Sponsor/Sponsor representative, or the site may use a Sponsor Approved Form. The record must be kept current and must contain the

dates and quantities of drug received from central supply (for Sponsor provided therapy), subjects for whom the products was dispensed (identification number and/or initials or supply number as applicable), the date and quantity of IMP dispensed and remaining, if from individual subject drug units, as well as the initials of the dispenser. Edoxaban and centrally sourced SOC must additionally be accounted for and reconciled in IXRS. All unused drug and containers whether provided by the sponsor or provided locally must be brought back to the study site for accountability to reinforce appropriate dosing instructions to the subject.

At the end of the study, or as directed, all products, including unused, partially used, or empty containers, will be destroyed, after full accountability. If drug destruction occurs at the study center, this must be approved in writing by the Sponsor and the Sponsor has received copies of the study center's drug handling and disposition standard operating procedures (SOPs). Locally sourced SOC should be destroyed locally. (Local destruction is preferred method of destruction, compared to return for depot destruction.)

For Sponsor provided and locally supplied drug, dosage form (ie, tablet, granule bottles, and syringes) site level accountability documentation is required as part of the disposition records of IP. The dosage form site level accountability documentation should be appended to the Certificate of Destruction, if available.

The IMP will only be returned to a designee as instructed by the Sponsor if the study center is unable to perform the products destruction. Investigational product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return/destruction of products must be documented. At the end of the study, a final product reconciliation statement must be completed by the Investigator/designee and provided to the Sponsor.

Dosage form (ie, tablet, granule bottles, and syringes) site level accountability documentation is to be included with each drug supply return shipment (or other returning facility, such as another depot). This is required as part of the receiving records for return shipments.

All inventory forms must be made available for inspection by a Sponsor-authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the study center.

5.3. Dose Interruptions and Reductions

If a subject's treatment with study drug must be interrupted for medical or surgical reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery, thrombocytopenia due to cytotoxic medication, or dental work); use of a prohibited concomitant medication; or other reasons (eg, temporary situation that prevents subject adherence with the study drug administration schedule, etc.), the subject's study drug should be resumed as early as the situation allows. Edoxaban should be discontinued for 24 hours prior to the initiation of the procedures (depending on PK/PD data in children). Subjects should be encouraged to restart study drug after an interruption except when absolutely contraindicated. The duration of study drug interruption can vary depending upon the individual circumstances, and study drug may be resumed regardless of the duration of time that it had been interrupted. Any subject who temporarily interrupts study drug for more than 3 days will have the reason recorded in the electronic case report form (eCRF).

5.3.1. Edoxaban Dose Reduction

During the treatment period, a subject may reduce the dose of edoxaban for any of the following reasons (Table 5.1):

- eGFR is 30-50% of normal for age and size (Appendix 17.7).
- Subject is receiving concomitant treatment with P-gp inhibitors.
- Body weight <5th percentile of subject's age (see Appendix 17.9).
- Subject is ≤28 days old (corrected for gestation age of 38 weeks). This may change based on the IDMC recommendation.

For subjects receiving P-gp inhibitors, the dose of edoxaban will only be reduced during the administration of the concomitant P-gp inhibitor. Subjects experiencing eGFR or body weight reduction will maintain their reduced edoxaban dose for the duration of the study. Once the subject turns >28 days old, the dose may be increased to 0.8 mg/kg.

5.4. Method of Assessing Treatment Compliance

Dosing compliance for subjects in the edoxaban treatment arm will be assessed by means of tablet/bottle counts remaining or bottles returned. All drug packaging will be returned at each subject visit and will be accountable including bottles with dilutions made for dosing. Administration of the IMP will be recorded in the case report form (CRF)/eCRF/Drug Accountability Record. As necessary, include method of compliance calculation based on the returned number of tablets/bottles. If zero tablets/bottles returned, ask subject whether any were disposed/thrown away, rather than taken orally.

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

5.5. Prior and Concomitant Medications

Medications that the subject has taken within 30 days before randomization will be recorded.

There are no concomitant medications required as part of the study design. The following drugs and devices (see Appendix 17.4) CANNOT be used during the entire study treatment period and their unavoidable use would require study drug therapy interruption unless specifically indicated for study drug discontinuation:

- Anticoagulants, other than the assigned study drugs, by any route – study drug discontinuation
- Fibrinolytic agents, if required to treat thromboembolism events, require study drug discontinuation and consideration of a transfusion of fresh frozen plasma;
- Single or dual antiplatelet therapy with any antiplatelet agent is prohibited except for low dose aspirin defined as 1-5 mg/kg/day with maximum of 100 mg/day. If a

clinical indication for antiplatelet therapy (other than low dose aspirin) arises after randomization, study drug should be discontinued.

- Chronic use of oral or parenteral NSAIDs including both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors other than aspirin for ≥4 days/week. Use of NSAIDs via other routes (eg, topical, inhaled, intranasal, intraocular, etc.) are not restricted (see Appendix 17.4.5).

All P-gp inhibitors (please refer to Appendix 17.4.6 for an example list of most commonly used P-gp inhibitors) excluding amiodarone will require dose reduction of edoxaban.

The Investigator is encouraged to contact a study physician (telephone number will be provided per country, per region; please refer to Study Manual for an appropriate phone number) if further guidance is needed.

Information regarding concomitant medications will be collected with start date, stop date, drug name, dose and dosing regimen for population PK analyses.

5.6. Subject Withdrawal or Discontinuation

Any subject who discontinues from the study treatment for any reason will have their study treatment discontinuation recorded. A subject may discontinue study treatment during the Main Treatment Period, however the subject should still remain as a study participant for scheduled visits through Month 3 (Visit 5) and the subsequent 30-day safety Follow-Up Visit.

Follow-Up Visit (visit 9) regardless if they stop all anticoagulant therapy or are placed on a treatment they have not been assigned at randomization. If a subject discontinues from treatment after Month 3, they should also be discontinued from the study and have a subsequent 30-day Follow-Up Visit.

5.6.1. Discontinuation from Treatment within the Main Treatment Period (Month 3)

Early discontinuation of study drug is discouraged. However if, in the Investigator's opinion, continuation of study drug would be detrimental to the subject's well-being or in specific clinical situations (eg, liver function test disturbances, severe renal insufficiency, recurrent VTE, bleeding), the study drug can be stopped permanently. Subjects who discontinue treatment during the Main Treatment Period should return to the clinical site per the study procedure schedule (Table 17.1) for all remaining safety and efficacy assessments through the scheduled Month 3 visit (Visit 5) regardless of what treatment, if any, they may subsequently be taking. A 30-day Follow-Up Visit (Visit 9) will be required for all subjects completing Month 3, regardless of discontinuation from treatment during the main treatment period. If a subject discontinues study medication before Month 2, the follow up visit may be combined with Month 3 Visit.

A telephone call for follow-up assessment may be conducted in exceptional circumstances when the subject is not able or willing to present to the study center.

The reasons for discontinuation from treatment must be documented.

If a subject discontinues study treatment prior to Month 3, the Investigator will complete and report the observations as thoroughly as possible at scheduled visits including the date of last treatment and the reason for discontinuation of study treatment through 3 months of observation.

5.6.2. Discontinuation from Treatment and Study beyond Month 3 up to 12 Month

During the extension period (beyond 3 months of treatment), all subjects who discontinue from the study treatment and the study during the extension period will return to the study center for a discontinuation visit (Visit 8) and 30 day Follow-Up Visit (Visit 9) after the discontinuation visit.

Note: those subjects in the extension do not need to be followed through 12 months of study procedures and can be discontinued from treatment and study per Investigator discretion at any time with a discontinuation visit after Month 3.

5.6.3. Reasons for Discontinuation of Study Treatment

Subjects may **discontinue the treatment** for any of the following reasons

1. End of requirement for anticoagulant therapy
2. Reasons related to adverse events (AEs):
    - Initiating or continuing study drug places the subject at undue hazard as determined by the Investigator;
    - Serious adverse event (SAE) or other safety concern that is related to study drug treatment as determined by the Investigator;
    - Major bleeding event as determined by the Investigator;
    - Aggravation or new occurrence of renal insufficiency with eGFR ≤30% of normal for age and size;
    - Hepatic test abnormalities as follows:
        - Elevation of ALT and/or AST ≥3 × ULN and TBL ≥2 × ULN simultaneously.
        - ALT and/or AST ≥8 × ULN requires an immediate interruption of study drug treatment and prompt repeat testing to confirm abnormality.
    - Clinical jaundice requires an immediate interruption of study drug treatment and prompt repeat testing to confirm abnormality;
    - Any elevation of transaminases combined with clinical symptoms of liver injury;
    - If a subject discontinues study drug due to confirmed liver enzyme abnormalities or jaundice, the subject will have additional evaluations at the discretion of the Investigator as follows:
        - Hepatitis A, B, C, and E screening (anti-HAV IgM, HBsAg, anti-HCV plus viral titer, and evaluation for Hepatitis E);
        - Abdominal ultrasound;
        - Antinuclear antibody (ANA) and anti-SmAb;
        - Cytomegalovirus (CMV);
        - Epstein-Barr virus (EBV);

- Additional evaluations as deemed appropriate by the Investigator to exclude other causes of liver enzyme and bilirubin elevations.

Subject's follow-up will be required on a weekly basis until the values (transaminases and total bilirubin) return to baseline or clinically acceptable levels in the judgment of the Investigator. For the above laboratory blood tests, using the central laboratory is recommended. However, if circumstances warrant the use of a local laboratory, copies of the local laboratory results will be required. All clinically significant hepatic enzyme abnormalities and/or hepatic events are to be documented in the eCRF and prompt submission of the adjudication dossier should also occur for events that led to study drug discontinuation or were reported as SAEs.

3. Unplanned cardiac surgery due to aggravation of cardiac conditions;
4. Pregnancy;
5. Study terminated by Sponsor;
6. Protocol violation;
7. Lack of efficacy.

Those subjects extended beyond Month 3 (Visit 5) will have study procedures terminated at the time of discontinuation from study with a discontinuation visit with a subsequent 30-day safety Follow-Up Visit (Section 6.4.3).

If the subject discontinued study treatment due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

5.6.4. Reasons for Withdrawal at any Time During the Study

Withdrawal of a subject will only occur by definition if no additional protocol scheduled visits or Follow-Up Visit is possible. The withdrawal definition is mostly appropriate for those cases that occur in the Main Treatment Period because of the requirement to continue subjects on scheduled visits even if they discontinue treatment prior to Month 3 (Visit 5). If a subject withdraws after Month 3 this would be classified as a discontinuation from treatment and study.

The cases appropriate for withdrawal during the Main Treatment Period are:

- Withdrawal of subject consent by subject or legal guardian(s)
- Death
- Lost to follow-up (attempts should be made to not have any subject lost to follow-up)
- AE that occurs during the Main Treatment Period that requires withdrawal.

5.6.5. Discontinuation Procedures

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to discontinue study treatment or withdraw consent for participation in the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

While subjects are encouraged to complete all study evaluations, they may discontinue study treatment or withdraw from the study at any time and for any reason without penalty. Every effort will be made to determine why any subject discontinues study treatment or withdraws from the study prematurely. This information should be recorded.

The most likely reasons for withdrawal are death, lost to follow-up or withdrawal of consent, or an AE in which case all subsequent visits will NOT be possible as stated in the protocol.

All subjects who classify as discontinued from the study treatment with an ongoing AE must be followed until the event is resolved or deemed stable even if they are not willing to participate in the study any longer. If a subject discontinues study treatment or withdraws after dosing, all data normally collected prior to study discharge should be collected at the time of discontinuation from study treatment or withdrawal, and at the scheduled visit of the study.

In case of withdrawal, a genuine effort must be made to determine the reason(s) why a subject fails to return for the necessary visits. If the subject is unreachable by telephone, a registered letter, at the minimum, should be sent to the subject requesting him/her to contact the study center.

If a subject is withdrawn or discontinued from study treatment, the IXRS will be called by the study center to register the subject status.

Please see suggested classification of discontinuation and withdrawal status in Table 5.2.

Table 5.2: Classification of Discontinuation and Withdrawal Status for Subjects by Scheduled Visit

	Discontinue Treatment	**Discontinue Study**	**Withdrawal**
Randomization through Month 3	Eligible	Not Eligible (Need to follow through Month 3 with Follow-Up Visit)	Eligible (Assumes no additional visit is possible)
Beyond Month 3 through Month 12	Eligible	Eligible (A discontinuation study visit will be conducted with Follow-Up Visit)	Not Eligible (Unless no discontinuation visit is possible)

5.6.6. Follow-up Procedures

A 30-day follow-up for safety assessment will be scheduled after the Month 3 visit for all subjects participating in the 3-month Main Treatment Period (for Cohort 5, the intended duration of treatment is 6-12 weeks).

Subjects who extend toward 12 months of study treatment and decide to no longer participate will have a subsequent 30-day Follow-Up Visit after their discontinuation visit during the extension period.

A 30-day Follow-Up Visit may be performed with a phone call if the following conditions have NOT occurred:

- An SAE was not experienced by the subject at the last visit or during the interval of time from the last visit to the Follow-Up Visit,
- An event (recurrent VTE, or bleeds) was not experienced by the subject at the last visit or during the interval of time from the last visit to the Follow-Up Visit.

5.6.6.1. Temporary Interruption of Study Drug

If a subject's treatment with study drug must be interrupted for medical or surgical reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery, thrombocytopenia due to cytotoxic medication, or dental work); use of a prohibited concomitant medication; or other reasons (eg, temporary situation that prevents subject adherence with the study drug administration schedule, etc.), the subject's study drug should be resumed as early as the situation allows. Edoxaban should be discontinued for 24 hours prior to the initiation of the procedures (depending on PK/PD data in children). Subjects should be encouraged to restart study drug after an interruption except when absolutely contraindicated. The duration of study drug interruption can vary depending upon the individual circumstances, and study drug may be resumed regardless of the duration of time that it had been interrupted. Any subject who temporarily interrupts study drug for more than 3 days will have the reason recorded in the eCRF.

5.6.6.2. Subject Re-Screening Procedures

Re-screening (retesting of laboratory test results) is permitted only once for any subject with Sponsor approval who failed to meet eligibility criteria upon initial screening related to a specific inclusion/exclusion criteria. If a subject needs to be re-screened for any time dependent module (ie, laboratory, vital signs, etc.), the Investigator will perform an unscheduled visit **within 30 days of the original Screening visit** and the appropriate module will be used to accommodate new data that would make the subject eligible to be randomized. The subject identification number will remain the same at the time of rescreening.

The initial screening information and the reason why the subject is ineligible for the initial evaluation will be uploaded into the EDC system. Re-screening of a subject may occur only once. If there is a failure to meet study entry criteria, the failed subject will be recorded in the Screening Log and EDC.

