CLINICAL STUDY PROTOCOL

AN OPEN-LABEL, RANDOMISED, PARALLEL-GROUP, MULTICENTRE, OBSERVATIONAL TRIAL TO EVALUATE SAFETY AND EFFICACY OF EDOXABAN TOSYLATE IN CHILDREN FROM 38 WEEKS GESTATIONAL AGE TO LESS THAN 18 YEARS OF AGE WITH CARDIAC DISEASES AT RISK OF THROMBOEMBOLIC EVENTS.

DU176b-C-U313

IND NUMBER 63,266

EUDRACT NUMBER 2017-000475-90

VERSION 4.0, 03 JUN 2019

VERSION 3.0, 27 MAR 2018

VERSION 2.0 16 OCT 2017

VERSION 1.0 27 JUN 2017

DAIICHI SANKYO INC.

211 MOUNT AIRY ROAD

BASKING RIDGE, NJ 07920

INVESTIGATOR AGREEMENT

AN OPEN-LABEL, RANDOMISED, PARALLEL-GROUP, MULTICENTRE, OBSERVATIONAL TRIAL TO EVALUATE SAFETY AND EFFICACY OF EDOXABAN TOSYLATE IN CHILDREN FROM 38 WEEKS GESTATIONAL AGE TO LESS THAN 18 YEARS OF AGE WITH CARDIAC DISEASES AT RISK OF THROMBOEMBOLIC EVENTS.

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
Senior Director, Clinical Development, Specialty Medicine	June 3, 2019
Title	**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 Council for 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 attached comparison document (tracked changes) of Clinical Study Protocol Version 3.0 (dated 27 Mar 2018) versus the Version 4.0 (dated 03 Jun 2019) for actual in-text changes. The summary of changes below is a high-level summary of major changes in the Clinical Study Protocol.

High-Level Changes From Version 3.0 to Version 4.0

Change Number	Change Description
1	**Addressed that the first dose of study treatment is not required to be on the same day of Randomization (Day 1)** The following sections of the protocol were updated: • Section 6.3 Randomization (Day 1, Visit 2) • Table 17.1 Schedule of Events
2	**Additional dosing details added for enoxaparin dosing in infants** The following sections of the protocol were updated: • Synopsis • Section 5.2.1.2 Standard of Care Treatment Arm
3	**Additional details added for edoxaban packaging for subjects 6 to <12 years old** The following sections of the protocol were updated: • Synopsis • Section 5.2.1.1 Edoxaban (Randomization through Month 12)

Change Number	Change Description
4	**Modifications to Schedule of Events including the following:** Row to add Interactive Web/Voice Response System transaction for Screening Visit and Visits 3 through 8 Added body weight measurement at randomization Minor footnote clarifications to study drug dispensing and study drug compliance Clarified necessity of activated partial thromboplastin time and international normalized ratio (INR) assessments Footnote updated to collect PK samples at pre-dose and 1 to 3 hours post-dose Clarified PD sample collection, 24-hour wash-out for pharmacodynamic assessments Moved pregnancy test from Screening Visit to Randomization and modified footnote The following sections of the protocol were updated: • Table 17.1 Schedule of Events • Section 6 Study Procedures • Section 6.2 Screening/Qualification Visit (At Least Day -30 to Day 1, Visit 1) • Section 6.3 Randomization (Day 1, Visit 2) • Section 6.4.4 Month 3 (Visit 5; End of Main Treatment Period) Procedures • Section 9.8.7 Urine Pregnancy Testing • Appendix 17.3 Effective Methods of Birth Control
5	**Modified lists of P-gp inducers and P-gp inhibitors** The following sections of the protocol were updated: • Appendix 17.5.6 P-gp Inducers (Prohibited Medication) • Appendix 17.6.1 P-gp Inhibitors List
6	**Removed adjudication timeline** The following section of the protocol was updated: • Section 6 Study Procedures
7	**Permitted Screening and Randomization to occur on the same date** The following sections of the protocol were updated: • Section 6.2 Screening/Qualification Visit (At Least Day -30 to Day 1, Visit 1) • Section 6.3 Randomization (Day 1, Visit 2) • Table 17.1 Schedule of Events

Change Number	Change Description
8	**Allowed for use of local laboratory for Screening** The following sections of the protocol were updated: • Section 6.2 Screening/Qualification Visit (At Least Day -30 to Day 1, Visit 1) • Section 9.8 Clinical Laboratory Evaluations • Table 17.1 Schedule of Events
9	**Update to treatment compliance (clarified procedures that only apply to edoxaban)** The following section of the protocol was updated: • Section 5.4 Method of Assessing Treatment Compliance
10	**Update to drug accountability (when documentation should be appended to Certificate of Destruction)** The following sections of the protocol were updated: • Section 5.2.6.1 Edoxaban • Section 5.2.6.2 Standard of Care
11	**Removed 40-day requirement from prescription for locally sourced standard of care treatment.** The following section of the protocol was updated: • Section 6.3 Randomization
12	**Corrected protocol number referenced in introduction, added minor updates** The following sections of the protocol were updated: • Section 1.2 Study Rationale • Section 1.3 Risk/Benefit
13	**Added inclusion criterion 5 (new requirements relating to history of TE)** The following sections of the protocol were updated: • Synopsis • Section 4.1 Inclusion Criteria
14	**Updated exclusion criterion 1 to replace "evidence" with "history" of the subsequent list of medical characteristics** The following sections of the protocol were updated: • Synopsis • Section 4.2 Exclusion Criteria
15	**Updated exclusion criterion 7 (into 3 parts) to add clarity** The following sections of the protocol were updated: • Synopsis • Section 4.2 Exclusion Criteria

Change Number	Change Description
16	**Updated exclusion criterion 16 (participation in an interventional clinical study with 30-day wash-out period)** The following sections of the protocol were updated: • Synopsis • Section 4.2 Exclusion Criteria
17	**Added exclusion criterion 17 (New requirement to exclude subjects with a newly detected unorganized thrombus prior to randomization)** The following sections of the protocol were updated: • Synopsis • Section 4.2 Exclusion Criteria
18	**Added exclusion criterion 18 (Hypersensitivity to the active ingredient or to any of the excipients of any components of the trial treatment)** The following sections of the protocol were updated: • Synopsis • Section 4.2 Exclusion Criteria
19	**Added exclusion criterion 19 (for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome)** The following sections of the protocol were updated: • Synopsis • Section 4.2 Exclusion Criteria
20	**Updated relevant time period for subjects who discontinue study treatment for primary efficacy objective, a secondary safety objective (comparing edoxaban with SOC with respect to all bleedings), and an exploratory analysis** The following sections of the protocol were updated: • Synopsis • Section 2.1.1 Primary Objectives • Section 2.1.2.1 Key Secondary Objectives • Section 2.3.1 Primary Safety Endpoint • Section 2.3.2 Secondary Safety Endpoints • Section 11.4.1.2 Exploratory Efficacy Analysis • Section 11.4.3.1 Analysis of Bleeding Events

Change Number	Change Description
21	**Added body weight criteria to allow dose adjustments in extension phase** The following sections of the protocol were updated: • Synopsis • Section 5.1.1 Treatment Groups • Section 5.1.1.1 Edoxaban-Treatment Arm (Randomization through Month 12, and All SOC Subjects Converted to Edoxaban after Month 3) • Table 5.1 Edoxaban Dose Recommended for 3 Cohorts (12 to <18 years, 6 to <12 years, and 2 to <6 years) • Section 5.3.1 Edoxaban Dose Reduction
22	**Clarified that the Cockcroft-Gault formula applies to determining renal impairment in pediatric subjects equal to 12 years of age** The following sections of the protocol were updated: • Table 5.1 Edoxaban Dose Recommended for 3 Cohorts (12 to <18 years, 6 to <12 years, and 2 to <6 years) • Section 5.6.3 Reasons for Discontinuation from Study Treatment • Appendix 17.9 Estimated Glomerular Filtration Rate (eGFR) Assessment
23	**Clarification on INR testing to initiate SOC post screening** The following section of the protocol was updated: • Section 5.2.4.3 To Initiate SOC Treatment

Change Number	Change Description
24	**Modified echocardiogram assessments to not specifically require a transthoracic echocardiogram** The following sections of the protocol were updated: • Synopsis • Section 4.2 Exclusion Criteria • Section 6.1 Note Concerning Transthoracic Echocardiogram • Section 6.2 Screening/Qualification Visit (At least Day -30 to 1, Visit 1) • Section 6.4.4 Month 3 (Visit 5; End of Main Treatment Period) Procedures • Section 6.5.3 Month 12/Discontinuation Visit (Visit 8; Appropriate for subjects completing Month 12 or treated beyond Month 3 and discontinuing study prior to Month 12) • Section 7.1 Assessments for Efficacy Endpoint(s) • Table 7.2 Recommended Diagnostic Imaging Methods • Table 17.1 Schedule of Events
25	**Updated the required INR range to ≤2.5 for subjects to transition from standard of care (SOC) treatment to edoxaban** The following sections of the protocol were updated: • Section 5.1.1 Treatment Groups • Section 5.1.1.1 Edoxaban-Treatment Arm (Randomization through Month 12, and All SOC Subjects Converted to Edoxaban after Month 3)
26	**Updated reporting requirements for serious adverse events** The following sections of the protocol were updated: • Section 5.6.3 Reasons for Discontinuation from Study Treatment • Section 9.5 Serious Adverse Events and Adverse Event of Special Interest Reporting – Procedure For Investigators
27	**Added the option and process for the Principal Investigator to schedule a visit for subjects who switch from SOC to edoxaban in the extension period.** The following section of the protocol was updated: • Section 6.5 Extension Period (beyond Month 3 – Month 6, 9, and 12; Visits 6, 7, and 8)

Change Number	Change Description
28	**Updated re-screening procedures to limit to retesting of laboratory test results related to a specific inclusion/exclusion criteria** The following section of the protocol was updated: • Section 5.6.8 Subject Re-screening Procedures
29	**Modified the provided dosage forms of enoxaparin SOC treatment** The following section of the protocol was updated: • Section 5.2.1.2 Standard of Care (Randomization through Month 3)
30	**Updated list of key study personnel** The following sections of the protocol were updated: • Section 15.12.1 Sponsor's Responsible Medical Officer and Clinical Study Leader • Section 15.12.2 Sponsor's Safety Contacts

PROTOCOL SYNOPSIS

EudraCT:	2017-000475-90
IND Number	IND 63,266
Protocol Number:	DU176b-C-U313
Investigational Product:	Edoxaban (DU-176b)
Active Ingredient(s)/INN:	Edoxaban tosylate: N-(5-Chloropyridin-2-yl)-N'-[(1S,2R,4S)-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:	An open-label, randomised, parallel-group, multicentre, observational trial to evaluate safety and efficacy of edoxaban tosylate in children from 38 weeks gestational age to less than 18 years of age with cardiac diseases at risk of thromboembolic events.
Study Phase:	Phase 3
Indication Under Investigation:	Anticoagulant prophylaxis (either as primary or secondary prevention) in pediatric subjects with cardiac disease at risk of thromboembolic events (TE).
Study Objectives:	**Primary Objective** The primary objective is to compare the safety of edoxaban with the standard of care (SOC) in pediatric subjects with cardiac diseases at risk of thromboembolic complications who need primary or secondary anticoagulant prophylaxis with regard to the combination of major and clinically relevant non-major (CRNM) bleedings per International Society on Thrombosis and Haemostasis [ISTH] definition[1] occurring in the Main Treatment Period: from the date of first dose of study drug to Month 3 Visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier. **Secondary Objectives** The key secondary objectives are: • To compare the efficacy of edoxaban against SOC with regard to the development of symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways including deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, systemic embolic event (SEE), myocardial infarction (MI), and

asymptomatic intracardiac thrombus identified by cardiac imaging occurring from randomization to Month 3 Visit.