6. STUDY PROCEDURES

Potential subjects will have the study risks and possible benefits explained to them, the ICF reviewed with them, and all questions answered for them. Subjects will undergo procedures specific to study qualification (Section 6.1) only after the ICF is signed by the subject/or the subject's legal representative, and age appropriate assent obtained from subjects capable of doing so. Subjects who complete the screening period and are determined to be eligible for study participation per the inclusion and exclusion criteria will be randomized in a 1:1 ratio to either the edoxaban-treatment arm or the SOC-treatment arm.

All subjects will undergo safety objectives evaluations at the EOT at Month 3 and at 30-days thereafter. Subjects who participate in the Extension Period will undergo safety objectives evaluations (recurrent VTE events, bleeding events, or any other AEs) at Months 6, 9, and 12, and 30-days after cessation of treatment if treatment up to 12 months is required.

The Schedule of Events for this study is provided in Appendix 17.1.

6.1. Screening: Study Qualification (At least Day -5 to -1, Visit 1)

Any protocol-specified study qualification procedures/tests not already done as part of routine care will be conducted only after the subject signs the ICF and before randomization.

Note: A newly diagnosed VTE or diagnostic workup may have been performed prior to identifying the subject for the study and signing the consent.

Prior to signing the ICF, potential subjects and their parent(s)/guardian(s) will have the study risks and benefits explained to them, the associated ICF and assent form if applicable will be reviewed, and all questions answered for them. Written informed consent must be signed by the parent(s)/guardian(s) of all subjects, and assent obtained from the child, when and where applicable, prior to entry into the study.

- It is anticipated that some subjects will have had some of the study qualification procedures done as part of routine care outside the auspices of this study (for example, diagnostic work-up and associated care for index VTE). As long as these procedures were done for the newly diagnosed index VTE before randomization, they may be used to complete the Screening eCRF.
- A Screening eCRF must be completed for every subject with a signed ICF. Any protocol-specified study qualification procedures/tests not already done as part of routine care will need to be conducted after the parent(s)/guardian(s) signs the ICF and before randomization.
- Register the subject for screening within IXRS Screening Visit and subject number will be provided.
- For subjects who did not have any protocol-specified screening procedures done as part of routine care for the newly diagnosed index VTE before randomization, the following study qualification procedures must be completed to ensure that the subject is eligible for the study.
  - Review inclusion/exclusion criteria

  - VTE Radiologic Image: After index VTE diagnosis is confirmed through the appropriate imaging techniques (see Section 7.1) send the results to the Clinical Evaluation Committee for adjudication
  - Record demographic information (date of birth/age, sex, ethnicity, and race)
  - Record medical/surgical history,
  - Record prior medication (up to 30 days prior to screening)
  - Perform physical examination including:
    - Vital signs (BP, heart rate, and body temperature after resting in a sitting or supine position [Note: the appropriate cuff size base on arm circumference will be used.] see Section 9.9)
    - Height and body weight (may be performed by an Investigator or other healthcare provider designated by the Investigator).
- Assess the subject for active bleeding, high risk for bleeding and any other contraindications for treatment with LMWH, or UFH, SP anti-FXa, VKAs or NOACs.
- INR assessment and aPTT measurement to monitor coagulation for all subjects
- Ensure that the subject qualifies with regard to the following laboratory tests for exclusion criteria:
  - Liver function assessments (ALT, AST, TBL, ALP)
  - Serum chemistry panel, Serum creatinine, and eGFR
  - Hematology
  - Urinalysis
  - Urine pregnancy test (for post-menarchal females)
- Samples taken as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the tests (INR, aPTT, ALT, TBL, eGFR and platelets) were performed for the newly diagnosed index VTE before randomization. Alternatively, the central laboratory may be used for the above study qualification laboratory tests. If central laboratory is also used at the same visit with a resulting discrepancy for exclusion criteria, the local laboratory result will still be used to qualify the subject.
- Review concomitant medications for assessment of exclusion criteria.
- Assess for and record AEs and concomitant medications.

Full documentation for the above qualifying procedures and related results are required even if local laboratory results were used to qualify the subject.

6.1.1. Screening Period Prior to Randomization

Initial treatment using LMWH or SP Xa inhibitor or UFH for index VTE prior to randomization must be within the range of 5 to 15 days and up to 20 days with Sponsor approval. In addition, prior to being randomized to edoxaban or SOC, subjects initially treated with VKA are recommended to have an INR ≤2.5.

6.2. Randomization (Day 1, Visit 2)

If all procedures and tests done before randomization confirm the subject's eligibility (Section 4.1) for the study, then the IXRS will be contacted to randomize the subject. Randomization may occur in IXRS the day prior to dosing for clinical logistics. The following activities should be done at the time of randomization:

- Record any prior medications used since the last visit.
- Record any AEs since screening visit.
- Urine pregnancy test (for post-menarchal females)
- Dispense study drug and record amount (number of tablets/bottles) dispensed. Locally sourced SOC study therapy will need to be supported by a prescription identifying the type of SOC to be provided;
- Explain the study medications and the proper daily dosing to the parent/guardian and subject (if applicable) using the study medication dosing calendar, and confirm that the subject understands the proper daily dosing of study medication.
- Instruct subject to bring all medications including study drug packaging and bottles to each visit.

Provide parent(s)/legal guardian(s) or legally acceptable representative parent(s)/guardian(s) and subject (if applicable) information with detailing symptoms suggestive of recurrent VTE and bleeding. Parent(s)/guardian(s)/subject will be asked to immediately contact the Investigator if these symptoms occur.

The following information will be provided to the parent/subject (information booklet):

- The local medical contact person and emergency telephone number
- The visit schedule provided by the IXRS (fax or email with dates of telephone and/or hospital visits)
- How to recognize and report signs and symptoms of possible recurrent symptomatic PE/DVT or bleeding (see Section 7.1 and Section 9.2.1).
- Instructions to keep empty medication packages
- How to use the study medications
- The scheduled dates of blood collections for the next INR control if VKA is dispensed
- Provide subjects with a subject identification safety card and a prohibited medication card

The Investigator will use discretion to decide when and how often to repeat INR or anti-FXa levels or aPTT measurements or fondaparinux levels. These measurements will be taken in the clinic, or alternatively, optional site-specific local laboratory (Appendix 17.2).

All suspected VTE and bleeding endpoints as well as hepatic abnormalities identified by the Investigator will be adjudicated by the CEC. Adjudication packages will contain copies of images (or films) of appropriate diagnostic tests, clinic notes, laboratory tests, discharge summaries, autopsy reports, etc. used in the subject work-up following a suspected event.

Investigators will maintain a confidential subject identification code list of names of all subjects randomized to study to allow the Investigator to reveal the identity of any subject when necessary.

6.3. Main Treatment Period

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

6.3.1. Subjects randomized to the edoxaban treatment arm:

For the approximately first 12 subjects of each age cohort randomized in edoxaban-treatment arm, two blood samples will be collected on Day 5+3 days. Dosing on Day 5 will be done in the study center. Note: If the subject did not initiate dosing of edoxaban on the randomization day (Day 1), the Day 5 PK/PD assessment should be scheduled when the actual Day 5 dose is taken.

Edoxaban will be started orally at the age/weight/renal function appropriate dose (depending on the results of the ongoing U157 study) for the treatment period. The study will start enrollment from older to younger children as data from the single dose PK, PD study become available for each age cohort (Study U157). After Month 3, dispense may be provided for a 3-month period to align with the visit schedule based on approval of the Sponsor.

For subjects in Cohort 5, the Principal Investigator (PI) may use medical discretion and clinical judgment to determine the duration of anticoagulation treatment. For these subjects, the intended duration of treatment should be at least 6 to 12 weeks. If 6 weeks' duration is chosen, a radiologic VTE image will be taken and will be assessed by the PI to determine if an additional 6 weeks of treatment is required. After 12 weeks, an additional radiologic VTE image will be taken by the PI to assess whether the subject should continue on treatment into the extension.

Approximately 12 subjects from each age cohort (total of approximately 53 to 60 subjects) will participate in the multiple-dose PK/PD assessment (subject number is determined by evaluable blood specimens demonstrating edoxaban exposure). For the youngest Cohort 5 (birth to <6 months), 5 to 12 subjects on edoxaban will be enrolled.

- Ages 12 to <18 years (N≈12)
- Ages 6 to <12 years (N≈12)
- Ages 2 to <6 years (N≈12)
- Ages 6 months to <2 years (N≈12)
- Ages birth to <6 months (N≈5-12)

6.3.1.1. Study Day 5 (+3 days) for Subjects Randomized to Edoxaban Only (Visit 2a)

Subjects participating in the Day 5 edoxaban evaluation will need to bring their edoxaban treatment (wallet card or bottle of granules) to the clinic for dosing that day. A witness should observe the edoxaban dose taken on Day 5 after the pre-dose blood specimen is collected.

Each subject included in the multiple-dose PK/PD assessment will have a laboratory developed test (LDT) PK assay performed for edoxaban exposure verification. The first approximately 12 subjects participating in PK/PD assessment should be fasted one hour prior to the uptake of edoxaban dose and a maximum of 2 hours after taking edoxaban dose. If this is not feasible because of the subject's age or other needs, milk, or an equivalent substitute liquid (but not fruit juices or caffeinated drinks), will be allowed until 1 hour before and starting at 1 hour post-dose.

In preparation for the Study Day 5 visit, subjects will be instructed to do the following:

- Record date/time of the last 2 study drug doses taken before the Day 5 visit
- Record date/time of the last meal taken before the Day 5 visit
- Record time of study drug dose taken on visit day

The PK sampling windows (hours) on the day of the fifth dose of edoxaban (Day 5+3 days) is planned to occur as follows:

- PK Pre-dose sample for all participating subjects.
- PK Post-dose sample can be taken at either:
  - any time between 1.0 to 3 hours post-dose

    or
  - any time between 5 to 8 hours post-dose
- The PD sampling times on Day 5 for measurement of PT, aPTT and anti-FXa, will be the same time as the PK samples.
- An edoxaban PK analysis will be performed on Day 5 subjects in U312 study. If the analysis of the subjects confirms the edoxaban exposure predictions and based on emerging safety, the expanded enrollment in the same age cohort will be allowed to start. A notification will be sent to all Investigators that expansion of the age cohort is permitted after the PK analysis. In addition, a notification to the investigator will indicate that Day 5 PK/PD edoxaban exposure evaluation will no longer be necessary for future subjects randomized to edoxaban in the corresponding age cohort.
- For subjects in Cohort 5, specifically those ≤28 days old, a renal function test (RFT) will be performed on or around Day 5 (at the same time of PK sampling).

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

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

- Safety data analysis on the subjects of the next younger age cohort in U157.

PK and safety data will be reviewed by an IDMC, (Section 15.9) who will approve the start of the next younger age cohort.

In each age cohort, if the estimated median AUC based on the observed PK data in participating subjects in the Day 5 PK assessment is less than 1.5-fold the median AUC from the simulated subject population profiles (over-exposure and under-exposure), the enrollment of subjects in the corresponding age cohort will continue and enrollment in the next younger age cohort can begin.

The following will be performed at this visit:

- Review dosing instructions
- Safety review for AEs/SAEs
- Review for endpoint events (VTE, bleeding)

The Investigator will use discretion to decide when and how often to repeat INR or anti-FXa levels or aPTT measurements or fondaparinux levels. These measurements will be taken in the clinic, or alternatively, optional site-specific local laboratory (Appendix 17.2).

6.3.2. Subjects randomized to the SOC treatment arm:

Standard of Care treatment will be dispensed to the subject on a monthly visit schedule. After Month 3, dispense may be provided for a 3-month period to align with the visit schedule based on approval of the Sponsor. SOC will be provided by the Investigator. Subject will be treated with LMWH, VKA, or SP Xa inhibitors according to the site SOC treatment (Section 5.1.1.2). However, if there are regulatory or site hurdles providing the SOC, the Sponsor will provide SOC as enoxaparin or fondaparinux or warfarin (see below).

If Investigators choose to use the SOC supplied by the Sponsor, the subject will be treated as follows:

- Enoxaparin – Subjects will be treated with enoxaparin alone or can be switched to warfarin anytime during the study treatment period.
- Fondaparinux – Subjects will be treated with fondaparinux alone or can be switched to warfarin anytime during the study treatment period.
- For subjects in whom clinicians prescribe warfarin, this will be started on Day 1. Heparin (enoxaparin or fondaparinux or UFH depending on the therapy received during pre-randomization period) will be discontinued when INR ≥2.0 and ≤3.0 for 2 consecutive measurements obtained at least 24 to 48 hours apart. The subject will continue warfarin for the remainder of the study treatment period.

The Investigator will use discretion to decide when and how often to repeat INR or anti-FXa levels or aPTT measurements or fondaparinux levels. These measurements will be taken in the clinic, or alternatively, optional site-specific local laboratory (Appendix 17.2).

6.3.3. Monthly Visits (Months 1 and 2; Visits 3 and 4) for both arms:

Starting with the Month 1 visit, subjects will return to the clinic every 30 days ± 5 days (depending on the visit, see Schedule of Events in Appendix 17.1) until the Month 3 visit (Visit 5) or study withdrawal. For Cohort 5, the subjects may return to the clinic earlier after the first month, depending on the duration of the therapy (at least 6 to 12 weeks) and imaging at 6 weeks for thrombus resolution.

During study drug interruptions and after study drug discontinuation, subjects will be followed for efficacy and safety endpoints and SAEs until the Month 3 visit (Visit 5) or earlier in Cohort 5 subjects (6-12 weeks). A 30 day Follow-Up Visit (Visit 9) for safety assessment is required after the Month 3 visit (for Cohort 5, the intended duration of treatment is 6 to12 weeks).

At these monthly on-site visits, anti-FXa levels assessments and aPTT measurements will be performed for the subjects on SOC with LMWH or SP Xa inhibitor, fondaparinux levels if applicable, and INR assessments will be performed for the subject on SOC with VKA. Additional interim visits may be scheduled, at the Investigator's discretion, for anti-FXa levels/INR monitoring.

6.3.3.1. Month 1 Visit (Visit 3) Procedures

The following will be performed at this visit:

- Record concomitant medications
- Count unused study drug tablets/ bottles/syringe and calculate compliance
- Dispense study drug medication and review dosing instructions
- Perform physical examination (see Section 9.10)
- Record vital signs (Section 9.9)
- Take blood samples for the following laboratory tests (See Table 17.1):
  - Liver function tests [ALT, AST, TBL, and ALP]
  - Serum creatinine
- Safety review for AEs/SAEs
- Review for endpoint events (VTE, bleeding)

6.3.3.2. Month 2 (Visit 4) Procedures

- Record concomitant medications
- Count unused study drug tablets/ bottles/syringe and calculate compliance
- Dispense study drug medication and review dosing instructions
- Perform physical examination (see Section 9.10)
- Record vital signs (Section 9.9)
- Safety review for AEs/SAEs

- Review for endpoint events (VTE, bleeding)
  - The follow-up imaging performed if needed, must be always performed with the same modality as the initial diagnostic study

6.3.4. End of Main Treatment Period Visit (Month 3 or at least 6-12 weeks for Cohort 5, Visit 5) Procedures

All randomized subjects including those that have discontinued treatment will have an EOT assessment at Month 3 (within a ±5-day window).

The following will be performed at this visit:

- Perform physical examination (see Section 9.10)
- Vital signs (Section 9.9)
- Review concomitant medications
- Count unused study drug tablets/ bottles/syringe and calculate compliance
- Safety review for AEs/SAEs
- Review for endpoint events (VTE, bleeding)
  - Radiologic examination using the same diagnostic technique used at baseline to determine the thrombotic burden (see Section 7.1).
  - VTE Radiologic Imaging (see Section 7.1).
- Take samples for the following:
  - Liver function tests [ALT, AST, TBL, and ALP]
  - Serum creatinine
  - Hematology
  - Urine pregnancy test
- Dispense study drug medication and review dosing instructions per subject/parent's request and at the Investigator's decision to extend study treatment. After Month 3, the distribution of edoxaban or SOC may be for a 3-month period to align with the visit schedule, with the Sponsor's approval.

6.4. Extension Period (beyond Month 3 - Month 6, 9 and 12; Visits 6, 7, 8)

Per subject/parent's request and at the Investigator's decision, study treatment can be extended up to 12 months. At any time during the extended period, a subject can discontinue treatment and the study. In such a case a discontinuation study visit will be performed with a subsequent 30-day safety Follow-Up Visit (see Table 17.1).

The subjects on extended treatment will be followed for safety and efficacy assessment including bleeding events, recurrent VTE, and any treatment-related AEs at visit for Months 6 (Visit 6), 9 (Visit 7), and 12/ Discontinuation (Visit 8). Additionally, the subject will have a Follow-Up Visit (Visit 9) for safety assessment 30 days after treatment cessation. At Month

12/Discontinuation Visit, or at any time the subjects discontinues from the study after Month 3, the study drug will be collected from the subject and the subject will be switched to SOC anticoagulation treatment if necessary, at the discretion of the Investigator. All subjects who require continued SOC anticoagulation treatment at the end of study treatment in accordance with the current CHEST guidelines will be transitioned to the SOC determined by the Investigator. The transition algorithms are provided in Appendix 17.5. The visits will occur every 3 months and the following procedures performed.

At these monthly visits, anti-FXa levels assessments and aPTT measurements will be performed for the subjects on SOC with LMWH or SP Xa inhibitor, fondaparinux levels if applicable, and INR assessments will be performed for the subject on SOC with VKA. Additional interim visits may be scheduled, at the Investigator's discretion, for anti-FXa levels/INR monitoring.

Drug dispensing will occur monthly. After Month 3, the distribution of edoxaban or SOC may be for a 3-month period to align with the visit schedule, with the Sponsor's approval.

6.4.1. Month 6 (Visit 6) Procedures:

- Record concomitant medications.
- Count unused study drug tablets/bottles/syringes and calculate compliance.
- Dispense study drug medication and review dosing instructions
- Perform physical examination (see Section 9.10)
- Record vital signs (Section 9.9)
- Review for endpoint events (VTE, bleeding)
- Safety review for AEs/SAEs
- Collect blood samples for serum creatinine test

6.4.2. Month 9 (Visit 7) Procedures:

- Record concomitant medications.
- Count unused study drug tablets/bottles/syringes and calculate compliance
- Dispense study drug medication and review dosing instructions
- Perform physical examination (see Section 9.10)
- Record vital signs (Section 9.9)
- Review for endpoint events (VTE, bleeding)
- Safety review for AEs/SAEs
- Collect blood samples for the following laboratory tests:
  - Liver function tests [ALT, AST, TBL, and ALP]
  - Serum creatinine

6.4.3. Month 12 / Discontinuation Visit (Visit 8; Appropriate only for subjects treated beyond Month 3 and discontinuing study prior to Month 12 Procedures):

Discontinuation from study visit will only be required for those extended into the study beyond Month 3 because all subjects are to be followed though Month 3.

Procedures for subjects who withdraw from the study or are discontinued from the study treatment for any reason are discussed in Section 5.6.

All randomized subjects extended beyond Month 3 who wish to discontinue treatment and study will have discontinuation visit (Visit 8) performed when the last dose of study drug is administered after Month 3, to Month 12.

The following will be performed at this visit:

- Record concomitant medications.
- Count unused study drug tablets/bottles/syringes and calculate compliance
- Perform physical examination (see Section 9.10)
- Vital signs (Section 9.9)
- Safety review for AEs/SAEs
- Review for endpoint events (VTE, bleeding)
- Collect blood samples for the following laboratory tests:
  - Liver function tests [ALT, AST, TBL, and ALP]
  - Serum creatinine
  - Hematology
- Urine pregnancy test (for post-menarchal females)
- VTE Radiologic Imaging

6.5. Required 30 Day Follow-Up Visit (Visit 9)

6.5.1. Follow-up for Subjects Ending/ Completing Study at Month 3

All randomized subjects completing or discontinuing study therapy prior to Month 3 will have end-of-study safety Follow-Up Visits 30 days after Month 3. Note all study subjects will be followed monthly through Month 3 with study procedures even if discontinuing study therapy.

A 30-day Follow-Up Visit may be performed with a phone call if the following conditions have NOT occurred:

- An SAE was not experienced by the subject at the last visit or during the interval of time from the last visit to the Follow-Up Visit,
- An event (recurrent VTE, or bleeds) was not experienced by the subject at the last visit or during the interval of time from the last visit to the Follow-Up Visit.

6.5.2. Follow-Up for Subject Continuing Study beyond Month 3

Subjects discontinuing study after Month 3 will have a Follow-Up Visit 30 days after their discontinuation visit or after completing 12 months of study therapy.

Note: withdrawal for study subjects (death, lost to follow-up, withdrawal consent, AE) by definition will not have a follow-up.

The following will be recorded or collected:

- AEs
- Review endpoint events (VTE, Bleeding)
- Concomitant medication

7. EFFICACY ASSESSMENTS

7.1. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the composite endpoint consisting of incidence of symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden (defined below) during the first 3-month period (for Cohort 5, the intended duration of treatment is 6-12 weeks).

All efficacy endpoints described below will be adjudicated in a blinded manner by the clinical events committee.

Radiologic examination

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

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

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

Diagnosis of symptomatic recurrent VTE requires the confirmation by appropriate diagnostic imaging (see imaging criteria of recurrent VTE) and at least one of the symptoms of VTE in the following table:

- Symptoms of VTE:

Locations	Symptoms
VTE in Upper limb (CVL or non-CVL related)	• Collateral dilated vein on the chest • Superior vena cava syndrome • Chylothorax • Pain and/or Swelling in index limb • Reddish or purple discoloration
VTE in Lower extremity (CVL or non-CVL related)	• Reddish or purple discoloration • Swelling • Pain

Catheter-related thrombosis	• Dysfunction of catheter (inability to aspirate blood) not attributed to catheter kinking • Catheter-sepsis • Thrombocytopenia (especially neonates)
Pulmonary embolism	• Dyspnea • Pain thorax-pleuritic chest pain • Hypoxemia-low O_2 saturation • Hemoptysis • Cough • Tachycardia • Tachypnea, • Fever • Syncope • Right heart failure • Cardiopulmonary arrest
Sinovenous thrombosis	• Seizures (focal, generalized) • Depressed level of consciousness and coma • Lethargy • Nausea, Vomiting • Headache • Visual impairment (transient obscurations, reduced acuity, blindness) • Papilledema • Hemiparesis • Hemisensory loss • Ataxia • Speech impairment, Mutism • Cranial nerve palsies (VI) • Acute psychiatric symptoms • Respiratory failure (in neonates) • Jittery movements (in neonates) • Hydrocephalus
Splanchnic vein thrombosis Portal vein, Splenic vein, Mesenteric vein	• Abdominal distension/pain • Splenomegaly

	• Upper gastrointestinal-bleed and/or melena with esophageal varices (portal hypertension)
Hepatic vein/Vena cava	• Abdominal distension with ascites and hepatomegaly • Dilated veins in anterior abdominal walls
Renal Vein	• Palpable flank mass • Macro or micro hematuria • Thrombocytopenia

- Imaging criteria of recurrent VTE:
  - Abnormal compression ultrasonography where compression had been normal or, if non-compressible during screening, an increase in diameter of the thrombus during full compression;
  - An extension of the echogenic intra-luminal thrombus or absence of flow in the central venous system on Doppler ultrasonography.
  - An extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.
  - An extension of an intraluminal filling defect, or a new intraluminal filling defect on computed tomography angiogram (CTA).

Locations	Recommended Diagnostic methods
VTE in Upper limb (CVL or non-CVL related)	• Ultrasonography (US) for peripheral upper limb as axillary, subclavian and jugular veins • MRV for central intra-thoracic veins <u>Alternative imaging techniques:</u> • Multi-detector CT venography (MDCT venography)
VTE in Lower extremity (CVL or non-CVL related)	• Doppler US (± repeated 1 week) • MRV
Catheter-related thrombosis	• Doppler US • Echocardiography • Conventional venography • MRV
Pulmonary embolism	• V/Q scanning

	• Spiral CT pulmonary angiography (CTPA) • Magnetic resonance pulmonary angiography (MRPA) <u>Alternative imaging techniques:</u> • Cardiac angiography • Conventional pulmonary angiography • echocardiography
Sinovenous thrombosis	• Brain MRI, including T2 imaging and MRI with venography (MRV) • Pre and post-contrast CT scan with venography (CTV) <u>Alternative imaging techniques:</u> • Doppler flow US; if fontanelle open
Renal Vein thrombosis	• US
Splanchnic and hepatic veins and vena cava	• Doppler/US • CT/Scan

In certain cases, the use of 2 techniques may be required to objectively confirm the diagnosis of recurrent VTE. Further recommendations will be provided in the imaging manual but will be left for Investigator's discretion.

<u>Diagnosis of fatal VTE</u> is based on 1 or more of the following:

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

<u>Thrombotic burden</u> will be assessed by comparison of the diagnostic method used at baseline and at Month 3 ± 5 days (for Cohort 5, at 6 to 12 weeks ± 5 days) in the absence of symptomatic recurrent VTE. Hence, the same imaging technique that is used at the enrollment of the subject into the study will be required to be used at the end of the observational period ± 3 days. A thrombotic burden endpoint will be registered if there is no regression of the thrombus size or extension of the thrombus at Month 3 visit ± 3 days (for Cohort 5, at 6 to 12 weeks ± 3 days) after randomization.

Additionally, thrombotic burden will be assessed at Month 12 ± 5 days / Discontinuation Visit, for those subjects who participate in the Extension Period.

7.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints include:

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

7.3. Exploratory Efficacy Endpoint(s)

Not applicable.

7.4. Clinical Outcome Endpoint

The clinical outcome endpoint is:

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

7.5. Appropriateness of Selected Efficacy Endpoint(s)

Definitions of outcomes in U312 are based on presentations/discussions at the Perinatal and Paediatric Haemostasis Subcommittee meetings during the 56th–58th Scientific and Standardization Committee (SSC) Meetings of the International Society on Thrombosis and Haemostasis (ISTH)[21].

The proposed primary efficacy endpoint in the Phase 3 VTE study (U312) is a composite endpoint consisting of the incidence of symptomatic recurrent venous thromboembolic disease, death as a result of VTE, or no change or extension of thrombotic burden within the 3-month +3 days study period.

In children with VTE disease, the incidence of "no change in thrombotic burden" has been reported in several clinical pediatric studies as 14.8%[16], 17% and 18%[17]. Lack of thrombus resolution has been reported as a prognostic factor for the development of post-thrombotic syndrome (PTS)[18]. PTS is a known complication of VTE that children must endure as chronic sequelae that adversely impacts quality of life (QOL) for many decades. Goldenberg et al. conducted a systematic review of PTS in children in 2010. A total of 997 subjects were assessed

for PTS. In this review, the frequency of PTS post DVT (Upper Extremity/Lower Extremity) was reported as high as 26%. In Goldenberg's review, the lack of thrombus resolution was mentioned as a prognostic factor for the development of PTS.

The clinical significance of "no change in thrombotic burden" in the incidence of PTS is therefore clearly documented. In order to ensure adequate adjudication of this endpoint, the Sponsor will be implementing several steps:

1. The same imaging technique that is used at the enrollment of the subject into the study will be required to be used at the end of the observational period
2. Detailed instructions ensuring consistency in obtaining images for each of the techniques will be provided to the study sites
3. Both initial and follow-up imaging will be independently and blindly assessed by an appropriately qualified central adjudication committee.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

Approximately, the first 12 subjects of each age cohort (total of approximately53 to 60 subjects) randomized to the edoxaban treatment arm will participate in the multiple-dose PK/PD assessment (Table 8.1) on Day 5 (+3 days, Visit 2a) as follows (subject number is determined by evaluable blood specimens demonstrating edoxaban exposure):

- Ages 12 to <18 years (N≈12)
- Ages 6 to <12 years (N≈12)
- Ages 2 to <6 years (N≈12)
- Ages 6 months to <2 years (N≈12)
- Ages birth to <6 months (N≈5-12)

Blood samples will be collected on the day of the fifth dose of edoxaban (Day 5+3 days, Visit 2a) for all age cohorts, including:

- PK pre-dose sample.
- PK post-dose sample can be taken at either:
  - any time between 1.0 to 3 hours post-dose

    or
  - any time between 5 to 8 hours post-dose
- The PD sampling times on Day 5 for measurement of PT, aPTT and anti-FXa, will be taken at the same time as the PK samples.
- A PK analysis will be performed on subjects in U312 study. If the analysis of the subjects confirms the exposure predictions and based on emerging safety, the expanded enrollment in the same age cohort will be allowed to start. A notification will be sent to all Investigators that expansion of the age cohort is permitted after the PK analysis. In addition, a notification will be sent indicating that recruitment for Day 5 edoxaban-treated subjects will no longer be necessary for that particular cohort.
- One blood sample will be drawn for RFT (serum creatinine and blood urea nitrogen) on or around Day 5 (at the same time of PK sampling).

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

- PK analysis performed on subjects in the prior older age cohort in U312.
- Safety data analysis on subjects in the prior older age cohort in U312.
- PK analysis of the subjects in the next younger age cohort in U157.
- Safety data analysis on the subjects of the next younger age cohort in U157.

PK and safety data will be reviewed by an IDMC (Section 15.9) who will approve the start of the next younger age cohort.