- To compare the safety of edoxaban against SOC with regard to all bleedings that occur in the Main Treatment Period: from the date of first dose of study drug to Month 3 Visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier.
- To compare the efficacy of edoxaban against SOC with regard to death as a result of a TE occurring from randomization to Month 3 Visit
- To compare edoxaban against SOC with regard to all-cause mortality from randomization to Month 3 Visit.
- To assess the safety of edoxaban with regard to the combination of major and CRNM bleedings occurring during the Extension Period (from Month 3 Visit to last dose plus 30 days).
- To assess the efficacy of edoxaban with regard to the development of symptomatic TE or asymptomatic intracardiac thrombus identified by cardiac imaging occurring during the Extension Period.
- To assess the safety of edoxaban with regard to all bleedings occurring during the Extension Period.
- To assess the efficacy of edoxaban with regard to death as a result of a TE occurring during the Extension Period.
- To assess the efficacy of edoxaban with regard to all-cause mortality occurring during the Extension Period.
- To evaluate the population pharmacokinetics and pharmacodynamics of edoxaban in relation to the efficacy and safety endpoints in subjects with cardiac conditions at risk of TE.

Exploratory Objectives

The exploratory objectives are:

- To assess the quality of life using validated questionnaires.

	• To compare the intra-patient safety (Investigator reported bleeding) and efficacy (Investigator reported TE) during the Main Treatment Period compared with the prior treatment occurring within 3 months of randomization. • To compare edoxaban regimen with available existing historical data based on literature review and search for registered clinical trials with similar endpoints. • To analyze the primary prevention and secondary prevention of TE.
Study Design:	This is a Phase 3, open-label, randomized, parallel-group, multicenter, observational trial to evaluate safety and efficacy of edoxaban against SOC. 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. Subjects who discontinue treatment from the Main Treatment Period prior to Month 3 will continue to be followed monthly according to the Schedule of Events (Table 17.1) through the Month 3 visit (Visit 5) and have a 30-day Follow-Up Visit. If treatment discontinuation occurs prior to Month 2 visit, the 30-day Follow-Up Visit will occur on the same day as the Month 3 visit. Subjects who complete the Main Treatment Period (Month 3) but do not continue into the Extension Period will have a Month 3 Visit and with a Follow-Up Visit 30 days after last dose of study drug, and discontinued from the study. Subjects who withdraw from the study (meaning the subject can no longer participate in the study due to withdrawal of consent) will have an attempted Follow-Up Visit phone call 3 months from date of randomization to ascertain if any events (TE and/or bleeding events) have occurred since withdrawal.

- The Extension Period is discretionary for the subject based on the Investigator's judgment of risk burden 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). All subjects entering the Extension Period will be given edoxaban for the duration of the Extension Period.
- All subjects after Month 3 will be provided with edoxaban at the dosage appropriate for the subject's age and weight.

  Subjects who discontinue the treatment and study at any time after Month 3 will have a Discontinuation Visit performed with a subsequent 30-day Follow-Up.

  Subjects who complete Extension Period treatment at Month 12 (Visit 8) will have a Follow-Up Visit, 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. After subjects are assessed for eligibility to participate in the study per the inclusion/exclusion criteria, they will be:

- Stratified by:

  Type of underlying heart disease

  - Kawasaki disease
  - Fontan surgery
  - Heart failure
  - Others (which can include post-surgical procedures for congenital heart diseases other than Fontan surgery)

  Subjects with underlying disease other than Kawasaki will be further stratified by concomitant use of low dose aspirin (1 to 5 mg/kg/day)
- About 150 subjects will be recruited globally and be randomized in a 2:1 ratio (edoxaban:SOC, respectively) into 1 of 2 treatment arms:

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

Or

SOC-treatment arm subjects will receive SOC anticoagulant according to clinical site's SOC treatment practice, as follows (alone or in combination):

- Heparin, including unfractionated heparin (UFH) or low molecular weight heparin (LMWH)
- Vitamin K antagonist (VKA) with potential bridging with heparin based therapy until VKA international normalized ratio (INR) is in therapeutic range

Locally sourced SOC is the preferred option for the study. However, centrally sourced SOC can be provided when country or clinical site requirements deem it necessary.

Subjects from 1 to <18 years of age will be enrolled in the study as soon as the dosing regimen is established for each age cohort in the Phase 1 single-dose U157 study. U157 has 5 dosing age cohorts which are similar to this study:

Ages 12 to <18 years

Ages 6 to <12 years

Ages 2 to <6 years

Ages 6 months to <2 years

(In Cohort 4 [6 months to <2 years], enrollment may open after the protocol data requirement for Independent Data Monitoring Committee [IDMC] review for subjects less than 1 year old [from study U157] is met and the IDMC reviews and approves the data. Sites will be notified that enrollment of subjects 6 month old to <1 year old may also open.)

Ages birth to <6 months.

A review of safety data of 10%, 25%, 50%, and 75% of subjects completing the Main Treatment Period of 3 months will be performed on a routine basis by the IDMC. In addition, the IDMC will review the edoxaban exposure analysis and safety

	data from each age cohort in the U157 study to approve the proposed dose for the same age cohort in U313 study. Additionally, in U313, subjects less than 1 year of age will be admitted to the study after review by the IDMC of safety data of 50% of subjects in the 1 to <18 years age group who have completed the Main Treatment Period of 3 months (50 subjects in edoxaban arm and 25 subjects in SOC arm). The older cohort (12 to <18 years of age) will receive tablets (15 and/or 30 mg strength, see Table 5.1) or be offered granules for oral suspension if swallowing is an issue. Subjects 6 to <12 years of age may take edoxaban tablets or edoxaban granules for oral suspension, which will provide more flexibility to adjust mg/kg dose. All subjects <6 years old will receive edoxaban granules oral suspension (see Table 5.1). Subjects will be instructed to take the edoxaban dose orally once a day, at the same time every day, preferably in the morning, with or without food. One bottle of edoxaban granules will be used for each dosing day. Tablets should be swallowed with a glass of water.
Study Duration:	The total duration of the study is expected to be approximately 3 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-day Follow-Up) and maximum of 13 months (3-month Main Treatment Period, 9-month Extension Period and 30-day Follow-Up).
Clinical Sites and Location:	This study will be conducted in North America, European Union, and Rest of the World (ROW).

Subject Eligibility Criteria:

Inclusion Criteria

Subjects must satisfy all of the following criteria to be eligible for the study:

1. Children with cardiac diseases who are at risk for thromboembolic complications and require at least 3 months antithrombotic anticoagulant prophylaxis.

   Either one of the following criteria may apply:

   a. Children with cardiac disease who have a history of cardiac shunt occlusion/thrombosis, with shunt still in place (secondary prevention).

      OR

   b. Children with cardiac disease who require (including those already taking, and those not yet taking) anticoagulation for primary prevention of TE.

   Cardiac conditions known to significantly increase the risk of thrombosis (hence, indications for primary TE prevention) are defined in Antithrombotic Therapy and Prevention of Thrombosis.[1] Some examples of cardiac conditions at risk of thrombosis are Fontan surgery, heart failure, Kawasaki disease, and Blalock-Taussig and Glenn surgery.

2. Male or female children between 1 and <18 years of age. Children between 38 weeks gestational age and 1 year of age will be included in the study, however, only after the safety and efficacy data of 50 subjects between 1 and <18 years of age in the edoxaban arm have been evaluated at the end of the 3-month treatment period.
3. 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.
4. Female subjects of childbearing potential must test negative for pregnancy at Randomization and must consent to avoid becoming pregnant by using a locally approved contraception method throughout the study.

For locally approved contraceptive methods, see Appendix 17.3.

5. If the subject has a history of a TE that meets all of the following criteria:
   - Old, organized and/or resolved per the discretion of the Principal Investigator (confirmation of an old, organized and or resolved TE is not required by any imaging studies), and
   - The subject is asymptomatic, and
   - The subject continues to require at least 3 months of anti-coagulation treatment, and
   - There is no intracardiac thrombus or thrombi on the screening echo, and
   - All other inclusion and exclusion criteria are met.

Exclusion Criteria

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

1. Subjects with a history of the following up to randomization:
   - Symptomatic venous or arterial TE
   - Asymptomatic venous or arterial TE found by routine imaging
   - Asymptomatic intracardiac thrombosis confirmed by an echocardiogram during the study screening period.

     Note: Valid echocardiograms are images taken within 5 weeks prior to Randomization Visit.
2. Subjects with mechanical heart valves.
3. Subjects with active bleeding or high risk of bleeding contraindicating treatment with anticoagulant.
4. Subjects with a contraindication to the use of heparin (UFH or LMWH) and/or VKA (see Appendix 17.4).
5. Co-administration of antithrombotic therapy is contraindicated in edoxaban arm and SOC arm except for low dose aspirin defined as 1 to 5 mg/kg/day with maximum of 100 mg/day (see Appendix 17.5).

6. Administration of rifampin is prohibited during the study and subjects on concomitant use of rifampin are excluded Appendix 17.5.6.
7. 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 at Screening.
8. Subjects with estimated glomerular filtration rate (eGFR) <30% of normal for age and size (see Appendix 17.9)
9. Subjects with stage 2 hypertension defined as blood pressure systolic and/or diastolic confirmed >99th percentile plus 5 mmHg (see Appendix 17.10).
10. Subjects with thrombocytopenia (thrombocytes <50 × 10^9/L).
11. Subjects with Fontan procedure with a history of or signs/symptoms suggestive of protein-losing enteropathy.
12. Subjects with a life expectancy less than the expected study duration (3 months).
13. Subjects who are known to be pregnant or breastfeeding.
14. Subjects who are not using an approved method of contraception (see Appendix 17.3).
15. 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 17.5.
16. Subject who participated in another interventional clinical study or treated with an experimental therapy with less than a 30-day wash-out period prior to Screening Visit.
17. If any imaging is performed prior to randomization and results show a newly detected unorganized thrombus, these subjects are NOT eligible for the study.

	18. Hypersensitivity to the active ingredient or to any of the excipients of any components of the trial treatment. 19. 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.
Dosage Form, Dose and Route of Administration:	**Randomization to Edoxaban-Treatment Arm** Edoxaban treatment will be packaged and dispensed to the subject on a monthly schedule, even though after Month 3 the clinic visitation schedule is every 3 months. For subjects who cannot pick up their study therapy on a monthly basis, accommodations will be made to allow the Investigator to distribute up to a 3-month supply of study drug to match the scheduled study visit interval. The following dosage forms will be provided for this study: • Edoxaban 15 mg and 30 mg tablets • Edoxaban granules for oral suspension 60 mg are provided in individual bottles. Granules will be reconstituted in 8 mL water to provide a 6 mg/mL liquid suspension). One bottle will be used for each daily dose. For subjects 12 to <18 years old; • 60 mg dose will be dispensed as two 30 mg tablets or as 10 mL from an individual bottle of oral suspension 60 mg • 45 mg dose will be dispensed as one 30 mg tablet plus one 15 mg tablet or as 7.5 mL from an individual bottle of oral suspension 60 mg • 30 mg dose will be dispensed as one 30 mg tablet or as 5 mL from an individual bottle of oral suspension 60 mg • Doses provided by the granulation formulation will be dispensed with a dosing syringe according to the recommended dose shown in Table 5.1. One bottle will be used for each daily dose. • If a subject does not have the capacity to swallow tablets in the 12 to <18 year old or 6 to <12 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 an existing gastric tube, if needed.

For subjects 6 to <12 years old;

- 60 mg dose will be dispensed as two 30 mg tablets or as 10 mL from an individual bottle of oral suspension 60 mg.
- 45 mg dose will be dispensed as one 30 mg tablet plus one 15 mg tablet or as 7.5 mL from an individual bottle of oral suspension 60 mg.
- Dose other than 45mg and 60mg provided by the granulation formulation will be dispensed with a dosing syringe according to the recommended dose shown in Table 5.1. One bottle will be used for each daily dose.

Subjects younger than 6 years of age will only receive edoxaban granules for oral suspension, which will give more flexibility to adjust mg/kg dose. Doses for all age groups will be selected to elicit target exposures comparable to those achieved from the adult Phase 3 study of 60 mg. Table 5.1 indicates the edoxaban doses to be given for subjects of the ages 2 to <18 years of age. Doses for all subsequent age cohorts will be by separate notification to the investigative sites outside the content of this protocol after the IDMC has approved the proposed edoxaban doses and safety data from the U157 study.

Pediatric dosing regimen will be determined from Phase 1 single-dose U157 study.

Additionally, there is ongoing review of safety data of 10%, 25%, 50%, and 75% of subjects completing Month 3 of the study by the IDMC in the U313 study.

Subjects will be instructed to take edoxaban (tablets or granules) orally once a day, at the same time every day, preferably in the morning, with or without food. Tablets should be swallowed with a glass of water. Doses provided from the granulation formulation will be provided by a dosing syringe. One bottle will be used for each daily dose.

Edoxaban dosage regimen will be reduced (see Section 5.3.1) for the following reasons. Refer to Table 5.1 for dosing instruction for subjects of age 2 to <18 years of age:

- Body Weight:

For subjects 12 to <18 years old with body weight <5th percentile of subject's age (see Appendix 17.11), edoxaban doses will be permanently changed

For subjects 12 to <18 years old with body weight ≥60 kg, will receive edoxaban 60 mg. However, if the body weight is ≥30 - <60 kg, edoxaban dose would be 45 mg daily. If the patient body weight ≥60 kg, then edoxaban dose would be escalated to 60 mg daily.

For subjects <12 year olds: Doses will be provided by mg/kg or a dose may be suggested, subsequent to exposure modeling, based on an age range (see Table 5.1).

- 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 17.9). 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. If the repeat measurement confirms the decrease, the edoxaban dose will be reduced permanently.
- Additionally, if a subject requires concomitant administration of a certain P-glycoprotein (P-gp) inhibitor (Appendix 17.6.1), the edoxaban dose will be reduced during P-gp administration and re-established to the original dose once P-gp inhibitor administration had concluded.

Randomization to Standard of Care Treatment Arm

SOC randomized subjects will be treated with SOC though Month 3 (Visit 5) then offered edoxaban through Month 12 (Visit 8). SOC treatment will be packaged and dispensed to the subject on a monthly visit schedule. After Month 3, all subjects will be transitioned to edoxaban at the appropriate dose for their age and weight.

Local Sourcing of SOC:

	Local SOC sourcing is the primary method for providing heparin and/or VKA: The SOC will be provided by the Investigator. Alternatively, local supply depots within each country will provide SOC directly to the clinical sites. Subject will be treated with heparin (UFH or LMWH), and/or VKA according to the clinical site's SOC treatment regimen (see Section 5.2). Note: If standard practice for bridging VKA to therapeutic levels is achieved with a heparin based treatment, the clinical site will be responsible for providing the bridging therapy to subjects randomized to VKA. Central/Sponsor Sourcing: If there are regulatory or site hurdles providing the SOC locally, the Sponsor will provide SOC only as LMWH (enoxaparin) or VKA (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 as solution for subcutaneous injection in pre-filled syringes with only 60 mg/0.6 mL, 80 mg/0.8 mL, or 100 mg/1 mL concentration for injection, or as multiple dose vials (for subjects <20 kg) for injection. • Warfarin (VKA) will be supplied as tablets (0.5 mg, 1 mg, and 3 mg). Note: Clinical sites or treating physicians will provide aspirin (as per local SOC practice).
Study Endpoints:	All safety and efficacy endpoints described will be adjudicated in a blinded manner by the Clinical Events Committee (CEC). An Independent Data Monitoring Committee (IDMC) will monitor safety throughout the duration of the study. **Primary Safety Endpoint** The primary safety endpoint is a combination of major bleeding events and CRNM bleeding events per ISTH definition occurring during the Main Treatment Period: from the date of first dose of study drug to Month 3 Visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier.

Secondary Safety Endpoints

The secondary safety endpoints are:

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

Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

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

Pharmacokinetic (PK)/Pharmacodynamic (PD)/Biomarker Endpoint(s)

	Plasma concentrations of edoxaban and its metabolite, D21-2393, will be assessed in subjects who receive at least 1 dose of edoxaban treatment and have measurable concentrations of edoxaban and/or D21-2393. Population PK analysis will be conducted to characterize the PK profiles of edoxaban in this target subject population. The PD biomarkers of coagulation, PT, aPTT, and anti-activated Factor X (FXa) will be assessed as secondary endpoints in edoxaban-treated subjects. Other biomarkers may be tested related to coagulation and/or edoxaban's mechanism of action.
Planned Sample Size:	The total number of subjects planned is 150 subjects. Of these, 100 subjects will be treated with edoxaban and 50 subjects will be given SOC.
Statistical Analyses:	**Analysis Sets:** Randomized Analysis Set will include all subjects who sign the informed consent form and are randomized. Safety Analysis Set will include all subjects in the Randomized Analysis Set who received at least 1 dose of study drug. Analysis will be based on the study drug the subject actually received. Modified intention-to-treat Analysis Set will include all subjects in the Randomized Analysis Set who received at least 1 dose of study drug. Analysis will be based on the study drug the subject was randomized to receive. PK Analysis Set will include all subjects in the Safety Analysis Set who had at least 1 PK sample with measurable concentration. PD Analysis Set will include all subjects in the Safety Analysis Set who had at least 1 measurable PD sample. **Safety Analyses:** **Analysis of Primary Safety Endpoint** A descriptive statistical analysis will be performed for the primary safety endpoint, ie, the composite of major and CRNM bleeding events that occur during the Main Treatment Period: from the date of first dose of study drug to the Month 3 Visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier. This analysis will be based on CEC adjudication results.

The time to major or CRNM bleeding occurring during the Main Treatment Period will be compared between treatment groups for subjects in the Safety Analysis Set, using the Cox proportional hazards regression model including treatment group, concomitant usage of aspirin, and underlying disease (Kawasaki disease, Fontan surgery, Heart Failure or Other) as covariates. Hazard ratio between edoxaban and SOC treatment group will be calculated with corresponding 95% confidence interval. The incidence, annualized event rate, and rate difference between edoxaban and SOC treatment groups will also be calculated.

Analysis of Secondary Safety and Efficacy Endpoints:

The incidence, annualized event rate, and rate difference between edoxaban and SOC treatment groups of other secondary safety and efficacy endpoints for the Main Treatment Period will be summarized by treatment group.

The incidence and annualized event rate of other secondary safety and efficacy endpoints for the Extension Period will be summarized for the edoxaban treatment group.

Exploratory Analysis:

Quality of life will be assessed using validated questionnaires.

Intra-patient safety (Investigator-reported bleeding) and efficacy (Investigator-reported TE) during the Main Treatment Period will be compared with the previous 3-month pre-randomization period of anticoagulant regimen.

The incidence and event rate of safety and efficacy endpoint in the Main Treatment Period will be summarized for comparing edoxaban regimen with available existing historical control data based on literature review and search for registered clinical trials with similar endpoints.

A separate sub-analysis of primary prevention and secondary prevention events will be provided if data allow. TE will be classified as primary prevention and secondary prevention events and summarized by treatment group for events occurring during the Main Treatment Period.

Interim Assessment:

There is no formal statistical interim analysis planned. However, an interim assessment by the IDMC of safety endpoints of the study will take place after the first 50 subjects in the edoxaban treatment group and 25 subjects in the SOC arm from 1 to <18

years of age complete the first 3 months of treatment. This will allow for enrollment of subjects <1 year of age.

PK and PD Analysis (Edoxaban Subjects Only):

Plasma concentration and biomarker data will be summarized by age, dose and time point using descriptive statistics. The plasma concentration data will be pooled with data from other studies for a population PK analysis using nonlinear mixed effects modeling.

Exposure-response relationships will be evaluated for the safety and efficacy endpoints through a model based approach, if data allow.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANA	antinuclear antibody
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
ATE	arterial thromboembolism
BMI	body mass index
BP	blood pressure
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHD	congenital heart disease
CI	confidence interval
CMV	cytomegalovirus
CRF	case report form
CRNM	clinically relevant non-major
CRO	Contract Research Organization
CT	computed tomography
CVL	central venous line
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EIU	exposure in utero
FXa	activated Factor X
GCP	Good Clinical Practice
ICF	informed consent form

ABBREVIATION	DEFINITION
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
INN	international non-proprietary name
INR	international normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
IV	intravenous
IXRS	Interactive Web/Voice Response System
LFT	liver function test
LMWH	low molecular weight heparin
LOA	List of Abbreviations
MI	myocardial infarction
mITT	modified intention-to-treat
MRI	magnetic resonance imaging
MRV	magnetic resonance imaging with venography
NSAID	non-steroidal anti-inflammatory drug
NVAF	nonvalvular atrial fibrillation
PCC	prothrombin complex concentrate
PD	pharmacodynamic
PE	pulmonary embolism
P-gp	P-glycoprotein
PK	pharmacokinetic
PT	prothrombin time
QD	once a day
QOL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation

ABBREVIATION	DEFINITION
SEE	systemic embolic event
SOC	standard of care
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TE	thromboembolic event
TEAE	treatment-emergent adverse event
UFH	unfractionated heparin
ULN	upper limit of normal
US	ultrasonography
VKA	vitamin K antagonist
VTE	venous thromboembolism
WBC	white blood cell

1. INTRODUCTION

1.1. Background

Children with cardiac diseases, including cardiomyopathy and congenital heart disease (CHD) constitute a major proportion of children seen in tertiary hospitals with thromboembolic disease. In addition, more than 80% of the children receiving primary anticoagulant prophylaxis are being treated for complex CHD or severe acquired cardiac illnesses.