In each age cohort, if the estimated median AUC based on the observed PK data in a subset of subjects in the Day 5 PK assessment is less than 1.5-fold the median AUC from the simulated subject population profiles (over-exposure and under-exposure), the enrollment of subjects in the corresponding age cohort will continue and enrollment in the next younger age cohort can begin.

Table 8.1: Edoxaban PK/PD Sampling Visits and Collection Times

Sampling Visits and Times	Samples per Subject	Number of Subjects
Day 5 + 3 days Edoxaban Dosing 1. First PK sample (Baseline); t=0, 2. Second PK sample can be taken at either: • any time between 1.0 to 3 hours post-dose **or** • any time between 5 to 8 hours post-dose	2	53 to 60
Day 5 + 3 days Edoxaban Dosing 1. First PD sample (Baseline); t=0, 2. Second PD sample is taken at the same time as the PK samples	2	53 to 60
PD Biomarker Assays	PT, aPTT, anti-FXa	

8.1. Pharmacokinetic (PK) Endpoint(s)

Using population PK analysis, the following PK parameters for edoxaban will be estimated:

- Apparent systemic clearance (CL/F)
- Apparent volume of distribution (V/F) of edoxaban

8.2. Pharmacodynamic (PD) Endpoint(s)

The following biomarkers of coagulation will be estimated: PT, aPTT, anti-FXa.

8.3. Biomarker Endpoint(s)

Not applicable.

8.4. Immunogenicity

Not applicable.

8.5. Pharmacogenomic Analysis

Not applicable.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Event Collection and Reporting

In the event of a Medical Emergency, the Investigator at the study site will institute any medical procedures deemed appropriate. A 24-hour Urgent Medical Contact will be provided to contact the Medical Monitor for further guidance.

Sites will receive a contact card where the following numbers (24-hour Urgent Medical Contact) are provided:

PPD (primary number)

PPD (alternative number)

The medical call center will contact Medical Monitor for the assigned region.

All AEs (see Section 9.4.1 for definitions) occurring after the subject signs the Informed Consent Form and up to 30 days after the last dose of study drug (ie, the Follow-Up Visit), whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event CRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Informed Consent will be recorded as part of medical history.

All AEs, serious adverse events (SAEs), bleeding, and events of special interest are to be reported according to the procedures in Section 9.5.

All laboratory results and vital signs should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results or vital sign findings should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. Parents will be guided to look out for signs and symptoms related to bleeding risks. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. In this pediatric population, specifically in the youngest cohort (Cohort 5) hospitalized (subjects who are ≤28 days old), site staff will contact the parents by phone on approximately Day 2, Day 7, and every week thereafter until Month 1 (Visit 3) post discharge to inquire about AEs, SAEs, and bleeding events.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to

signing the Informed Consent Form) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

The Investigator should follow subjects with adverse events until the event has resolved or the condition has stabilized. In case of unresolved adverse events, including significant abnormal laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

9.2. Safety Endpoint Event(s)

All potential safety endpoints will be adjudicated by an independent CEC. Study endpoints and safety data will be periodically reviewed by an IDMC to ensure the safety of study participants.

The safety related secondary objectives are:

- To compare edoxaban against SOC with regard to the combination of major and CRNM bleedings occurring during treatment or within 3 days of completing or interrupting or stopping study during the first 3-month treatment period (for Cohort 5, the intended duration of treatment is at least 6 to 12 weeks).
- To compare edoxaban against SOC with regard to all bleedings which occur from first to the last dose + 30 days.
- To compare edoxaban against SOC with regard to a composite combination of major and CRNM bleedings from first to the last dose + 30 days.

The corresponding safety endpoints are:

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

9.2.1. Bleeding

Bleeding is a protocol-specified endpoint and a known concern associated with anticoagulant therapy including edoxaban and VKAs (including warfarin). All bleeding events will be reported in the eCRF as either an AE or SAE depending upon the seriousness criteria along with completion of the bleeding event form. All bleeding events will be adjudicated by the CEC.

Bleeding definitions are based on presentations/discussions at the Perinatal and Paediatric Haemostasis Subcommittee meetings during the 56th-58th Scientific and Standardization Committee (SSC) Meeting of the ISTH.[21]

Major bleeding is defined as a composite (ie, any) of the following:

- Fatal bleeding; and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, pulmonary, or pericardial, or intramuscular with compartment syndrome; and/or
- Bleeding causing a decrease in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of the equivalent of two or more units of whole blood or red blood cells (RBCs).

Clinically relevant non-major bleeding is defined as either of the following:

- Acute or sub-acute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:
  - A hospital admission for bleeding;
  - A physician-guided medical or surgical treatment for bleeding or
  - A change in antithrombotic therapy (including interruption or discontinuation of study drug).

Minor bleeding is defined as follows:

- Any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or clinically relevant, non-major bleeding

Minimal criteria defining a significant bleeding per ISTH[27] are as follows:

For each specific bleeding symptom, the ISTH/Scientific and Standardization Committee (SSC) joint working group proposed minimal criteria in order to classify a symptom as significant:

1. Epistaxis:
   - Any nosebleed, especially occurring after puberty that causes subject concern (eg, interference or distress with daily or social activities) is considered significant.
   - In general, epistaxis should not be considered significant when it lasts less than 10 minutes, has a frequency of <5 episodes/year, has a seasonal occurrence, or is associated with infections of the upper respiratory tract or other identifiable cause (e.g., dusty dry air).
2. Cutaneous bleeding:
   - Bruises are considered significant when 5 or more (>1 cm) in exposed areas;
   - Petechiae are considered significant when adequately described by the subject or relatives;
   - Hematomas are considered significant when occurring without trauma.

3. Minor cutaneous wound:
    - Any bleeding episode caused by superficial cuts (eg, by shaving razor, knife, or scissors) or that requires frequent bandage changes is considered significant.
    - Insignificant bleeding from wounds includes those of duration <10 minutes and lesions that usually require stitches in normal subjects (eg, under the chin).
    - Symptoms should also be manifest on more than 1 occasion to be considered significant.
4. Oral cavity bleeding:
    - Gum bleeding should be considered significant when it causes frankly bloody sputum and lasts for 10 minutes or longer on more than one occasion.
    - Tooth eruption or spontaneous tooth loss bleeding should be considered significant when it requires assistance or supervision by a physician, or lasts at least 10 minutes (bleeding associated with tooth extraction is considered separately).
    - Bleeding occurring after bites to lips, cheek, and tongue should be considered significant when it lasts at least 10 minutes or causes a swollen tongue or mouth.
5. Hematemesis, melena, and hematochezia:
    - Any gastrointestinal bleeding that is not explained by the presence of a specific disease should be considered significant.
6. Hematuria:
    - Only macroscopic hematuria (from red to pale-pink urine) that is not explained by the presence of a specific urologic disease should be considered significant.
7. Tooth extraction:
    - Any bleeding occurring after leaving the dentist's office and requiring a new, unscheduled visit or prolonged bleeding at the dentist's office causing a delay in the procedure or discharge should be considered significant.
8. Surgical bleeding:
    - Any bleeding judged by the surgeon to be abnormally prolonged, that causes a delay in discharge, or requires some supportive treatment is considered significant.
9. Menorrhagia:
    - Any bleeding that interferes with daily activities such as work, housework, exercise or social activities during most menstrual periods should be considered significant.
    - Criteria for significant bleeding may include any of the following: changing pads more frequently than every 2 hours; menstrual bleeding lasting 7 or more days; and the presence of clots >1 cm combined with a history of flooding.

10. Muscle hematomas or hemarthrosis.
    - Any spontaneous joint/muscle bleeding (not related to traumatic injuries) is considered significant.
11. Central nervous system bleeding.
    - Any subdural or intra-cerebral hemorrhage is considered significant

All safety and efficacy endpoints described will be adjudicated in a blinded manner by the CEC.

The CEC will require all available details about the bleeding event and related information to allow successful objective adjudication of the event. Details may include, but are not limited to, information such as the following:

- Location of the bleeding;
- Duration of the bleeding;
- Fatality
- Treatment for bleeding event, including notes or summary of the recommendations from a healthcare professional from whom medical treatment was obtained;
- Magnitude of the bleeding (including size if skin or subcutaneous hematoma);
- Hemoglobin levels at randomization and at the time of the bleeding event, lowest value, pre- and post-transfusion values, and after resolution of the bleeding event;
- Diagnostic tests done to evaluate the bleeding such as endoscopy (GI bleed), ENT consult (ear, nose, throat bleed), urology consult (hematuria or urogenital bleeding), surgical consult (skin and soft tissue, including intra-abdominal bleeding), gynecological consult (uterine or vaginal bleeding), neurological consult (intracranial bleed), or ophthalmology consult (intraocular bleed);
- Diagnostic scans (CT scans or MRIs), ultrasounds or x-rays performed to evaluate the bleeding (intracranial bleed)
- Any other information that can be of help to the CEC to allow successful objective adjudication of the bleeding event.

9.3. Events of Special Interest

9.3.1. Liver Enzyme Abnormalities/Liver Dysfunction

Liver function is an area of special interest. Critical liver laboratory assessments include ALT, AST, TBL, and ALP. Particular attention will be paid to subjects with ALT or AST ≥3 × ULN and TBL ≥2 × ULN simultaneously without evidence of cholestasis (ALP ≥2 × ULN is considered evidence of possible cholestasis) and without alternative etiology for hepatocellular damage.

Liver enzyme abnormalities that lead to study drug interruption/discontinuation as well will be adjudicated in a blinded manner by the CEC. The CEC charter includes a process by which selected cases will be adjudicated by a liver disease specialist.

In cases of liver laboratory abnormalities, it is important to ensure that the nature and the extent of liver injury is identified and study subjects are monitored until the liver laboratory assessments return to normal.

If the subject discontinued study drug due to liver enzyme abnormalities, the subject will have additional evaluations in order to determine the nature and severity of the liver injury. The documents to be sent for adjudication:

- Results of confirmatory tests and diagnostic evaluation
- The hepatic event adjudication worksheets.

If a subject temporarily interrupts (or discontinues) study drug due to confirmed liver enzyme abnormalities or jaundice, the subject will have additional evaluations as described in Section 5.6.3 at the discretion of the Investigator.

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case [ALT or AST ≥3 × ULN with simultaneous TBL ≥2 × ULN] should always be reported to the Sponsor using a SAVER form, in addition to reporting it in eCRF, with the Investigator's assessment of seriousness, causality, and a detailed narrative. These events should be reported within 24 hours of Investigator's awareness of the event.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations until clinically acceptable resolution in order to determine the nature and severity of the potential liver injury.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered adverse events.

9.4.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,

- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the Informed Consent Form) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Severity Assessment

The following definitions should be used to assess intensity of adverse events:

- Mild: Awareness of sign or symptom, but easily tolerated, ie, does not interfere with subject’s usual function.
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Incapacitating with inability to work or do usual activity, ie, interferes significantly with subject’s usual function.

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event.

9.4.4. Causality Assessment

The Investigator should assess causal relationship between an adverse event and the study drug on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:

  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.

- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Dose Reduced: The dosage of study drug was reduced.
- Drug Interrupted: The study drug was temporarily stopped.
- Dose Increased: The dosage of study drug was increased.
- Not Applicable: (eg Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment)

9.4.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or OTC medication was required to treat the adverse event.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

9.4.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed.
- Recovering/Resolving

  - The adverse event improved but has not fully resolved.
- Not Recovered/Not Resolved
  - The adverse event itself is still present and observable.
- Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.
- Fatal
  - Fatal should be used when death is a direct outcome of the adverse event.
- Unknown

9.5. Serious Adverse Events and Adverse Event of Special Interest Reporting–Procedure For Investigators

All AEs, SAEs, including efficacy and safety endpoints that will be adjudicated will be reported in the CRF.

In the event of a Medical Emergency, the Investigator at the study site will institute any medical procedures deemed appropriate. A 24-hour Urgent Medical Contact will be provided to contact the Medical Monitor for further guidance.

Sites will receive a contact card where the following numbers (24-hour Urgent Medical Contact) are provided:

PPD (primary number)

PPD (alternative number)

The medical call center will contact Medical Monitor for the assigned region.

Serious events that are also efficacy endpoints (such as VTE and PE) and/or safety endpoints (such as bleeding events that are not life-threatening or fatal) will be exempted from SAE processing and expedited reporting. All efficacy and safety endpoints will be captured on specifically designed eCRFs. These events are clinically anticipated events in the target treatment population, and will be periodically reviewed by the IDMC to ensure prompt identification of any clinically concerning safety issues.

The following types of events should be reported by the Investigator on a Serious Adverse Events Reporting (SAVER) form within 24 hours of awareness:

- SAEs (see Section 9.4.2 for definition), including life-threatening or fatal bleeds.
- All SAEs resulting in death, regardless of whether they are waived endpoints for processing and expedited reporting, will be processed by the CRO for entry into the Sponsor's global safety database.
- Hepatic events meeting combination abnormalities [ALT or AST ≥3 × ULN with simultaneous TBL ≥2 × ULN] (potential Hy's Law case), both serious and non-serious (see Section 9.3.1 for additional details).

All events (serious and non-serious, including efficacy and safety endpoint events) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided where indicated. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study center and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

See Section 15.12 for contact information for SAE reporting. Please call your study monitor for any questions on SAE reporting.

9.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee

Daiichi Sankyo and/or CRO will inform Investigators, Institutional Review Boards/Ethics Committees (IRBs/ECs), and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study centers or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

In the European Economic Area (EEA) states, it is the Sponsor's responsibility to report SUSARs to all ECs.

9.7. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving edoxaban and within 30 days of discontinuing the study drug.

Although pregnancy is not technically an adverse event, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum

complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory evaluations will be shipped to a central laboratory for analysis. Results of all clinical laboratory tests will be reported in the subject's eCRF or merged electronically with the clinical database.

For the Screening Visit (Visit 1) samples taken as part of routine care outside study auspices may be analyzed by local clinical laboratories and the results used to qualify the subject provided the tests were performed for the newly diagnosed index VTE before randomization. Only local laboratory results for qualification purpose will be entered in the EDC (liver function test (LFT), serum creatinine, platelets, aPTT and INR).

9.8.1. Hematology

The ethylenediaminetraacetic acid (EDTA) tube of blood will be drawn for the hematology assessments listed in Table 9.1. These will be measured from samples obtained at the Screening /Qualification visit (Visit 1), Month 3 (Visit 5) and Month 12/ Discontinuation Visits (Visit 8).

Table 9.1: Hematology Analyses

Hemoglobin
Hematocrit
Red blood cell (RBC) count (with indices)
White blood cell (WBC) count
Platelet count

9.8.2. Blood chemistry

A serum separating tube of blood will be drawn for the blood chemistry assessments listed in Table 9.2. These will be measured from samples obtained at the Screening /Qualification Visit (Visit 1). For the Screening /Qualification visit, samples taken as part of routine care may be analyzed by local laboratories. The results may be used to qualify the subject, provided the tests were performed for the newly diagnosed index VTE before randomization. If central laboratory is also used at the same visit with a resulting discrepancy for exclusion criteria, the local laboratory result will still be used to qualify the subject.