In children with cardiac disease, thromboembolic disease develops as a result of altered hemodynamics, prosthetic materials, surgically damaged blood vessels, intravenous (IV) catheters, and cardiopulmonary bypass. To prevent this potential life-threatening complication, some categories of pediatric cardiac patients, including patients with Fontan circulation, severe cardiomyopathy, and mechanic heart valve prostheses, are treated with vitamin K antagonists (VKAs) or heparin.

Many children with CHD require long-term thromboprophylaxis to decrease the morbidity and mortality secondary to the thromboembolic phenomenon. The advances in medical and cardio-surgical techniques have led to improved survival in children with CHD; thus, the overall use of anticoagulation has increased. The overall incidence of thrombotic complications in patients undergoing cardiac surgery for CHD remains difficult to evaluate due to a lack of data. Giglia et al[2] showed an incidence of clinically evident TE of 3.6% of 1930 total cardiac operations performed. More recently, Manlhiot et al[3] revealed that 11% of cardiac operations over a 39-month period were complicated by TEs.

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 low molecular weight heparin (LMWH) and VKAs. The important disadvantages of LMWH (such as enoxaparin) are subcutaneous (SC) administration, thrombocytopenia, and therapeutic level management. 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 international normalized ratio (INR), an unpredictable and variable pharmacological response, and food and drug interactions requiring frequent dosage adjustment. Monagle et al showed that 41% of all warfarin measurements were below the target range, which is not uncommon in children taking warfarin[4]. 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.

Edoxaban is an oral direct inhibitor of activated Factor X with predictable pharmacokinetics and pharmacodynamics. 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.

In 2015, edoxaban was approved for the following indications in the United States:

- To reduce the risk of stroke and systemic embolism in subjects with nonvalvular atrial fibrillation (NVAF) with limitation of use in patients with creatinine clearance (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 European Economic Area and Japan, edoxaban was approved in 2015 for the following indications:

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

As of 21 Oct 2018, edoxaban is authorised in 45 countries and is marketed in 30 countries worldwide.

This study will compare the safety of edoxaban with the standard of care (SOC) treatment in pediatric subjects with cardiac disease who need anticoagulation to prevent primary and secondary thromboembolic disease. Further data on edoxaban development are provided in the most recent Investigator's Brochure[5].

1.3. Risk/Benefit

Although pediatric subjects are at less risk than adults for the development of thromboembolic event (TE), embolic disease remains an uncommon condition, but it does occur and is well described in children and adolescents with or without risk factors. Thrombosis is an increasingly recognized complication occurring primarily in children with serious underlying conditions and most often associated with IV catheters,[6] and is also recognized in neonatal and pediatric practice due to more sophisticated diagnostic tools being available. In children with cardiac disease, thromboembolic disease develops as a result of altered hemodynamics, prosthetic materials, surgically damaged blood vessels, intravenous catheters, and cardiopulmonary bypass. To prevent this potential life-threatening complication, some categories of pediatric cardiac patients, including patients with heart failure, Fontan circulation, severe cardiomyopathy (Kawasaki disease), and mechanic heart valve prostheses, are treated with less advanced therapy such as VKAs or heparin which requires intensive therapeutic monitoring.

Many children with CHD require long-term thromboprophylaxis to decrease the morbidity and mortality secondary to the thromboembolic phenomenon. The advances in medical and cardio-surgical techniques have led to improved survival in children with CHD; thus, the overall use of anticoagulation has increased. The overall incidence of thrombotic complications in patients undergoing cardiac surgery for CHD remains difficult to evaluate due to a lack of data. Giglia et al[2] showed an incidence of clinically evident TE of 3.6% of 1930 total cardiac operations performed. More recently, Manlhiot et al[3] revealed that 11% of cardiac operations over a 39-month period were complicated by TEs.

Symptomatic thrombotic manifestation is recorded in 0.07/10,000 children, 5.3/10,000 admissions of children and 24/10,000 admissions of newborns to intensive care units.[1,7,8] According to the U.K. registry (British Pediatric Surveillance Unit), the estimated incidence of thromboembolic events was 0.07/10,000 children (excluding stroke), with 89% having venous involvement[7]. Besides the greater awareness, an objective increase in childhood thrombosis is attributed to medical advances in the treatment of critically ill patients. This seemingly contradictory observation is readily explained by the increasing use of central catheterization and innovative interventional procedures in the treatment of premature infants, neonates and older children who are critically ill, suffering from complex cardiac defects, and from malignant disease, respectively.

Safety and effectiveness of edoxaban development is an ongoing program with 2 Phase 3 studies in the pediatric population (venous thromboembolism [VTE-U312 study] and arterial thromboembolism [ATE-U313 study]). In principle, based on current adult data obtained on edoxaban, edoxaban is also considered to be suitable for the pediatric population and supported by the FDA and EMA request for pediatric studies in select populations.

The DU176b-A-U157 study (currently ongoing in the US, Canada, and Rest of the World [ROW]) will evaluate and establish the pharmacokinetics (PK), the pharmacodynamics (PD), the safety and tolerability of edoxaban in pediatric patients following single-dose oral administration. It will also evaluate the palatability of the liquid oral suspension of edoxaban. Pediatric patients who are at risk of thromboembolic events and may need anticoagulation are eligible for inclusion in the study. The goal of this study is to identify pediatric doses that are age appropriate and provides comparable exposure to adult efficacious doses to guide dose selection for the Phase 3 studies in a pediatric population who have confirmed VTE (U312 study) or patients with cardiac disease at risk of thromboembolic events (U313 Study) which require anticoagulant therapy.

The dose for 3 of the 5 age cohorts 12 to <18, 6 to <12, and 2 to <6 years has been defined from the U157 study, and age cohort enrollment in the U312 VTE study and U313 will be sequential based on the availability of data derived from U157. Note: doses for age cohorts 6 months to <2, and 38 weeks gestation to <6 months) need to be defined. No safety concerns related to study drug have been observed in these subjects. In addition, approximately 135 subjects (12 to <18 years) and 35 subjects (6 to <12 years) as of April 2019 in the Phase 3 U312 VTE study have been enrolled without clinical sequelae as reviewed by the Independent Data Monitoring Committee (IDMC).

There are potential benefits for trial participation as well as receipt of the study drugs in this open label design, as patient compliance and lifestyle will be improved by taking an oral medication compared to an injectable (enoxaparin) or and VKA which has therapeutic monitoring requirements and potential food interactions. Indirect benefits to the patients enrolled in this trial are the free medical tests received at screening and during the study. The data derived from this study could potentially benefit pediatric patients when the study data is disclosed and becomes publically available or lead to a possible update of the edoxaban drug label for pediatric use.

The safety monitoring practices employed by this protocol, DU176b-C-U313, (ie, physical examinations, vital signs, AEs, clinical laboratory and coagulation assessments, and urinalysis)

are considered adequate to protect the patients' safety. The IDMC can recommend termination of the study based on concern about significantly higher bleeding risk relative to one of the study arms, concern about drug-induced liver injury or any other safety concern based on benefit/risk evaluation. Therefore, any risk associated with participation in this trial is fully evaluated during the course of the trial by an IDMC to ensure patient risk is minimized.

In conclusion, for the individual pediatric patient, any benefit associated with participation in this trial is based on the confirmed efficacy and safety profile of edoxaban compared to SOC in the adult population from large Phase 3 studies, and the predicted benefit for the overall pediatric population. Any risk is minimized, as the trial is an open label design, is highly monitored by an IDMC and associated risks controlled and evaluated for the individual patient. Indirect benefits to the patients enrolled in this study are the free medical tests received at screening and during the study. However, the data derived from this study could potentially benefit pediatric patients if it leads to an extension of the edoxaban label. This research may give rise to new or better drug treatments for this vulnerable patient population. The information from this study may benefit other pediatric patients in the future.

2. STUDY OBJECTIVES, HYPOTHESIS AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective is to compare the safety of edoxaban with the SOC in pediatric subjects with cardiac diseases at risk of thromboembolic complications who need primary or secondary anticoagulant prophylaxis with regard to the combination of major and clinically relevant non-major (CRNM) bleedings per International Society on Thrombosis and Haemostasis [ISTH] definition[1] occurring in the Main Treatment Period: from the date of first dose of study drug to Month 3 Visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier.

2.1.2. Secondary Objectives

2.1.2.1. Key Secondary Objectives

The key secondary objectives are:

- To compare the efficacy of edoxaban against SOC with regard to the development of symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways including deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, systemic embolic event (SEE), myocardial infarction (MI), and asymptomatic intracardiac thrombus identified by cardiac imaging occurring from randomization to Month 3 Visit.
- To compare the safety of edoxaban against SOC with regard to all bleedings which occur in the Main Treatment Period: from the date of first dose of study drug to Month 3 Visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier.
- To compare the efficacy of edoxaban against SOC with regard to death as a result of a TE occurring from randomization to Month 3 Visit
- To compare edoxaban against SOC with regard to all-cause mortality from randomization to Month 3 Visit.
- To assess the safety of edoxaban with regard to the combination of major and CRNM bleedings occurring during the Extension Period (from Month 3 Visit to last dose plus 30 days).
- To assess the efficacy of edoxaban with regard to the development of symptomatic TE or asymptomatic intracardiac thrombus identified by cardiac imaging occurring during the Extension Period.
- To assess the safety of edoxaban with regard to all bleedings occurring during the Extension Period.
- To assess the efficacy of edoxaban with regard to death as a result of a TE occurring during the Extension Period.

- To assess the efficacy of edoxaban with regard to all-cause mortality occurring during the Extension Period.
- To evaluate the population pharmacokinetics and pharmacodynamics of edoxaban in relation to the efficacy and safety endpoints in subjects with cardiac conditions at risk of TE.

2.1.2.2. Other Secondary Objectives

Not applicable.

2.1.3. Exploratory Objectives

The exploratory objectives are:

- To assess the quality of life (QOL) using validated questionnaires.
- To compare the intra-patient safety (Investigator reported bleeding) and efficacy (Investigator reported TE) during the Main Treatment Period compared with the prior treatment occurring within 3 months of randomization.
- To compare edoxaban regimen with available existing historical data based on literature review and search for registered clinical trials with similar endpoints.
- To analyze the primary prevention and secondary prevention of TE.

2.2. Study Hypothesis

This study is designed to assess the hypothesis that the administration of edoxaban will be at least as safe as the current SOC (unfractionated heparin [UFH] or LMWH and/or VKA) with regard to the combination of major and CRNM bleedings after 3 months of therapy in pediatric subjects with cardiac disease at risk of thromboembolic events.

2.3. Study Endpoints

All safety and efficacy endpoints described will be adjudicated in a blinded manner by the Clinical Events Committee (CEC). An Independent Data Monitoring Committee (IDMC) will monitor safety throughout the duration of the study.

2.3.1. Primary Safety Endpoint

The primary safety endpoint is a combination of major bleeding events and CRNM bleeding events per ISTH definition, occurring during the Main Treatment Period: from the date of first dose of study drug to the Month 3 Visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier.

2.3.2. Secondary Safety Endpoint(s)

The secondary safety endpoints are:

- All bleeding events occurring during the Main Treatment Period: from the date of first dose of study drug to the Month 3 Visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier.

- A combination of major and CRNM bleedings from the day after Month 3 Visit to the date of the last dose of study medication plus 30 days for subjects who participate in the Extension Period.
- All bleeding events from the day after the Month 3 Visit to the date of last dose of study medication plus 30 days for subjects who participate in the Extension Period.

2.3.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The combination of symptomatic TE in the systemic arterial or venous pathways including DVT, PE, stroke, intracardiac thrombus, SEE, and MI, and asymptomatic intracardiac thrombus identified by cardiac imaging, that occur from randomization to the Month 3 Visit.
- Deaths as a result of TE that occurs from randomization to the Month 3 Visit.
- All-cause mortality from randomization to the Month 3 Visit.
- The combination of symptomatic TE in the systemic arterial or venous pathways and asymptomatic intracardiac thrombus identified by cardiac imaging, which occur from the day after the Month 3 Visit to the date of the last dose of study drug plus 30 days for subjects who participate in the Extension Period.
- Deaths as a result of TE that occurs from the day after Month 3 Visit to the date of the last dose of study drug plus 30 days for subjects who participate in the Extension Period.
- All-cause mortality from the day after the Month 3 Visit to the date of the last dose of study drug plus 30 days for subjects who participate in the Extension Period.

2.3.4. Pharmacokinetic (PK)/Pharmacodynamic (PD)/Biomarker Endpoint(s)

Plasma concentrations of edoxaban and its metabolite, D21-2393, will be assessed in subjects who receive at least 1 dose of edoxaban treatment and have measurable concentrations of edoxaban and/or D21-2393. Population PK analysis will be conducted to characterize the PK profiles of edoxaban in this target subject population.

The PD biomarkers of coagulation, PT, activated partial thromboplastin time (aPTT), and anti-activated Factor X (FXa), will be assessed as secondary endpoints in edoxaban-treated subjects.

Other biomarkers may be tested related to coagulation and/or edoxaban's mechanism of action.

2.3.5. Quality of Life Assessment

A pediatric QOL questionnaire will be issued at randomization and at the end of the Main Treatment Period to assess such categories as: health and activities, feelings about themselves, relationships with others, and school behavior. Note the QOL can be filled out by either a parent or the study participant. The same person should complete the QOL at Month 3.

PedsQL version 4.0, generic core scale will be used in the study.

The following questionnaires will be used:

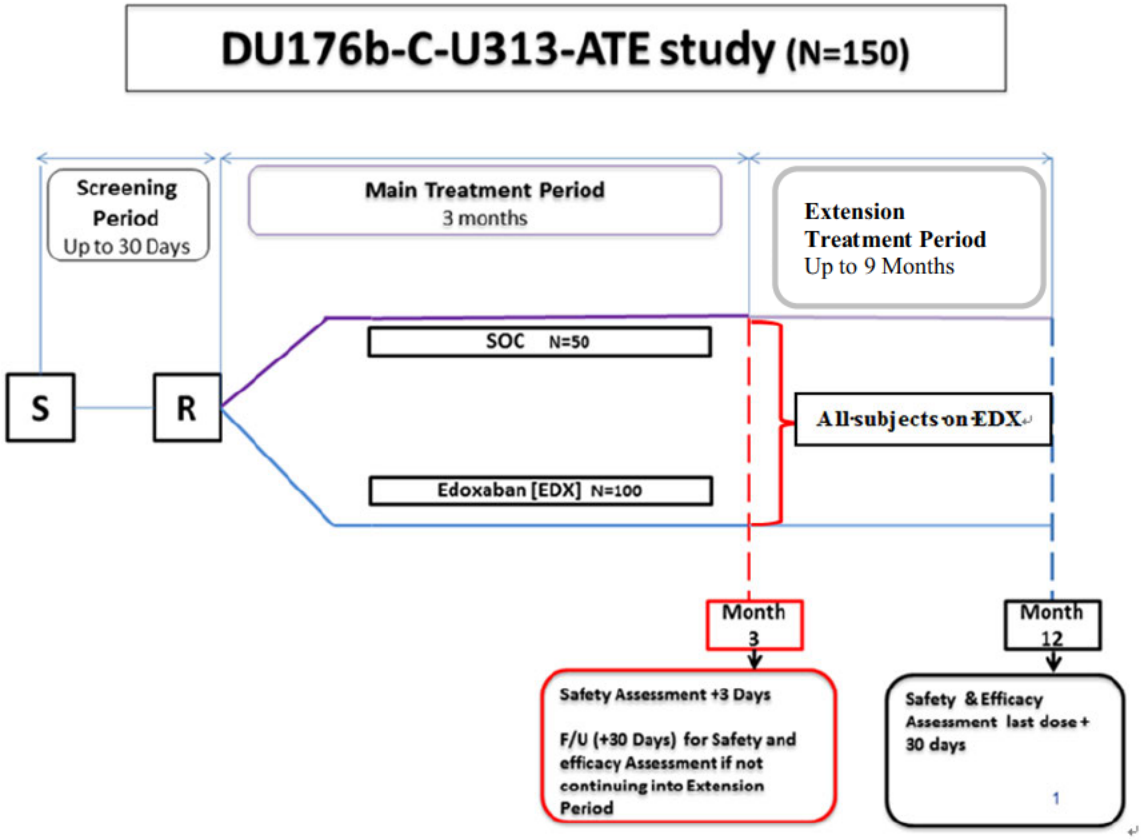
- Adolescent (13-18) Self report
- Adolescent (13-18) Parent report
- Child (8-12) Self report
- Child (8-12) Parent report
- Young child (5-7) Self report
- Young child (5-7) Parent report
- Toddler (2-4) Parent report

3. STUDY DESIGN

3.1. Overall Design

This is a Phase 3, open-label, randomized, parallel-group, multicenter, observational trial to evaluate and compare the safety and efficacy of edoxaban against SOC. The adjudication of the efficacy and safety endpoints will be conducted by a blinded adjudication committee. The overall study design is shown in Figure 3.1.

Figure 3.1: DU176b-C-U313 Overall Study Design



3.2. Discussion of Study Design

This study is designed to compare the safety of edoxaban with SOC in pediatric subjects with cardiac conditions at risk of thromboembolic events. The adjudication of the efficacy and safety endpoints will be conducted by a blinded adjudication committee.

The study includes 2 periods.

- The Main Treatment Period is defined as the time from randomization, until the end of Month 3 of treatment.

  Subjects who discontinue treatment from the Main Treatment Period prior to Month 3 will continue to be followed monthly according to the Schedule of Events (Appendix 17.1) through the Month 3 visit (Visit 5), and have a 30-day Follow-Up Visit. If treatment discontinuation occurs prior to Month 2 visit, the 30-day Follow-Up Visit will occur on the same day as the Month 3 visit.

  Subjects who complete the Main Treatment Period (Month 3) but do not continue into the Extension Period will have a Month 3 Visit and a Follow-Up Visit, 30 days after last dose of study drug and be discontinued from the study.

  Subjects who withdraw from the study prior to Month 3 (meaning the subject can no longer participate in the study due to withdrawal consent), will have a Follow-Up phone call 3 months from the date of randomization to ascertain any events (TE and/or bleeding events) that may have occurred since withdrawal.

- The Extension Period is discretionary for the subject based on the Investigator judgment of risk burden 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).All subjects entering the Extension Period will be given edoxaban for the duration of the Extension Period.

  After Month 3, all subjects will be transitioned to edoxaban at the appropriate dose for their age and weight at informed consent.

  Subjects who discontinue the treatment and study at any time after Month 3 will have a Discontinuation Visit performed with a subsequent 30-day Follow-Up.

  Subjects who complete Extension Period treatment at Month 12 (Visit 8) will have a Follow-Up Visit, 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 (Appendix 17.7).

About 150 subjects from sites selected globally will be randomized in a 2:1 ratio (edoxaban:SOC, respectively) ratio into this study.

Subjects from 1 to <18 years of age will be enrolled in the study as soon as the dosing regimen is established for each age cohort in the Phase 1 single-dose U157 study. U157 has 5 dosing age cohorts that are similar to the U313 study:

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

- Ages 6 months to <2 years

  (In Cohort 4 [6 months to <2 years], enrollment may open after the protocol data requirement for IDMC review for subjects less than 1 year old is met and the IDMC reviews and approves the data. Sites will be notified that enrollment of 6 month olds to <1 year olds may also open.)

- Ages birth to <6 months.

A review of safety data of 10%, 25%, 50%, and 75% of subjects completing the Main Treatment Period of 3 months will be performed on a routine basis by the Independent Data Monitoring Committee (IDMC). In addition, the IDMC will review the edoxaban exposure analysis from the U157 study in addition to the safety data from each age cohort to approve the proposed dose for the same age cohort in the U313 study.

Additionally, subjects less than 1 year of age will be admitted to the study after review by the IDMC of safety data of 50% of subjects in the 1 to <18 years of age group who have completed the Main Treatment Period of 3 months (50 subjects in edoxaban arm and 25 subjects in SOC arm).

3.3. End of Study

This study will continue to randomize subjects until approximately 150 subjects (100 edoxaban- and 50 SOC-treated subjects) complete at least 3 months of treatment. All subjects in the Extension Period will complete treatment as judged by the Investigator after the last subject is randomized and completes 3 months of treatment.

Primary safety endpoints are achieved during the first 3-month treatment period, ie, safety (bleeding) events occur across both treatment groups for the safety analysis set during the first 3-month treatment period anytime from the date of first dose of study drug through the final Month 3 Visit in all randomized subjects who receive at least one dose of randomized study drug. 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 1 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 based on EOT will be placed on SOC at Investigator discretion. All safety and efficacy 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 eligible for the study:

1. Children with cardiac diseases who are at risk for thromboembolic complications and require at least 3 months antithrombotic anticoagulant prophylaxis.

   Either one of the following criteria may apply:

   a. Children with cardiac disease who have a history of cardiac shunt occlusion/thrombosis, with shunt still in place (secondary prevention).

      OR

   b. Children with cardiac disease who require (including those already taking, and those not yet taking) anticoagulation for primary prevention of TE.

   Cardiac conditions known to significantly increase the risk of thrombosis (hence, indications for primary TE prevention) are defined in Antithrombotic Therapy and Prevention of Thrombosis[1]. Some examples of cardiac conditions at risk of thrombosis are Fontan surgery, heart failure, Kawasaki disease, and Blalock-Taussig and Glenn surgery.

2. Male or female children between 1 and <18 years of age. Children between 38 weeks gestational age and 1 year of age will be included in the study, however, only after the safety and efficacy data of 50 subjects between 1 and <18 years of age in the edoxaban arm have been evaluated at the end of the 3-month treatment period.

3. 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.

4. Female subjects of childbearing potential must test negative for pregnancy at Randomization and must consent to avoid becoming pregnant by using a locally approved contraception method throughout the study. For locally approved contraceptive methods, see Appendix 17.3.

5. If the subject has a history of a TE that meets all of the following criteria:

   - Old, organized and/or resolved per the discretion of the Principal Investigator (confirmation of an old, organized and or resolved TE is not required by any imaging studies), and
   - The subject is asymptomatic, and
   - The subject continues to require at least 3 months of anti-coagulation treatment, and
   - There is no intracardiac thrombus or thrombi on the screening echo, and
   - All other inclusion and exclusion criteria are met.

4.2. Exclusion Criteria

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

1. Subjects with a history of the following up to randomization:
   - Symptomatic venous or arterial TE
   - Asymptomatic venous or arterial TE found by routine imaging
   - Asymptomatic intracardiac thrombosis confirmed by an echocardiogram during study screening period.