Creatinine will also be measured on Month 1, 3, 6, 9, and Month 12 / Discontinuation Visits.

Table 9.2: Blood Chemistry

Sodium	Creatinine[a]
Potassium	Blood urea nitrogen
Bicarbonate	Alkaline phosphatase

AST	Total bilirubin
ALT	

[a] Serum creatinine will be measured at Screening, On-Treatment Study Visits (Month 1, 3, 6, 9 and Month 12/ Discontinuation)
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

9.8.3. Estimated Glomerular Filtration Rate (eGFR) Assessment

Estimated glomerular filtration rate (eGFR) will be estimated from serum creatinine (Appendix 17.7).

9.8.4. Urinalysis

Standard urinalysis including a microscopic examination will be conducted for all subjects at the Screening /Qualification Visit (Visit 1) (Table 9.3).

Table 9.3: Urinalysis Determinations

Specific gravity	Blood
pH	RBC
Protein	WBC
Glucose	Bilirubin
Ketones	Urobilinogen

Abbreviations: RBC = red blood cell; WBC = white blood cell.

For samples with findings on macroscopic analysis, microscopic examination for RBCs, white blood cells (WBCs), bacteria, and casts should be performed.

9.8.5. Hepatitis Serology (to be performed only when indicated and for Hy's Law cases [LFT ≥3 × and bilirubin ≥2 × ULN])

If a subject temporarily interrupts (or discontinues) study drug due to confirmed liver enzyme abnormalities or jaundice, the subject will have additional evaluations at the discretion of the Investigator as follows:

- Hepatitis A, B, C, and E screening (anti-HAV IgM, HBsAg, anti-HCV plus viral titer, and evaluation for Hepatitis E),
- Antinuclear antibody (ANA) and anti-SmAb,
- Cytomegalovirus (CMV), Epstein-Barr virus (EBV)

9.8.6. Pregnancy Testing

All female subjects must have a negative urine pregnancy test at the specified visits. A highly sensitive urine pregnancy test will also be performed at the Screening /Qualification Visit (Visit 1), On-Treatment Study Visits (Month 3 (Visit 5) and Month 12 (Visit 8) only) and Discontinuation Visits.

9.9. Vital Signs

BP, heart rate, and body temperature after resting in a sitting or supine position (Note: the appropriate cuff size base on arm circumference will be used). Vital signs are captured for selected scheduled visits.

9.10. Physical Examinations

Physical examination will be conducted for selected scheduled visits and includes:

- Height and body weight (may be performed by an Investigator or other healthcare provider designated by the Investigator).

A physical examination will consist of assessment of each of the relevant major body systems.

9.11. Other Examinations

Not applicable.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. Analysis Sets

Randomized Analysis Set will include all subjects who are randomized.

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

Modified ITT (mITT) Analysis Set will include all subjects in the Randomized Analysis Set who received at least one dose of randomized study drug.

Per-protocol (PP) Set will include all subjects in the mITT Analysis Set who are sufficiently compliant with the protocol. Criteria of sufficiently compliant will be detailed in SAP.

PK Analysis Set will include all subjects in the Safety Analysis Set who had at least one PK sample with measurable concentration.

PD Analysis Set will include all subjects in the Safety Analysis Set who had at least one measurable PD sample.

11.2. General Statistical Considerations

All efficacy analyses will be based on the mITT Analysis Set or PP Analysis Set and will be performed based on the treatment arm assigned at randomization. All statistical tests will be two-sided at a 5% significance level, unless otherwise specified.

Safety analysis will be performed using the Safety Analysis Set. Subjects will be analyzed according to actual treatment received.

Unless otherwise specified, the baseline value of an efficacy variable for a subject is the last non-missing measurement before the first administration of study drug, and the baseline value of a safety variable is the last non-missing measurement before the first dose of the study drug.

In general, missing data will not be imputed for the purpose of data analysis. No visit windows will be used for analysis.

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, and minimum and maximum values. Categorical variables will be summarized using frequency counts and percentages. Summary statistics will be presented by treatment arm.

11.3. Study Population Data

Subject disposition will be summarized for each treatment arm and in total for the Randomized Analysis Set. The number and percentage of randomized subjects who discontinued treatment prematurely will be tabulated by main reason for discontinuation and treatment arm.

The number of subjects for each defined analysis set by treatment arm as well as in total population will also be tabulated.

Subjects excluded from the analysis sets will be listed and summarized by treatment arm and reason for exclusion. A listing of all subjects with major protocol deviations will also be provided.

The demographic and baseline characteristics such as age, sex, race, type of index event, will be summarized descriptively for the mITT, PP, and Safety Analysis Sets.

Study drug exposure and study duration will be summarized using descriptive statistics by treatment arm for the Safety Analysis Set. Edoxaban compliance will also be summarized.

Study drug exposure and study duration will be summarized using descriptive statistics by treatment group for the Safety Analysis Set.

Subject disposition will be summarized for each randomized treatment group and in total for the mITT Analysis Set. The number of subjects for each defined analysis set by treatment group as well as in total population will also be tabulated.

Prior and concomitant medication will be summarized for the Safety Analysis Set.

11.4. Statistical Analysis

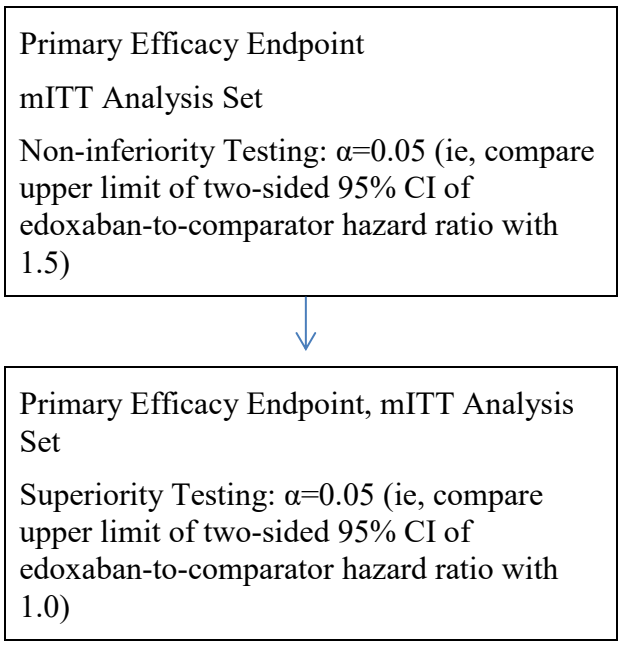
11.4.1. Efficacy Analyses

11.4.1.1. Primary Efficacy Analyses

The primary efficacy analysis will be based on mITT Analysis Set. Analyses will be based on the randomized treatment arm even if a subject inadvertently receives the incorrect study drug. The primary efficacy endpoint is an event driven and a composite endpoint including symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden from randomization to up to 3 months + 3 days from randomization. In this analysis, the time to the first event of the composite primary efficacy outcome will be analyzed using a Cox's proportional hazard regression model including treatment arm and age groups as covariates. Although this study is also stratified by region, region is not included in the model as a covariate because some age groups within regions may be very small due to the small overall sample size. The time to first event is defined as the time (days) from the day of randomization to the first event experienced by a subject during the 3 months + 3 days period. Subjects who did not have a primary efficacy outcome during the 3 months + 3 days period will be censored at 3 months + 3 days or the last day the subject had a complete assessment for study outcomes, whichever comes first. The edoxaban-to-comparator hazard ratio will be computed with 95% confidence interval (CI) (two-sided) based on this model. Edoxaban will be considered non-inferior to comparator if the upper limit of the 95% CI is $\leq$1.5.

If non-inferiority of edoxaban is established, edoxaban will be tested for superiority to comparator. Edoxaban will be considered superior to comparator if the upper limit of the 95% CI from above analysis is $\leq$1.0.

To control study-wise type I error, the testing for non-inferiority and superiority will follow the plan as described below.



The same proportional hazard model used for primary efficacy analysis will be performed for PP Analysis Set and Randomized Analysis Set as sensitivity analyses.

11.4.1.2. Secondary Efficacy Analyses

The following secondary efficacy analyses will be conducted:

- A composite endpoint, including symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden from the randomization to the date of the last dose of study drug + 30 days, the same Cox proportional hazards regression model used for the primary efficacy analysis will be used. The time to first event is defined as the time (days) from the day of randomization to the first event experienced by a subject from the randomization to the date of the last dose of study drug + 30 days. Subjects who did not have a primary efficacy outcome during the study period will be censored at the last day the subject had a complete assessment for study outcomes or the last study drug + 30 days, whichever came first. These efficacy analyses will be based on mITT and PP Analysis Sets. The incidence of this composite endpoint will also be summarized by treatment arm for the mITT and PP Analysis Sets.
- Incidence of all-cause mortality from randomization to the date of the last dose of study drug + 30 days will also be summarized by treatment arm for the mITT Analysis Set.
- The incidence of each component (symptomatic recurrent venous thromboembolic disease, death as result of VTE, and no change or extension of thrombotic burden) of the composite primary endpoint occurred during the first 3 month treatment period will be summarized by treatment arm for the mITT and PP Analysis Sets.

- The occurrence of DVT, catheter-related thrombosis, sinovenous thrombosis, and PE during the first 3-month treatment period, after the 3 month treatment period will be summarized by treatment arm for the mITT Analysis Set

11.4.1.3. Exploratory Efficacy Analyses

Not applicable.

11.4.1.4. Clinical Benefit Analysis

The following clinical outcome analysis will be conducted:

- Net clinical outcome, defined as the composite of symptomatic recurrent VTE events, death as a result of VTE, and major and CRNM bleeding that occurred from the date of the first dose of study drug to the date of last dose of study drug + 30 days, will be analyzed using the same Cox proportional hazards regression model used for the primary efficacy analysis for mITT Analysis Set. The incidence of this endpoint will also be summarized by treatment for the mITT and PP Analysis Sets.

11.4.2. Pharmacokinetic/Pharmacodynamic Analyses

11.4.2.1. Pharmacokinetic Analyses

Plasma concentration and biomarker data will be summarized by age, dose, and time point using descriptive statistics for PK Analysis Set in this study.

The plasma concentration data will be pooled with data from other studies for a population PK analysis using nonlinear mixed effects modeling; the results will be provided in a separate report from the clinical study report for this study.

Exposure response relationships will be evaluated using Bayesian estimates of edoxaban exposure metrics (such as C_{av}, C_{max}, C_{trough}, and AUC) to explore relationships with safety and efficacy endpoints through a model based approach; the results will be provided in a separate report from the clinical study report for this study.

11.4.2.2. Pharmacodynamic Analyses

Pharmacodynamic data will be summarized by age, time point, and treatment arm using descriptive statistics for PD Analysis Set in this study.

11.4.2.3. Biomarker Analyses

Not applicable.

11.4.2.4. Pharmacogenomic Analyses

Not applicable

11.4.3. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set, unless specified otherwise. Analyses will be based on the randomized treatment arm, unless a subject inadvertently receives

the incorrect drug during the entire study, in which case, the subject will be grouped according to the treatment actually received.

11.4.3.1. Analysis of bleeding events

An analysis will be performed for the composite safety endpoint of major and CRNM bleeding events which occur on-treatment from the first dose of study drug to 3 months + 3 days, or to the last dose of the study drug + 3 days if the subject permanently discontinued study drug prior to Month 3. The analysis of this endpoint is based on an "on treatment" approach. An event will be considered as an "on-treatment" event if it occurred while on study drug or within 3 days of randomized study drug interruption or discontinuation.

The time to "on-treatment" major and CRNM bleeding will be compared between treatment arms for subjects in the Safety Analysis Set, using the same Cox proportional hazards regression model as used for the primary efficacy analysis. Subjects who did not have an event will be censored at 3 days after the day of permanent study treatment discontinuation, or at 3 month + 3 days, or 6 to 12 weeks for Cohort 5, whichever occurred first.

Similar analyses will be conducted for all bleeding, as categorized below, occurred from the date of the first dose of study drug to the date of the last dose of study drug + 30 days using the Safety Analysis Set. Subjects who did not have corresponding event will be censored 30 days after the day of permanent study drug discontinuation.

Bleeding events will be summarized and analyzed for the following categories:

- Major and CRNM bleeding combined
- Any bleeding (major, CRNM, and nuisance, combined)

A sensitivity analysis will be conducted for major and CRNM bleeding, occurring while on-treatment, from the date of the first dose of study drug to the date of the last dose of study drug + 3 days during the whole study period. Subjects who did not have corresponding event will be censored 3 days after the day of permanent study drug discontinuation.

The incidence of bleeding events will also be summarized by treatment arm for on-treatment period up to 3 months + 3 days, on-treatment up to the date of last dose of study drug + 3 days, and from the date of the first dose of study drug to the date of the last dose of study drug + 30 days, using Safety Analysis Set.

11.4.3.2. Adverse Event Analyses

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs (TEAEs) are defined as AEs that occur, having been absent before the initial of study treatment, or worsen in severity after the initiation of study treatment administration. Adverse events that start or worsen after the 30th day following the calendar date of the dose of the last study drug are defined as post-treatment AEs.

The incidence of TEAEs will be presented for the Safety Analysis Set for the on treatment period and from the date of the first dose of study drug to the date of the last dose of study drug, respectively, by System Organ Class, by preferred term, and by treatment arm. TEAEs will be

further summarized by relationship to the study drug, and by severity. Frequent TEAEs (reported by ≥5% of subjects in any treatment arm) will also be summarized by treatment arm for the on-treatment period and from the date of the first dose of study drug to the date of the last dose of study drug, respectively. The incidence of death, SAEs, drug-related SAEs, and AEs leading to discontinuation of study drug will also be summarized. All AEs will be included in a data listing and a listing to display the coding of AEs will be prepared as well.

Similarly, the number and percentage of deaths, subjects reporting treatment-emergent SAEs, and TEAEs leading to discontinuation of study treatments will be tabulated.

A by-subject AE (including treatment-emergent) data listing including but not limited to verbatim term, preferred term, system organ class, preferred term, and relationship to study drug will be provided. Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study drug, will be listed.

11.4.3.3. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation and by treatment arm for the Safety Analysis Set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study drug. In addition, mean change from baseline will be presented by treatment arm for the maximum and minimum post-treatment values and the values at the Discontinuation Visit.

Shift tables (in categories of low, normal, and high) will be provided for each treatment arm for selected clinical laboratory parameters. Also, the number and percentage of subjects with clinically relevant abnormal clinical laboratory values while on study drug will be calculated for each treatment arm for selected clinical laboratory parameters. All abnormal clinical laboratory values will be presented in a listing. Specifically, the number and percentage of subjects with elevation of liver enzymes (ALT, AST) and TBL, according to various multiples of ULN will be summarized by treatment arm. The number and percentage of subjects with concurrent elevation of ALT or AST ≥3 × ULN and TBL ≥2 × ULN will also be summarized by treatment arm.