     Note: Valid echocardiograms are defined here as images taken within 5 weeks prior to Randomization Visit.
2. Subjects with mechanical heart valves.
3. Subjects with active bleeding or high risk of bleeding contraindicating treatment with anticoagulant.
4. Subjects with a contraindication to the use of heparin (UFH or LMWH) and/or VKA (see Appendix 17.4).
5. Co-administration of antithrombotic therapy is contraindicated in edoxaban arm and SOC arm except for low dose aspirin defined as 1 to 5 mg/kg/day with maximum of 100 mg/day (see Appendix 17.5).
6. Administration of rifampin is prohibited during the study and subjects on concomitant use of rifampin are excluded (see Appendix 17.5.6).
7. 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 (TBL) >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 at Screening.
8. Subjects with estimated glomerular filtration rate (eGFR) <30% of normal for age and size (see Appendix 17.9).
9. Subjects with stage 2 hypertension defined as blood pressure (BP) systolic and/or diastolic confirmed >99th percentile plus 5 mmHg (see Appendix 17.10).
10. Subjects with thrombocytopenia (thrombocytes <50 × 10^9/L).
11. Subjects with Fontan procedure with a history of or signs/symptoms suggestive of protein-losing enteropathy.
12. Subjects with a life expectancy less than the expected study duration (3 months).
13. Subjects who are known to be pregnant or breastfeeding.

14. Subjects who are not using an approved method of contraception (see Appendix 17.3).
15. 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 17.6.
16. Subject who participated in another interventional clinical study or treated with an experimental therapy with less than a 30-day wash-out period prior to the Screening Visit.
17. If any imaging is performed prior to randomization and results show a newly detected unorganized thrombus, these subjects are NOT eligible for the study.
18. Hypersensitivity to the active ingredient or to any of the excipients of any components of the trial treatment.
19. 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 Study:

An Independent Data Monitoring Committee (IDMC) may recommend termination of the study. Termination may be made for any of the following reasons:

- Concerns about significantly higher bleeding risk relative to one of the study arms,
- Concerns about drug-induced liver injury,[9]
- Any other safety concerns based on benefit/risk evaluation by the IDMC.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Groups

All subjects will be assessed for eligibility in the study in accordance with the inclusion/exclusion criteria. Eligible subjects will be stratified and randomized as follows:

- All eligible subjects will be stratified by:

  Type of underlying heart disease:

  Kawasaki disease

  Fontan surgery

  Heart failure (HF)

  Others (which can include post-surgical procedures for congenital heart disease other than Fontan surgery)

  Subjects with underlying disease other than Kawasaki will be further stratified by concomitant use of low dose aspirin (1 to 5 mg/kg/day).

- Randomized in a 2:1 ratio (edoxaban:SOC, respectively) into 1 of 2 treatment arms:

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

  OR

  SOC-treatment arm: subjects will receive SOC anticoagulant according to clinical site's SOC treatment, as follows (alone or in combination):

  Heparin, including UFH or LMWH

  Vitamin K antagonist (VKA) with potential bridging with heparin based therapy until VKA INR is in therapeutic range

After Month 3, all subjects who continue in the Extension Period and are on SOC will be offered edoxaban treatment and dosed according to their cohort age at the time of subject consent. During the extension period of the study, check the body weight prior to dosing and adjust dosage accordingly. Frequency of dosage changing is up to the Investigator's discretion.

Subjects from 1 to <18 years of age will be enrolled in the study as soon as the dosing regimen is established for each age cohort in the Phase 1 single-dose U157 study.

Additionally, subjects less than 1 year of age will be admitted to the study after review by the IDMC of safety data of 50% of subjects in the 1 to <18 years of age group who have completed the Main Treatment Period of 3 months (50 subjects in edoxaban arm and 25 subjects in SOC arm).

Subjects younger than 6 years of age will only receive edoxaban granules for oral suspension, which will give more flexibility to adjust mg/kg dose. Doses for all age groups will be selected to elicit target exposures comparable to those achieved from the adult Phase 3 study of 60 mg.

Table 5.1 indicates the edoxaban doses to be given for subjects of the ages 2 to <18 years of age. Doses for all subsequent age cohorts will be by separate notification to the investigative sites outside the content of this protocol after the IDMC has approved the proposed edoxaban doses and safety data from the U157 study.

Doses for Cohorts 1, 2 and 3 have been established. Doses for the remaining subsequent age cohorts will be by separate notification to the investigative sites outside the content of this protocol after the IDMC has approved the proposed edoxaban doses and safety data from the U157 study.

Study treatment should be administered on the same day as randomization (Day 1) if INR is ≤2.5 for subjects receiving VKA prior to randomization.

5.1.1.1. Edoxaban-Treatment Arm (Randomization through Month 12, and All SOC Subjects Converted to Edoxaban after Month 3)

Edoxaban treatment will be packaged and dispensed to the subject on a monthly visit schedule. For subjects who cannot pick up their study therapy on a monthly basis, accommodations will be made to allow the Investigator to distribute up to a 3-month supply of study drug to match the scheduled study visit interval. Edoxaban will be given orally at the appropriate dose depending on the results of the ongoing U157 study.

Cohort 1 (12 to <18 years old) and Cohort 2 (6 to <12 years old) will receive tablets (15 and/or 30 mg strength, see Table 5.1) or offered granules for oral suspension if swallowing is an issue. Subjects <2 years of age will take edoxaban granules for oral suspension which will provide more flexibility to adjust mg/kg dose. Subjects will be instructed to take the edoxaban dose orally once a day, at the same time every day, preferably in the morning, with or without food. Tablets should be swallowed with a glass of water. One bottle of edoxaban granules should be used for each dosing day. The recommended dosing for the 12 to <18, 6 to <12, and 2 to <6 year olds is shown in Table 5.1.

Dosing recommendations for the lower age cohorts will be provided as the U157 single-dose edoxaban study completes the PK exposure analysis for similar age cohorts. Doses for all subsequent age cohorts will be by separate notification to the investigative sites outside the content of this protocol.

During the extension period of the study, check the body weight prior to dosing and adjust dosage accordingly. Frequency of dosage changing is up to the Investigator's discretion.

Table 5.1: Edoxaban Dose Recommended for 3 Cohorts (12 to <18 years, 6 to <12 years, and 2 to <6 years)

Age	Body Weight at Randomization or at Subsequent Visit	Dose (Tablet)	Dose (Suspension) (6 mg/mL concentration)[c]	Dose Reduction[a]
12 to <18 years[b] (At date of consent)	≥60 kg	60 mg QD	10 mL	45 mg QD
	≥30 and <60 kg	45 mg QD	7.5 mL	30 mg QD
	<5th Percentile for Age[c]	30 mg QD	5 mL	NA
6 to <12 years (At date of consent)[d]	≥60 kg	60 mg QD	10 mL	45 mg QD
	<60 kg Dosed based on mg/kg[e]	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

Abbreviations: eGFR = estimated glomerular filtration rate; NA = not applicable; QD = once a day

[a] Conditions for dose reduction:
If a subject requires concomitant administration of P-glycoprotein (P-gp) inhibitor (Appendix 17.6.1), 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 17.9 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. If the repeat measurement confirms the decrease, 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 ≥30 and <60 kg at consent increasing 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 17.11.

[d] Per Principal Investigator's discretion, for subjects in Cohort 2 that require either 45 mg or 60 mg dose, the Principal Investigator may use edoxaban tablets instead of granules, if they wish.

[e] 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.

For subjects without prior anticoagulant therapy, edoxaban may be started the day of randomization (Day 1).

For subjects who received VKA treatment prior to randomization and are randomized to edoxaban, VKA treatment will be discontinued the day before randomization and edoxaban dose will be initiated when an INR ≤2.5 is reached.

5.1.1.2. Standard of Care Treatment Arm (Randomization to Month 3).

SOC randomized subjects will be treated with SOC though Month 3 (Visit 5) and then offered edoxaban through Month 12. SOC treatment will be packaged and dispensed to the subject on a monthly visit schedule. After Month 3, all subjects will be transitioned to edoxaban at the appropriate dose for their age and weight. Locally sourced SOC is the preferred option for this study, either by the Investigator or, alternatively local supply depots within each country that provide SOC directly to the clinical sites. However, centrally sourced SOC can be provided when the country or clinical site requirements deem it necessary. In the case of centrally sourced treatment, the Sponsor will only provide enoxaparin as LMWH and warfarin as VKA.

For subjects who did not receive VKA treatment prior to randomization and are randomized to SOC with VKA, VKA treatment may be started on the day of randomization (Day 1).

It is the Investigator's discretion based on his/her local practice and on the subject's underlying cardiac disease to consider if heparin bridging is necessary when initiating VKA post randomization until an INR between 2.0 and 3.0 is reached. Heparin bridging will be provided by the Investigator.

5.1.2. Method of Treatment Allocation

Eligible subjects will be stratified as mentioned in Section 5.1.1. An independent biostatistician will generate the randomization schedule in accordance with the operating procedure for allocating study drug.

At randomization, the Investigator provides the Interactive Web/Voice Response System (IXRS) with the clinical site number and the subject's presenting diagnosis and date of birth.

Dose will be reduced for subjects based on the following criteria:

- eGFR is 30-50% of normal for age and size (Appendix 17.9). 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. If the repeat measurement confirms the eGFR ≥30% to ≤50%, the edoxaban dose will be reduced permanently.
- Subject is receiving concomitant treatment with P-gp inhibitors. The dose will be reduced while on P-gp inhibitor and re-established to original dose once the concomitant medication is stopped (Appendix 17.6.1).
- Body Weight:

  For subjects 12 to <18 years old with body weight <5th percentile of subject's age (see Appendix 17.11), edoxaban doses will be permanently changed.

  For subjects 12 to <18 years old with body weight ≥60 kg, will receive edoxaban 60 mg. However, if the body weight is ≥30 - <60 kg, edoxaban dose would be 45 mg daily. If the patient body weight ≥60 kg, then edoxaban dose would be escalated to 60 mg daily.

For subjects <12 years old: Doses will be provided by mg/kg or a dose may be suggested, subsequent to exposure modeling, based on an age range (see Table 5.1).

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).

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 study drug for this study is edoxaban (DU-176b) and SOC anticoagulants (UFH/LMWH and VKA). The active ingredient is edoxaban tosylate and the international non-proprietary name is N-(5-Chloropyridin-2-yl)-N'-[(1S,2R,4S)-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.

5.2.1.1. Edoxaban (Randomization through Month 12)

Edoxaban will be packaged and supplied to the subject on a monthly visit schedule as tablets (15 and/or 30 mg strength) or granules for oral suspension (60 mg strength) even though after Month 3 the clinic visitation schedule is every 3 months. For subjects who cannot pick up their study therapy on a monthly basis, accommodations will be made to allow the Investigator to distribute up to a 3-month supply of study drug to match the scheduled study visit interval.

Subjects will be instructed to take edoxaban (tablets or granules) orally once a day, at the same time every day, preferably in the morning, with or without food. One bottle of edoxaban granules will be used for each dosing day. Tablets should be swallowed with a glass of water.

The doses will be dispensed as follows:

For subjects 12 to <18 years old:

- A 60 mg dose will be dispensed as two 30 mg tablets or 10 mL from an individual bottle of oral suspension 60 mg
- A 45 mg dose will be dispensed as one 30 mg tablet plus one 15 mg tablet or 7.5 mL from an individual bottle of oral suspension 60 mg

- A 30 mg dose will be dispensed as one 30 mg tablet or 5 mL from an individual bottle of oral suspension 60 mg
- Doses provided by the granulation formulation will be dispensed with a dosing syringe according to the recommended dose shown in Table 5.1.
- If a subject does not have the capacity to swallow tablets in the 12 to <18 year and 6 to <12 year old groups, 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 an existing gastric tube, if needed.

For subjects 6 to <12 years old:

- 60 mg dose will be dispensed as two 30 mg tablets or as 10 mL from an individual bottle of oral suspension 60 mg.
- 45 mg dose will be dispensed as one 30 mg tablet plus one 15 mg tablet or as 7.5 mL from an individual bottle of oral suspension 60 mg.
- Dose other than 45mg and 60mg provided by the granulation formulation will be dispensed with a dosing syringe according to the recommended dose shown in Table 5.1. One bottle will be used for each daily dose.

5.2.1.2. Standard of Care (Randomization through Month 3)

Treatment with SOC will only occur through Month 3. After that time all subjects will be offered edoxaban at a dose appropriate for age and weight. Local sourcing will be the preferred option for SOC drugs, either by the Investigator or local depot providing locally utilized therapy to treat TE. The Sponsor will supply central sourcing as an alternative option to local SOC sourcing.

Clinical supply will be packaged and dispensed to the subject on a monthly visit schedule.

If local sourcing is used, the Investigator is allowed to utilize any UFH or LMWH, and/or VKA according to the SOC treatment specific to that clinical site (no strength restrictions).

If central sourcing is used, only enoxaparin and warfarin will be supplied by the Sponsor at fixed doses as the LMWH and the VKA, respectively. If a subject is prescribed a dose of the LMWH or VKA different from the doses supplied, a combination of the various doses should be used to obtain the desired dose. Guidance on dosing and dispensing is provided in Appendix 17.2.

Note: If standard practice for bridging VKA to therapeutic levels is achieved with a heparin (UFH or LMWH) based treatment, the clinical site will be responsible for providing the bridging therapy for subjects randomized to VKA.

If required, the Sponsor will provide centrally sourced SOC treatment at the following fixed doses:

- Enoxaparin (LMWH) will be provided as solution for SC injection in pre-filled syringes with only 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 <20 kg).
- Warfarin (VKA) will be supplied as tablets (0.5 mg, 1 mg, and 3 mg). Various doses will be available for INR maintenance in the therapeutic range of 2 to 3.

5.2.1.3. Aspirin

Clinical sites or treating physicians will provide aspirin (as per local SOC practice).

5.2.2. Labeling and Packaging

5.2.2.1. Edoxaban

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

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

5.2.2.2. Standard of Care

Standard of care sourced locally either by the Investigator or by a local depot providing SOC to the clinical site will have no modification in labeling or packaging. Hence, locally sourced SOC treatment will have a label identical to the procured drug.

If required, centrally sourced SOC treatment will be presented in its commercial presentation with the clinical study over-label. SOC labels will include all information required by federal and local regulations.

Note: If standard practice for bridging VKA to therapeutic levels is achieved with a heparin based treatment, the clinical site will be responsible for providing the bridging therapy if the subject is randomized to VKA.

5.2.3. Preparation

5.2.3.1. Edoxaban

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 an existing gastric tube, if needed.

The edoxaban granules for oral suspension 60 mg will be provided in amber glass bottles (wide neck) with child-resistant 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. One bottle will be used for each daily dose. Instructions for reconstitution will be provided to the Investigator/designee and the caregiver.

5.2.3.2. Standard of Care

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

5.2.4. Administration

Study drug will be packaged and dispensed to the subject on a monthly visit schedule. For subjects who cannot pick up their study therapy on a monthly basis, accommodations will be made to allow the Investigator to distribute up to a 3-month edoxaban supply of study drug (for those continuing after Month 3 through Month 12) to match the scheduled study visit interval. Note that each monthly dispensing visit is not indicated in Table 17.1 because no additional procedures are expected at the monthly dispensing visits.

Locally sourced study drug will be provided by the Investigator or through a depot within the country of the clinical site. If required, centrally sourced study drug will be shipped to the clinical 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 until the next scheduled visit.

The Investigator/designee will also instruct the subject on reporting study drug or SOC administration and accountability. Subjects who miss 1 dose of study drug or SOC will be instructed to skip that dose and take the next dose at their drug administration schedule.

5.2.4.1. To Initiate Edoxaban Treatment at Randomization

For subjects without prior anticoagulant therapy, edoxaban may be started the day of randomization (Day 1).

For subjects who received VKA treatment prior to randomization and are randomized to edoxaban, VKA treatment will be discontinued the day before randomization and edoxaban dose will be initiated when an INR ≤2.5 is reached. It is per Investigator's discretion based on his/her local practice and on the subject's underlying cardiac disease to consider if heparin bridging is necessary during this period. Heparin bridging will be provided by the Investigator.

If heparin bridging is used, edoxaban will be started as below:

1. In case of bridging with a LMWH twice a day regimen, edoxaban dosing will start 12 ± 3 hours after the last LMWH dose
2. In case of bridging with a LMWH once a day regimen, edoxaban dosing will start 24 ± 3 hours after the last LMWH
3. In case of bridging with a UFH regimen, edoxaban dosing will start 4 ± 1 hour after the last UFH dose

5.2.4.2 Transition SOC-Treated Subjects during the Main Treatment Period to Edoxaban in the Extension Period

For subjects who received VKA treatment edoxaban dosing will be initiated when an INR ≤2.5 is reached. This may occur as early as next day of the Extension Period.

If the subject was originally randomized to UFH or LMWH, edoxaban will be started as below:

1. In case of LMWH twice a day regimen, edoxaban dosing will start 12 ± 3 hours after the last LMWH dose

2. In case of LMWH once a day regimen, edoxaban dosing will start 24 ± 3 hours after the last LMWH
3. In case of UFH regimen, edoxaban dosing will start 4 ± 1 hour after the last UFH dose

5.2.4.3 To Initiate SOC Treatment

If the subject is randomized to the SOC treatment and they use locally sourced SOC, they will receive the following SOC anticoagulant treatment according to the clinical site's usual treatment practice (alone or in combination):

- LMWH (alone or with VKA)
- UFH (alone or with VKA)
- VKA (alone or with LMWH or UFH)

For subjects who do not receive VKA treatment prior to randomization and are randomized to SOC with VKA, VKA treatment may be started on the day of randomization (Day 1).

It is per Investigator's discretion based on his/her local practice and on the subject's underlying cardiac disease to consider if heparin bridging is necessary post-randomization until an INR between 2.0 and 3.0 is reached. Heparin bridging will be provided by the Investigator.

If centrally sourced SOC treatment is required from the Sponsor, the subject will be treated as follows:

- For subjects randomized to enoxaparin: Neonates or children receiving either once- or twice-daily therapeutic enoxaparin should be monitored as per local practice.
- For subjects randomized to warfarin, it is recommended that the dose should be titrated to achieve a target INR of 2.0 to 3.0. It is per Investigator's discretion based on his/her local practice and on the subject's underlying cardiac disease to consider if heparin bridging is necessary during this period. 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.

For subjects on LMWH or UFH, periodic assessment of therapeutic level is recommended. The most widely used laboratory assay for monitoring UFH or LMWH therapy is the aPTT and anti-FXa activity. **All testing for therapeutic monitoring after randomization will be conducted locally**.

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.

Storage temperatures must be recorded using devices such as a maximum/minimum thermometer. Temperature measurements will be recorded on a temperature log excluding weekends and holidays.

5.2.6. Drug Accountability

5.2.6.1. Edoxaban

Edoxaban will be provided by the Sponsor. When a drug shipment is received, the Investigator or designee will confirm the amount and condition of the drug and confirm the appropriate local language in the label, drug expiration date, and temperature monitor readings. The Investigator or designee will also sign the Receipt of Shipment Form provided and the form should be returned as instructed on the form. The original form will be retained at the clinical site. In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment and quarantine the shipment until the resolution is obtained from the Sponsor.

At the end of the study, or as directed, all drug products, including unused, partially used, or empty containers, will be destroyed, after full accountability. If drug destruction occurs at the clinical site, this must be approved in writing by the Sponsor and the Sponsor has received copies of the clinical site's drug handling and disposition standard operating procedures (SOPs).

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

The study drug will only be returned to a designee as instructed by the Sponsor if the clinical site is unable to perform the products destruction. Study drug 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, tablets and granule bottles) clinical 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 clinical site.

5.2.6.2. Standard of Care

For both locally sourced SOC and Sponsor-provided SOC, a Drug Accountability Record will be used for the products. It may either be provided by the Sponsor or 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 the central or local 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 study drug dispensed and remaining, if from individual subject drug units, as well as the initials of the dispenser. All unused drug and containers whether provided by the Sponsor or provided locally, must be brought back to the clinical site for accountability to support appropriate dosing instructions to the subject.

At the end of the study, or as directed, all drug products, including unused, partially used, or empty containers, will be destroyed, after full accountability. If drug destruction occurs at the clinical site, this must be approved in writing by the Sponsor and the Sponsor has received copies of the clinical site's drug handling and disposition SOPs). Locally sourced SOC should be destroyed at the clinical site.

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

The study drug will only be returned to a designee as instructed by the Sponsor if the clinical site is unable to perform the products destruction. Study drug 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 clinical site.

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.

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 more than 3 days will have the reason recorded in the electronic case report form (eCRF).

Any study drug interruption due to an adverse event should be reported on the Adverse Event eCRF, even if it is less than 3 days. A patient may have multiple interruptions of treatment throughout their study participation.

5.3.1. Edoxaban Dose Reduction

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

- eGFR is 30-50% of normal for age and size (permanent dose reduction) (Appendix 17.9)

  NOTE: If the repeat measurement confirms the decrease, the edoxaban dose will be reduced permanently. This dose reduction will be permanent even if the subject experiences an improvement in the eGFR during the course of the study.

- Subject is receiving concomitant treatment with P-gp inhibitors (temporary dose reduction)

- Body Weight:

  For subjects 12 to <18 years old with body weight <5th percentile of subject's age (see Appendix 17.11), edoxaban doses will be permanently changed.

  For subjects 12 to <18 years old with body weight ≥60 kg, will receive edoxaban 60 mg. However, if the body weight is ≥30 - <60 kg, edoxaban dose would be 45 mg daily. If the patient body weight ≥60 kg, then edoxaban dose would be escalated to 60 mg daily.

  For subjects <12 years old: Doses will be provided by mg/kg or a dose may be suggested, subsequent to exposure modeling, based on an age range (see Table 5.1).

For subjects receiving P-gp inhibitors during the study treatment period, 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.

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 and/or drug packaging/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 study drug 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 or 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 (UFH, LMWH) treatment arm will be monitored for compliance by measuring anti-FXa levels or aPTT. Compliance should be assessed routinely by the Investigator to ensure the adequate doses are taken (Table 17.1). Monitoring of heparin based treatment or VKA will be performed locally.