11.4.3.4. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation and by treatment arm for the Safety Analysis Set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study drug.

11.4.3.5. Physical Examination Analyses

A listing of physical examination data will also be provided.

11.4.3.6. Other Analysis

Any additional exploratory analysis will be specified in the SAP.

11.5. Interim Analyses

An interim assessment of incidence rate of the composite efficacy endpoint in both treatment arms of the study will take place after first 140 subjects (about 50% of subjects) complete the first 3 months of treatment. This will allow for adjustment of number of subjects in the study if necessary. Because the sample size re-estimation will be based on overall event rate acrossing two treatment arms, no type I error adjustment is needed for this interim analysis. The detailed interim analysis will be specified in interim SAP (IASAP).

11.5.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee will monitor the safety data throughout the study and inform the Study Steering Committee on fixed intervals and will be detailed in DMC charter.

11.6. Sample Size Determination

This is an event driven trial and the total number of subjects randomized to treatment may be adjusted to ensure accumulation of 68 events in the mITT Analysis Set during the Main Treatment Period.

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

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

Based on the completed clinical trials and literature review[4, 14, 15, 16, 19, 22, 23, 24, 25], we expect an incidence of composite primary efficacy endpoint of 28% in the control arm during the Main Treatment Period. Based on these estimates, 274 subjects (137 each arm) are expected to be randomized to study drug in order to accrue 68 primary efficacy events in the mITT Analysis Set during the Main Treatment Period.

11.7. Statistical Analysis Process

The data analysis will be performed by a CRO under the guidance of the study biostatistician.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® Version 9.2 or higher.

12. DATA INTEGRITY AND QUALITY ASSURANCE

12.1. Monitoring and Inspections

The sponsor or designee's monitor and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study center facilities (eg, pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings. In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

This study employs electronic data capture. The eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. The eCRF will be completed, reviewed, and electronically signed by the Investigator. Guidelines will be provided to facilitate data entry in the electronic data capture modules.

All written information, study notes, and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood as source documentation.

12.3. Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the sponsor.

To ensure the quality of clinical data across all subjects and study centers, a Clinical Data Management review will be performed on subject data according to specifications given by the sponsor or designee's. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

Serious Adverse Events in the clinical database will be reconciled with the safety database.

All medical history entries (except terms pre-specified on the eCRF) and adverse events will be coded using MedDRA. All prior and concomitant medications will be coded using WHO Drug Dictionary.

12.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on electronic CRFs will be included on the Signature List.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects, date and outcome of screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the study center (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study center policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed CRFs, informed consent forms, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the EC/IRB and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study center, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

All essential documentation will be retained by the institution until told otherwise by the sponsor.

No study document should be destroyed without prior written agreement between the sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

All Investigators and site personnel must ensure subject confidentiality as outlined in Section 15.2.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with the CRO. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study related injury.

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March, 1997 and/or;
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 November, 2014;
- Other applicable local regulations.

15.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent and assent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC or IRB prior to being provided to potential subjects.

The subject's written informed consent along with the legal guardian(s) should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

Suggested model text for the ICF and assent for the study and any applicable subparts (genomic, PK, etc.) are provided in the Sponsor's ICF template for the Investigator to prepare the documents to be used at his or her study center. Updates to applicable forms will be communicated via letter from the Sponsor.

For studies in the US, an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

According to 21 CFR 50.55 subpart b it states, "In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate." In 21 CFR 50.55 subpart g it states, "When the IRB determines that assent is required, it must also determine whether and how assent must be documented." For this study, the IRB will determine the age that is appropriate for the assent. Generally, this age averages at 7 years of age. The IRB will also determine the verbiage that may be added, as well as ensure the document is written at a level understandable to the population who will be signing the assent. The IRB may also require separate assent forms based on the age groups (ie, separate assent forms for subjects 7 to 12 years and for subjects 13 to 17 years) to ensure the assents maintain their "maturity levels and understandability".

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator Brochure, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the EC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator must submit and, where necessary, obtain approval from the EC or IRB for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the EC or IRB of deviations from the protocol or SAEs occurring at the study center and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after approval by the relevant regulatory bodies.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authorities in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the Investigator becomes aware of.

15.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority (is), and which was given approval/favorable opinion by the IRBs/ECs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

15.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, ECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IEC/IRB. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator

or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by Daiichi Sankyo or the CRO. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all study centers in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes added as either a section to the new version or provided as a separate document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular study center(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB/EC and by regulatory authorities where appropriate, unless immediate implementation of the change is necessary for subject safety.

15.8. Study Termination

The IDMC may recommend termination of the study. Termination may be made for any of the following reasons:

- Concern about significantly higher bleeding risk relative to one of the study arms,
- Concern about drug-induced liver injury,
- Any other safety concern based on benefit/risk evaluation.

The IDMC will alert the Investigator/designee if there are any of the above concerns requiring protocol modifications or any other changes in the study.

The details about the roles and responsibilities of the IDMC and guidelines and rules for monitoring the study safety data will be described further in the IDMC charter.

15.9. Independent Data Monitoring Committee (IDMC)

An IDMC will be created to further protect the rights, safety, and well-being of subjects who will be participating in this study by monitoring their progress and results. The IDMC will comprise of qualified scientists, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The IDMC will be described in detail in the IDMC Charter. The IDMC will monitor data during the study. All activities of the IDMC will be documented. This documentation will include data summaries and analyses provided to the committee as well as minutes of the meeting. The IDMC can recommend study or treatment regimen/group termination to a study oversight committee based on pre-specified concerns described in the IDMC Charter.

An independent CRO study statistician will prepare the required data outputs and provide the outputs to the IDMC as per the IDMC charter. The statistician will prepare overall summary reports for the data including, but not limited to, subject disposition, subject demographics and baseline characteristics, subject treatment duration, subjects with bleeding (adjudicated by the CEC), subjects with liver enzyme and bilirubin abnormalities, subjects with SAEs, deaths, subjects permanently discontinued from study drug due to AEs, and subjects with efficacy endpoints such as VTE and CV mortality, and all-cause mortality etc. The PK and safety data will be reviewed by the IDMC who will approve the start of the next younger age cohort.

An interim assessment of incidence rate of the composite efficacy endpoint in both arms of the study will take place after first 140 subjects (about 50% of subjects) complete the first 3 months of treatment. This will allow for adjustment of number of subjects in the study if necessary.

15.10. Clinical Events Committee

A blinded independent study specific CEC will review and adjudicate key endpoint events: all deaths, VTEs, thrombotic burden, and other suspected efficacy endpoints, overt bleeding events that require medical attention, and liver enzyme abnormalities meeting predefined criteria (including all suspected clinical endpoint events from subjects who permanently discontinued study drug). Endpoints reported during telephone contacts will also be adjudicated.

An additional independent members of the CEC will be a radiologist who will assess the baseline index VTE image and follow-up image at Month 3 and Month 12/ Discontinuation visit (if applicable). Quantitative assessment of the change in thrombotic burden of the index VTE will be made.

The CEC will comprise qualified judges, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The CEC judges will remain blinded to treatment throughout the adjudication process and the study. The CEC-adjudicated data will be used in the final efficacy and safety analyses. The CEC and the events and radiologic images it will adjudicate will be detailed in the CEC Charter.

15.11. Steering Committee/Executive Committee

A Study Steering Committee will be created to provide clinical guidance on study implementation and conduct of the study, and interpretation of results as specified in the Committee Charter. It will consist of Principal Investigator(s), and key opinion leaders participating in the study (as requested), as well as designated Sponsor and CRO members.

15.12. Address List

A list of key study personnel (including personnel at the sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and updated in the Study Reference Manual.

15.12.1. Sponsor

Daiichi Sankyo, Inc.
211 Mount Airy Road
Basking Ridge, NJ 07920 USA
United States.

15.12.2. Contract Research Organization

IQVIA
5927 South Miami Boulevard
Morrisville, NC 27560
United States.

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17. APPENDICES

17.1. Schedule of Events

Table 17.1: Schedule of Events

Study Period	**Screening/ Qualification Visit**	**Randomization[a]**	**On-Treatment Study Visits**							**Required 30 Day Follow-Up Visit[b]**
			Main Treatment Period				**Extension Period (Optional)**			
Visit Number	**1**	**2**	**2a**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Day	**At least Day-5 to -1 Index VTE Event Identified Pre-randomization treatment selected by PI (LMWH or SP Xa inhibitor or UFH)**	**Day 1 1st EDX Dose**	**Day 5 EDX arm only N=53 to 60**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12/ Discontinuation Visit**	
Visit Window (Days)[c]			**+3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
IXRS transaction	X									
IXRS Randomization		X								
Study Informed Consent	X									
Confirm Diagnosis of Index VTE	X									
Inclusion/Exclusion Criteria	X									
Demographic Information	X									
Medical/Surgical History	X									

Table 17.1: Schedule of Events (Continued)

Study Period	**Screening/ Qualification Visit**	**Randomization[a]**	**On-Treatment Study Visits**							**Required 30 Day Follow-Up Visit[b]**
			Main Treatment Period				**Extension Period (Optional)**			
Visit Number	**1**	**2**	**2a**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Day	**At least Day-5 to -1 Index VTE Event Identified Pre-randomization treatment selected by PI (LMWH or SP Xa inhibitor or UFH)**	**Day 1 1st EDX Dose**	**Day 5 EDX arm only N=53 to 60**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12/ Discontinuation Visit**	
Physical Examination and Body Height/Weight Assessments[d]	X			X	X	X	X	X	X	

Table 17.1: Schedule of Events (Continued)

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

Table 17.1: Schedule of Events (Continued)

Study Period	**Screening/ Qualification Visit**	**Randomization[a]**	**On-Treatment Study Visits**							**Required 30 Day Follow-Up Visit[b]**
			Main Treatment Period				**Extension Period (Optional)**			
Visit Number	**1**	**2**	**2a**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Day	**At least Day-5 to -1 Index VTE Event Identified Pre-randomization treatment selected by PI (LMWH or SP Xa inhibitor or UFH)**	**Day 1 1st EDX Dose**	**Day 5 EDX arm only N=53 to 60**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12/ Discontinuation Visit**	
PK/PD assessment for first 12 subjects in each age cohort in EDX arm (see Section 8)			X							
VTE Radiologic Imaging[h]	X					X[n]			X	
Urinalysis	X									
Urine Pregnancy Test[i]	X	X				X			X	
AE/SAE Reporting[j]	**…… X ……**									
Endpoints Reporting (VTE, Bleeding)[k]	**…… X ……**									
Prior and Concomitant Medications[l]	X	X		X	X	X	X	X	X	X

Table 17.1: Schedule of Events (Continued)

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

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

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

[a] Randomization may occur in IXRS the day prior to dosing for clinical logistics.
[b] Follow-Up Visit will be performed 1 month after the subject completes the study (6 weeks - Month 3 or Month 12 or 30 days after discontinuation from study in the extension period).
[c] Scheduling of visits within windows should be done with caution to the drug supply available in a dispensing unit. PK/PD assessment on Day 5 cannot be performed before Day 5.
[d] Targeted physical examination performed by an Investigator or other healthcare professional designated by the Investigator.
[e] Vital signs include heart rate, body temperature, and sitting or supine blood pressure (Section 9.9).
[f] INR assessment for adjustment of VKA dosages will be performed every month as per SOC. Additional interim evaluations may be performed at the discretion of the Investigator. INR will be assessed at Screening/Qualification visit if prior VKA was given or to be taken.
[g] Investigator discretionary assessment of anti-FXa to be performed to determine if SP or LMWH are at therapeutic levels.
[h] If image was taken for recurrent VTE after Month 3 but before discontinuation, then no image is needed at Month 12/Discontinuation. Optional Month 3 imaging can be done if recurrent VTE occurs prior to Month 3.
[i] Highly sensitive urine pregnancy test to be performed for females of childbearing potential.
[j] AE/SAE reporting should occur throughout the study and not be restricted to specific visits.
[k] Endpoint events should be reported as soon as site personal learn of the event. Endpoint event should occur throughout the study and not be restricted to specific visits.
[l] Prior medications includes 30 days prior to Screening/Qualification visit.
[m] There is no dispensing or drug accountability requirement for Visit 2a for edoxaban arm for those subjects enrolled in the PK/PD evaluation because drug is expected to be dispensed on a monthly basis. The subject will need to bring in his/her edoxaban therapy for a single dosing treatment.
[n] For subjects in Cohort 5, a radiologic VTE image will be taken at the end of the intended treatment period (at least 6 to 12 weeks) or at the discontinuation visit if anticoagulant treatment is received for <3 months.
[o] Renal function test should be performed on or around Day 5 visit (at the same time of PK sampling).

17.2. Additional Information on Investigational Product Use in Pediatric Subjects

Recommendations per CHEST 2012 Guidelines[26]

Table 17.2: Doses of LMWH (enoxaparin) used in Pediatric Subjects

Drug	Age	Initial Treatment Dose	Initial Prophylactic Dose
Age –dependent Dose of Enoxaparin	<2 months	1.5 mg/kg/dose q12h	0.75 mg/kg/dose q12h
	>2 months	1.0 mg/kg/dose q12h	0.5 mg/kg/dose q12h
Enoxaparin has 110 anti-factor Xa units/mg			

Table 17.3: Protocol for Anticoagulation Therapy to maintain an INR between 2.0 and 3.0 for Pediatric Subjects (Warfarin treatment)

1	**Day 1**: if the baseline INR is 1.0 to 1.3: Dose 0.2 mg/kg orally	
2	**Loading** 0.2 mg/kg Days 2-4: if the INR is:	
	INR	**Action**
	1.1 - 1.3	Repeat initial loading dose
	1.4 - 1.9	50% of initial loading dose
	2.0 - 3.0	50% of initial loading dose
	3.1 - 3.5	25% of initial loading dose
	>3.5	Hold until INR ≤3.5; then restart at 50% decreased dose
3	**Maintenance** oral anticoagulation dose guidelines:	
	INR	**Action**
	1.1 - 1.4	Increase by 20% of dose
	1.5 - 1.9	Increase by 10% of dose
	2.0 - 3.0	No change
	3.1 - 3.5	Decrease by 10% of dose
	>3.5	Hold until INR ≤3.5; then restart at 20% decreased dose
INR = international normalized ratio		

Table 17.4: Doses of Fondaparinux

Fondaparinux Doses	**Target Therapeutic Fondaparinux Level**
0.1 mg/kg, once a day	0.5-1 mg/L (blood drawn at 3 hours post-dose)
0.05 mg/kg/day (for subjects with renal disease).	
Dose Adjustment of Fondaparinux	
Fondaparinux Level (mg/L)	**Doses Adjustment**
<0.3	Increase dose by 0.03 mg/kg
0.3 - 0.5	Increase dose by 0.01 mg/kg
0.5 - 1	No change
1 - 1.2	Decrease dose by 0.01 mg/kg
>1.2	Decrease dose by 0.03 mg/kg

17.3. Effective Methods of Birth Control

Women of childbearing age are defined as those women capable of conceiving, being pregnant with, and giving birth to children, and are eligible for the study based on the inclusion and exclusion criteria.

Female subjects of childbearing potential must test negative for pregnancy at Screening with a highly sensitive test and must consent to avoid becoming pregnant by using an approved contraception method throughout the study.

The following use of reliable method(s) of contraception, and/or abstinence, for the duration of therapeutic product exposure is recommended:

Highly effective methods of contraception, when used consistently and correctly, result in low failure rates. These may include:

- Combined (estrogen and progesterone-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progresterone-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine Device (IUD)
- Intrauterine Hormonal-Releasing System

- Bilateral Tubal Occlusion
- Vasectomized partner
- Sexual Abstinence

Effective methods may include:

- Barrier methods of contraception (eg, male condom, female condom, cervical cap, diaphragm, contraceptive sponge).

  Note: When used consistently and correctly, "double barrier" methods of contraception (eg, male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above.

Oral contraception is not contraindicated with edoxaban but maybe not recommended in patients with high risk of thromboembolic events. The use of oral contraception is per investigator's discretion.

17.4. Prohibited Concomitant Medications

The list here (in the protocol) is static and reflects the list at the time of the current version of the protocol. If there are changes to this list during the study, the changes will not be considered a protocol amendment and the list in this appendix will not be updated unless the protocol is being amended for other reasons as well.

Subjects on these drugs at the time of planned randomization will be excluded from the study. After randomization, use of these drugs will require a study drug permanent discontinuation unless advised otherwise in the sections below. The Investigator is encouraged to contact the Medical Monitor for further guidance.

Sites will receive a contact card where the following numbers (24-hour Urgent Medical Contact) are provided:

PPD (primary number)

PPD (alternative number)

17.4.1. Antiplatelet Drugs

Use of any antiplatelet medication as single or dual agent antiplatelet therapy is prohibited while on study drug except for low dose aspirin defined as 1-5 mg/kg/day with maximum of 100 mg/day. If there is a clinical indication for single or dual agent antiplatelet therapy, the subject will need to be discontinued from the study treatment.

Examples of non-aspirin oral antiplatelet agents include the following:

- Thienopyridienes: clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient®)
- Dipyridamole: Persantine®, Aggrenox®
- Cilostazol (Pletal®)
- Pentoxifylline (Trental®)

- Sulfinpyrazone (Anturane®)
- Ticagrelor (Brillanta®)

IV antiplatelet agents include the following:

- Glycoprotein IIb/IIIa inhibitors: Abciximab (ReoPro™), Eptifibatide (Integrilin®),
- Tirofiban (Aggrastat®)
- PGY12 Inhibitor: Cangrelor
- Dextran

17.4.2. Oral Anticoagulants Other than Study Drug

Oral anticoagulants including Factor IIa inhibitors (eg, dabigatran), and FXa inhibitors (eg, rivaroxaban, apixaban) are prohibited in both treatment arms. The only allowed oral anticoagulants are the study drugs.

17.4.3. Parenteral Anticoagulants

Parenteral anticoagulants are prohibited in the edoxaban treatment arm. Direct thrombin inhibitors are prohibited in edoxaban arm and in the SOC arm.

Examples of prohibited parenteral anticoagulant medications include the following:

- Low molecular weight heparins: enoxaparin (Lovenox®, Clexane®), dalteparin (Fragmin®), tinzaparin (Innohep®, Logiparin®), reviparin (Clivarin®), nadroparin (Fraxiparine®), ardeparin (Normiflo®), certoparin (Sandoparin®), parnaparin (Fluxum®)
- Direct thrombin inhibitors: bivalirudin (Angiomax®), argatroban, (Acova®), desirudin (Ipravask®), lepirudin (Refludan®)
- FXa inhibitors: fondaparinux (Arixtra®)

17.4.4. Intravenous Fibrinolytics

Examples of fibrinolytics include the following:

- Tissue plasminogen activator (tPA, alteplase, Activase®),
- TNK (tenecteplase, TNKase®),
- rPA (reteplase, Retavase®),
- Streptokinase (Streptase®),
- Anistreplase (Eminase®).

If a subject requires treatment with a fibrinolytic agent, then study drug must be discontinued.

17.4.5. NSAIDs (excluding aspirin)

While on study drug, NSAIDs cannot be taken for ≥4 days per week. Less frequent use of NSAIDs is permitted while on study drug. However, the Investigator should weigh the

benefit/risk of NSAID use in combination with an oral anticoagulant for the individual subject. Examples of NSAIDs include the following:

Aceclofenac	Acemetacin	Alclofinac
Amtolmetin	Axapropazone	Benoxaprofen
Bromfenac	Bufexamac	Carprofen
Clonixin	Dexibuprofen	Dexketoprofen
Diclofenac	Diclofenac/Hyaluronic Acid	Diflunisal
Dipyrone	Droxicam	Etodolac
Etofenamate	Felbinac	Felbufen
Fenoprofen	Fentiazac	Floctafenine
Flufenamic Acid	Flurbiprofen or fluribuprofen	Hydrocodone/Ibuprofen
Ibuprofen	Indomethacin	Indoprofen
Isoxicam	Ketoprofen	Ketorolac
Lansoprazole/Naproxen	Lornoxicam	Loxoprofen
Meclofenamate	Mefanamic Acid	Meloxicam
Morniflumate	Nabumetone	Naproxen
Niflumic Acid	Nimesulide	Oxaprozin
Oxycodone/Ibuprofen	Phenylbutazone	Piketoprofen
Pirazolac	Piroxicam	Piroprofen
Prophenazone	Proquazone	Sulindac
Suprofen	Tenidap	Tenoxicam
Tiaprofenac acid	Tolmetin	Zomepirac

17.4.6. P-gp Inhibitors List (Not Prohibited Medication but Requires Dose Adjustment)

Use of P-gp inhibitors during the treatment with edoxaban will require dose reduction either at randomization or during the course of the study. The only exemption from this rule is the use of amiodarone which will not require dose reduction.

Below are examples (but not limited to) the most commonly used P-gp inhibitors:

Table 17.5: P-gp Inhibitors List

Drug Class	Drug Name
Antiarrhythmics	Amiodarone, quinidine, verapamil, dronedarone, carvedilol, ranolazine
Antibiotics	Clarithromycin
Anti-fungal	Itraconazole
Others	Lapatinib, lopinavir, ritonavir, propafenone, saquinavir, telaprevir, and tipranavir

17.4.7. P-gp Inducers List (Prohibited Medication)

Rifampin is a P-gp inducer that has been shown to lower the edoxaban exposure. The example medications listed below (but not limited to) have not been tested with edoxaban but are also P-

gp inducers. These should be avoided during the study as their use may lead to a lower exposure of edoxaban than predicted for clinical efficacy. (http://www.straighthealthcare.com/p-glycoprotein.html#inducers)

- Rifampin
- Carbamazepine (Tegretol®)

17.5. Transition from Edoxaban to Other Anticoagulants

Subjects who require anticoagulation at the end of study participation will be transitioned to standard-of-care treatment as directed by the Investigator or treating physician.

At the end of edoxaban treatment, the subject will receive the last dose of edoxaban and all remaining edoxaban tablets/bottles will be collected from the subject by site staff.

When transitioning from edoxaban to VKA:

Subjects transitioning to any VKA from edoxaban will have their INR recorded at last study visit. Bridging with heparin may occur during VKA titration until the INR is at therapeutic level of between 2.0 and 3.0.

INR will need to be measured as frequently as necessary until the INR target of ≥2.0. Once the INR is ≥2.0 the heparin will be stopped and the subject will continue on the VKA alone.

When transitioning from edoxaban to another direct oral anticoagulant (eg rivaroxaban, apixaban, dabigatran):

- The first dose of the direct oral anticoagulant of choice will be given 24 hours post the last dose of edoxaban and will then be continued as per the novel anticoagulant's label.

For subjects who do not complete the Main Treatment Period, they will be followed with monthly visits until the end of Month 3 plus a Follow-Up Visit according to the Schedule of Events (Table 17.1).

For subjects who completed the Main Treatment Period but do not continue into the Extension Treatment Period, a Follow-Up Visit (9) will occur 30 days after the Month 3 visit.

For subjects who continue into the Extension Period, the Follow-Up Visit will occur 30 days after the Discontinuation Visit.

17.6. Management of Serious/Life-Threatening Bleeding

The following steps are currently recommended[26] for subjects with ongoing major bleeding (see Section 9.2.1):

- Withhold study drug and all antiplatelets / anticoagulants
- Institute SOC for major bleeding (large bore IV or central venous line, type and crossmatch blood, admit to the intensive care unit, provide hemodynamic and respiratory support)
- Administer packed red blood cells (or whole blood) as needed

- Administer antidotes if applicable

For LMWH:

The antidote for LMWH is protamine sulphate.

The dose of protamine sulphate given is dependent upon the dose of LMWH administered and the time of administration.

Suggestions from the Sponsor:

If protamine is given within 8 hours of the LMWH then a maximum neutralizing dose is 1 mg protamine/100 units (or 1 mg) of LMWH given in the last dose.

If more than 8 hours have passed since the dose of LMWH was given, administer 0.5 mg protamine per 1 mg (100 units) of LMWH given.

Protamine is administered by slow IV infusion (over 10 minutes) to avoid a hypotensive reaction.

Protamine is a medication that requires a high level of caution when being prescribed and administered. Outside cardiac surgery and ICU, consultant or fellow approval is required for the use of protamine- do not allow this to lead to delayed administration in the case of bleeding. Contact the appropriate senior person immediately.

For Warfarin:

Significant but not life-threatening bleeding: Administer Vitamin K 0.5 mg to 2 mg SC (NOT intramuscularly) plus FFP (20 mL/kg IV) to a maximum of 4 units.

Major bleeding (any INR) or requiring emergency surgery doses if INR >8

- Stop warfarin
- Vitamin K (30 μg/kg) IV, consider higher doses if INR >8
- Prothrombin complex concentrate (PCC) replacement therapy (NB FFP gives inferior correction and is not recommended):
  - Beriplex® [4-factor Prothrombin Complex Concentrate approved in several EU countries] (and Kcentra® approved in the US) (Discuss with on call haematologist)
  - Beriplex dosage is calculated based on the current INR and subject's weight (see table below)
  - Repeat the INR following PCC
  - Further doses of Beriplex or Vitamin K may be required

INR	Approximate Dose
2.0-3.9	1 mL/kg = 25 IU/kg
4.0-6.0	1.4 mL/kg = 35 IU/kg
>6.0	2 mL/kg = 50 IU/kg

For Edoxaban:

Although not evaluated in clinical trials, PCC, activated prothrombin complex concentrates (aPCCs), or recombinant Factor VIIa could be considered for the reversal of the anticoagulant effect of edoxaban. In healthy volunteers, a 3-factor PCC restored thrombin generation (AUC for thrombin generation curve) but did not normalize PT. Thus, a 3-factor PCC may be of some value in reversing anticoagulant effects of edoxaban (Study A-U150**).**

A specific reversal agent for edoxaban is not available. Although not evaluated in subjects, PCC (Beriplex® or Kcentra®), aPCCs, or recombinant Factor VIIa could be considered for the reversal of the anticoagulant effect of edoxaban.

The following are not expected to reverse the anticoagulant effects of edoxaban:

- protamine sulfate,
- vitamin K,
- tranexamic acid.

Hemodialysis does not significantly contribute to edoxaban clearance.

In the event of a Medical Emergency, the Investigator at the study site will institute any medical procedures deemed appropriate. A 24-hour Urgent Medical Contact will be provided to contact the Medical Monitor for further guidance.

Sites will receive a contact card where the following numbers (24-hour Urgent Medical Contact) are provided:

PPD (primary number)

PPD (alternative number)

The medical call center will contact Medical Monitor for the assigned region.

17.7. Estimated Glomerular Filtration Rate (eGFR) Assessment

Age (Sex)	Normal eGFR (Mean eGFR±SD) (mL/min/1.73 m^2)	30% eGFR for Study Qualification[a] (Mean eGFR) (mL/min/1.73 m^2)	eGFR Threshold for Dose reduction[b] (Mean eGFR) (mL/min/1.73 m^2)
1 week (males and females)	41 ± 15	10	15
2-8 weeks (males and females)	66 ± 25	10	20
>8 weeks (males and females)	96 ± 22	20	35
2-12 years (males and females)	133 ± 27	30	50
13-21 years (males)	140 ± 30	35	55
13-21 years (females)	126 ± 22	30	50

eGFR: estimated glomerular filtration rate; m: meters; min: minutes; mL: milliliter; SD: standard deviation
Ref: American Journal of Kidney Diseases, Vol 39, No 2, Suppl 1 (February), 2002: pp S46-S75

[a] may be enrolled if eGFR is at or greater to this value as determined by the age appropriate formula indicated below:

[b] eGFR must be less than this value for dose reduction (which corresponds to approximately ≤50% eGFR).

Modified Schwartz equation (pediatric subjects <12 years of age):

CrCl (mL/min/1.73 m^2) = (K * Ht) / Scr

height (Ht) in cm; serum creatinine (Scr) in mg/dL

K (proportionality constant): 656

Infant (LBW <1 year): K=0.33

Infant (Term <1 year): K=0.45

Female Child (<12 years): K=0.55

Male Child (<12 years): K=0.70

Cockcroft-Gault equation (pediatric subjects ≥12 years of age):

CrCL (mL/min) = [(140 - age) × weight in kg] / [Scr × 72] (× 0.85 if female)

17.8. Blood Pressure Levels for Boys and Girls by Age and Height

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

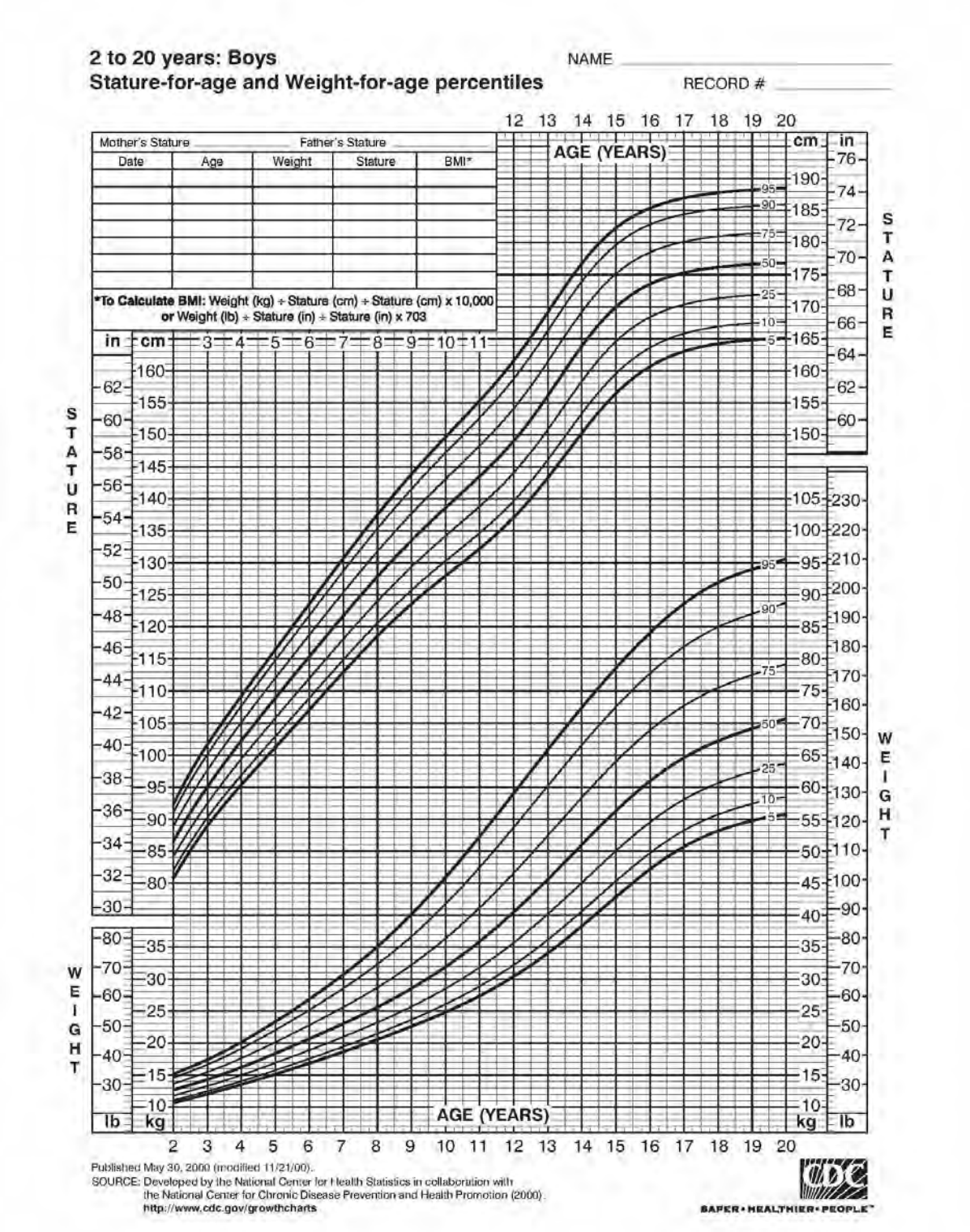
Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

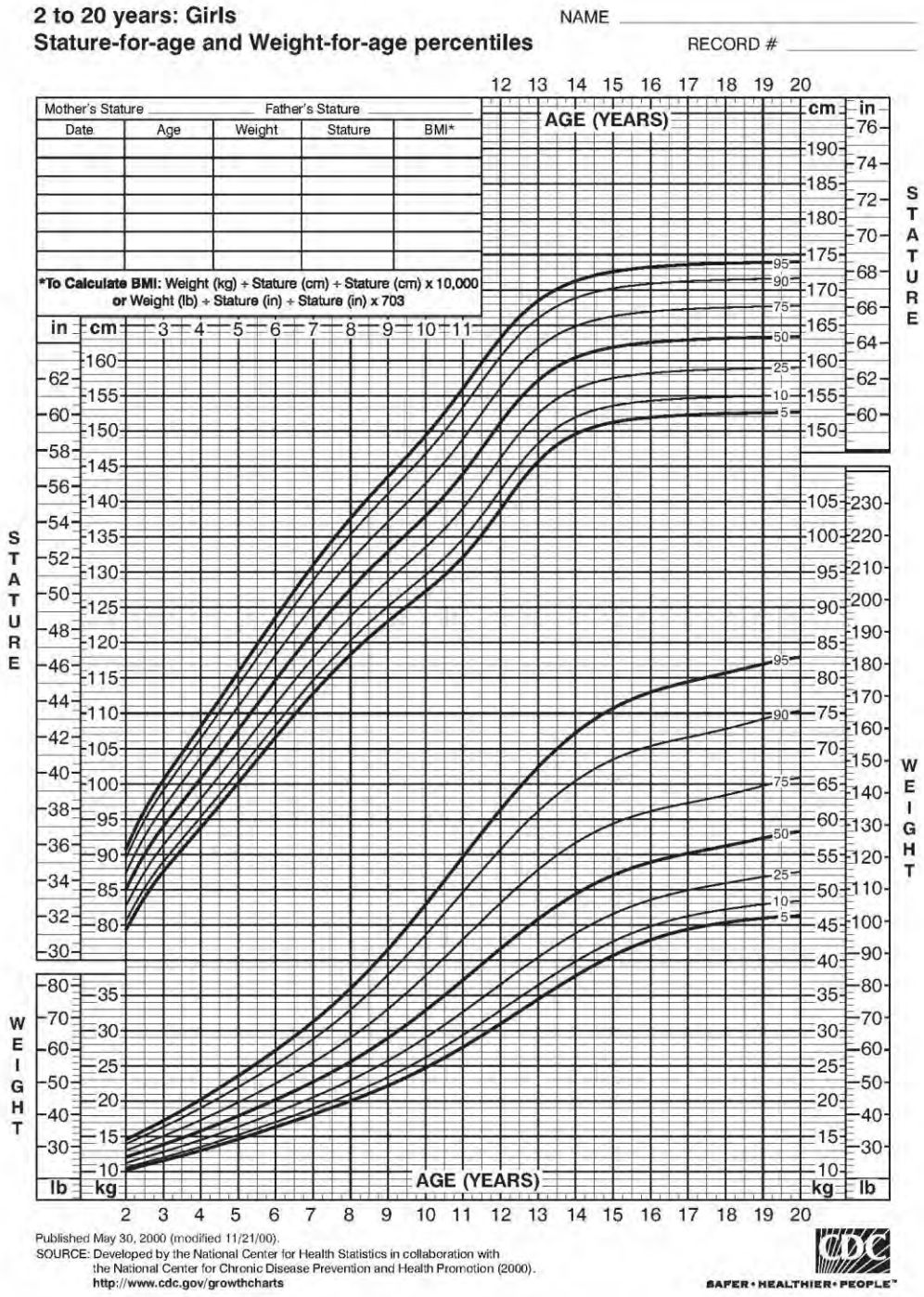
BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

17.9. Growth Chart (2 to 20 years and Birth to 24 Months)




2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
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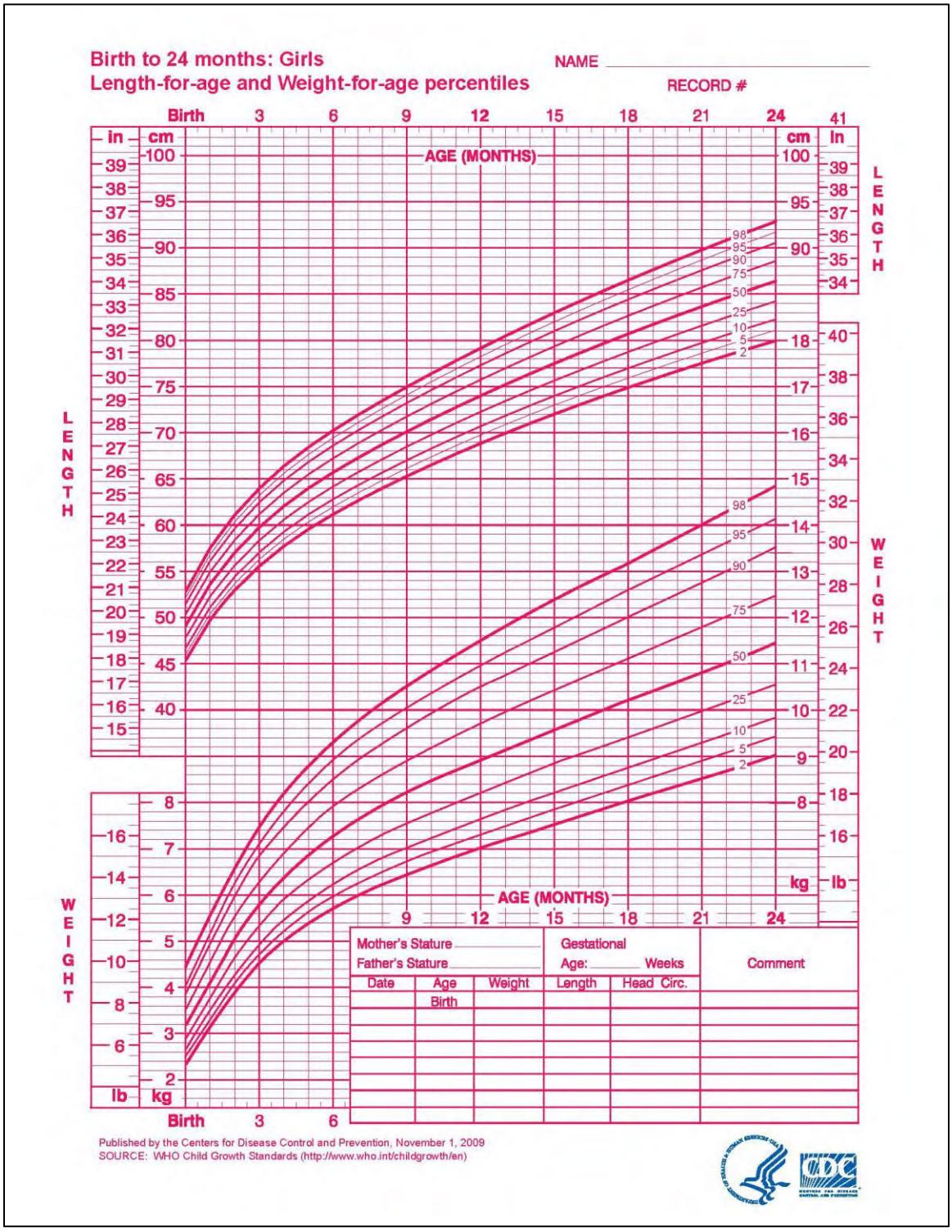
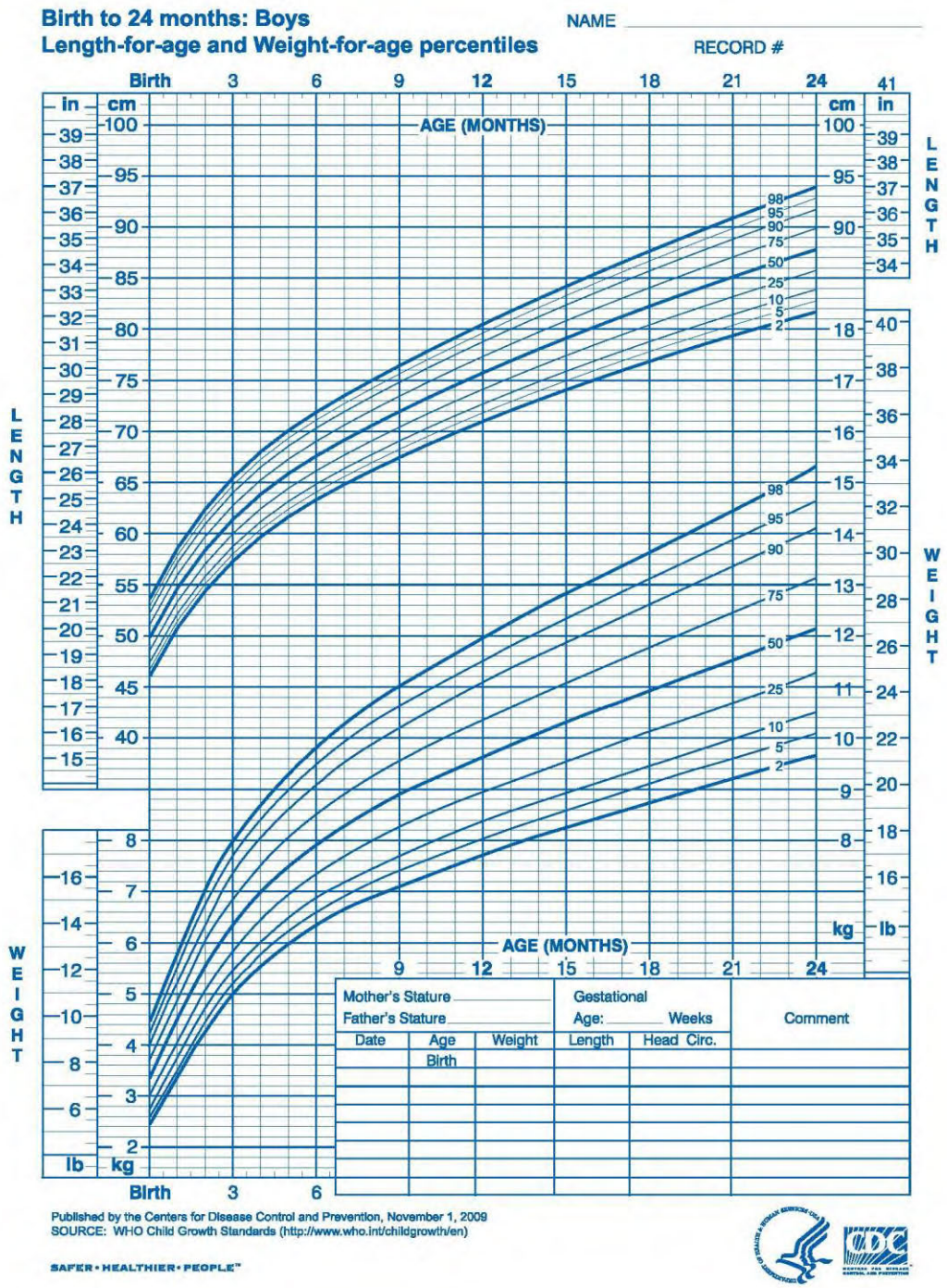

Birth to 24 months: Girls
Length-for-age and Weight-for-age percentiles
NAME
RECORD #
AGE (MONTHS)
LENGTH
WEIGHT
Mother's Stature
Father's Stature
Gestational Age: Weeks
Comment
Date
Age
Weight
Length
Head Circ.
Birth
Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)



17.10. Instructions for Specimen Collection, Storage and Shipment

A laboratory guidance manual will be provided by the central laboratory for specimen collection.