5.5. Prior and Concomitant Medications

Medications that the subject has taken within 30 days before screening will be recorded. In addition, anticoagulant and antiplatelet therapy will be recorded up to 3 months prior to randomization.

The following drugs and devices (see Appendix 17.5) 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 should be discontinued
- Single or dual antiplatelet therapy with any antiplatelet agent is prohibited except for low dose aspirin defined as 1 to 5 mg/kg/day with maximum of 100 mg/day. If a clinical indication for antiplatelet therapy (other than low dose aspirin) arises after randomization, study drug should be temporarily interrupted and use of any other anticoagulation therapy is permitted at the physician's discretion.
- Chronic use of oral or parenteral non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 and cyclooxygenase-2 inhibitors other than aspirin for ≥4 days/week. Use of NSAIDs via other routes (eg, topical, inhaled, intranasal, intraocular, etc) are not restricted (see Appendix 17.5.5).

All P-gp inhibitors (please refer to Appendix 17.6.1 for a list of the 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 at Month 1.

5.6. Subject Withdrawal/Discontinuation

Any subject who discontinues from the study treatment for any reason will have his or her 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). The subject should complete the subsequent 30-day Follow-Up Visit (Visit 9) regardless of whether they stop all anticoagulant therapy or are placed on a treatment that they were not assigned to at randomization.

If a subject discontinues from treatment after Month 3 he/she will be discontinued from the study and should still receive a Discontinuation Visit and a 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 [LFT] disturbances, severe renal insufficiency, TE, 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 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. 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 clinical site.

The reasons for discontinuation from treatment must be documented.

If a subject discontinues 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 from study treatment though 3 months of observation.

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

During the Extension Period (beyond 3 months treatment), all subjects who discontinue from the study treatment will also discontinue from the study and will return to the clinical site for a Discontinuation Visit (Visit 8) and a 30-day Follow-Up Visit (Visit 9) after the Discontinuation Visit.

Note: Subjects in the Extension Period do not need to be followed through 12 months of study procedures and can discontinue from treatment and study per Investigator discretion at any time with a Discontinuation Visit after Month 3 and a 30-day Follow-Up Visit after the Discontinuation Visit.

5.6.3. Reasons for Discontinuation from 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):
   - If initiating or continuing study drug places the subject at undue hazard as determined by the Investigator;
   - If the subject had a serious adverse event (SAE) or other safety concern that is related to study drug treatment as determined by the Investigator;
   - If the subject had a major bleeding event as determined by the Investigator;
   - If the subject has an aggravation or new occurrence of renal insufficiency with estimated eGFR <30% of normal for age and size (Cockcroft-Gault equation for pediatric subjects ≥12 years of age and modified Schwartz equation for pediatric subjects <12 years of age);
   - If the subject demonstrates hepatic test abnormalities including:

     Elevation of alanine transaminase (ALT) and/or aspartate transaminase (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.
   - If the subject demonstrates clinical jaundice that requires an immediate interruption of study drug treatment and prompt repeat testing to confirm abnormality;
   - If the subject has 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 Hep 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 TBL elevations.

Subjec t's follow-up will be required on a weekly basis until the values (transaminases and TBL) return to a clinically acceptable level. 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 with prompt submission of the adjudication dossier for events that led to study drug discontinuation or were reported as

SAEs where no alternative etiology has been found after work-up and where causal relationship to study drug cannot be ruled out.

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 whose participation extended beyond Month 3 (Visit 5) will have study procedures terminated at the time of discontinuation from treatment and study with a Discontinuation Visit (Section 6.5.3).

If the subject discontinued study treatment due to an AE, the Investigator will follow the subject until the AE has been clinically 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 visit or Follow-Up Visit is possible. The definition of withdrawal is 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.

Any subject who is withdrawn from the study treatment for any reason will have their reasons for withdrawal records.

Subjects may be withdrawn from the study after signing the informed consent form (ICF) during the Main Treatment Period for the following reasons:

- 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. Withdrawal Procedures

If a subject is withdrawn from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal. Subjects who withdraw from the study during the 3 month Main Treatment Period will also have a 3 month Follow-Up phone call to ascertain any events (TE and/or bleeding events) that may have occurred since withdrawal. The timeframe for the 3-month Follow-Up phone call assessment is from the date of subject randomization.

5.6.6. Procedures for Discontinuation from Treatment or Study; or Withdrawal from Study

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, discontinue from study, 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 study, 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 discontinue from the study treatment or study with an ongoing AE must be followed until the event is deemed resolved or clinically stable even if they are not willing to participate in the study any longer. If a subject discontinues study or withdraws after dosing, all data normally collected prior to study discharge should be collected at the time of discontinuation from study or withdrawal, or 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 clinical site.

If a subject is withdrawn or discontinued from study treatment or study, the IXRS will be called by the clinical site 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, 3-month Follow-Up phone call attempted from date of randomization)
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, in which case a phone call will be attempted)

5.6.7. Follow-Up Procedures.

Subjects who complete the Main Treatment Period (Month 3) but do not continue into the Extension Period, will have a their Month 3 Visit and a Follow-Up Visit 30 days after last dose of study drug and discontinued from the study. Follow-Up Visits may be conducted by phone, however, if the subject experienced an adverse event of concern (Serious) or an endpoint event since their Discontinuation Visit, an office visit is highly recommended.

Subjects who discontinue treatment from the Main Treatment Period prior to Month 3 will continue to be followed monthly according to the Schedule of Events (Appendix 17.1) through the Month 3 visit (Visit 5), and have a 30-day Follow-Up Visit. If treatment discontinuation occurs prior to Month 2 visit, the 30-day Follow-Up Visit will occur on the same day as the Month 3 visit.

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.

5.6.7.1. 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 will have the reason recorded in the eCRF.

5.6.8. 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 rescreened for any particular 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 re-screening. The initial screening information and the reason why the subject is ineligible for the initial evaluation will be uploaded into the electronic data capture (EDC) system.

Re-screening (re-testing of laboratory results) 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, the ICF reviewed, and all questions answered for them. Subjects will undergo procedures specific to study qualification (Section 6.2) 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 2:1 ratio to either the edoxaban-treatment arm or the SOC-treatment arm, respectively, for the first 3 months of the study, after which all subjects will be offered edoxaban at the appropriate dose for age and weight at the time of informed consent

All subjects will undergo evaluation for safety and efficacy evaluations at the EOT at Month 3 with a 30-day Follow-Up. Subjects who discontinue treatment prior to Month 3 will continue with the scheduled visits up to Month 3 with the 30-day Follow-Up. Subjects who participate in the Extension Period will undergo safety and efficacy endpoint evaluations (bleeding events, TE, 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. If treatment discontinuation occurs prior to Month 2 visit, the 30-day Follow-Up Visit will occur on the same day as the Month 3 visit.

Subjects will return to the clinical site on a monthly basis to receive study therapy even if there are no scheduled procedures. This process will ensure subject compliance and accountability for distribution/return of study drug. However, in cases where access to the clinical sites cannot occur monthly after Month 3, accommodations will be made to distribute up to 3 months of study drug to match the 3-month visit schedule.

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

6.1. Note Concerning Echocardiogram

All subjects will have an echocardiogram at study screening to rule out asymptomatic thrombosis. Subjects with evidence of symptomatic venous or arterial thrombosis during study screening period are not permitted in the study. Valid echocardiograms are images taken within 5 weeks prior to Randomization Visit.

A follow-up echocardiogram will be taken at Month 3 to ascertain asymptomatic thrombosis. **IF** there is a symptomatic thrombosis prior to Month 3 which would represent a thrombotic event, it should be documented by the appropriate imaging procedure. A Month 3 echocardiogram will NO LONGER be necessary at Month 3 visit if a symptomatic event was experienced by the subject and was documented by an appropriate image.

In the Extension Period after Month 3, any symptomatic event will be documented and a recommended image captured to support the event. The Month 12 echocardiogram will be optional in all circumstances.

A Month 3 echocardiogram is optional if the subject experiences a symptomatic TE documented by an image. A reported post-Month 3 symptomatic TE should have a supporting appropriate

image. If no symptomatic TE is reported during the Extension Period, the Investigator has the option to perform an echocardiogram at his/her discretion to rule out any asymptomatic TE at study discontinuation.

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

6.2. Screening/Qualification Visit (At Least Day -30 to Day 1, Visit 1)

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

Central laboratory specimens will be collected to determine the baseline qualification of the subject for inclusion/exclusion criteria and evaluation of particular analytes over time across the global study except for INR and aPTT which are performed at the clinical site or local laboratory.

All subjects at the Screening Visit should be assessed for INR and aPTT evaluated at the local laboratory.

Prior to signing the ICF, potential subjects and their parent(s) or guardian(s) will have the study risks and benefits explained, 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) or guardian(s) of all subjects, and assent obtained from the child, when and where applicable, prior to entry into the study.

- The Screening eCRFs must be completed for every subject with a signed ICF. Any protocol-specified study qualification procedures/tests identified for the Screening Visit, not already done as part of routine care within 2 weeks of the Screening Visit will need to be conducted after the parent(s) or guardian(s) signs the ICF as part of the Screening/Qualification Visit.
- The following study qualification procedures for the Screening/Qualification Visit must be completed to ensure that the subject is eligible for the study.

  Review inclusion/exclusion criteria

  Record demographic information (date of birth/age, sex, ethnicity, and race)

  Record medical/surgical history, including:

  - TE history and bleeding history since diagnosis of underlying disease and within the past 3 months
  - Date of diagnosis of underlying disease

  Record prior medication (up to 30 days prior to Screening). Anticoagulant and antiplatelet therapy will be captured up to 3 month prior to Screening Visit

  Assess for and record AEs and concomitant medications.

  Perform physical examination (Section 9.9) 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.])
- Height and body weight (may be performed by an Investigator or other healthcare provider designated by the Investigator).

- An aPTT and INR assessment will be done for all subjects at Screening at local laboratory. Ensure that the subject qualifies with regard to the following central safety laboratory and radiology tests for exclusion criteria:

  Echocardiogram. Note: Valid echocardiograms are images taken within 5 weeks prior to Randomization Visit. Note: The presence of a thrombus will disqualify the subject from the study.

  Liver function assessments (ALT, AST, TBL, ALP) (central laboratory)

  aPTT and INR (assessed locally)

  Serum chemistry panel, serum creatinine, and eGFR (central laboratory)

  Hematology (central laboratory)

  Urinalysis (at central laboratory if dipstick is abnormal)

Note: Urinalysis can be done at local laboratory. Results of urinalysis performed at Screening by local laboratory may be used for qualification

- To expedite qualification and randomization for subjects living a distance from the Investigator site, the site may choose to use their local laboratory for screening eligibility labs. The sample should be split with analysis at both the central laboratory as well as the local laboratory. For the purpose of eligibility, the local laboratory results (aPTT, INR, ALT, TBL, eGFR, and platelet) will be utilized and entered into the eCRF.

If subjects are fulfilling eligibility conditions at the Screening/Qualification Visit, the Investigator has the option to randomize the subject at any time within 30 days. The Screening Visit and Randomization Visit may occur on the same day.

6.3. Randomization (Day 1, Visit 2)

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. If all procedures and tests done before randomization confirm the subject's eligibility (Section 6.2) for the study, then the IXRS will be contacted to randomize the subject.

Urine pregnancy test in females of childbearing potential by definition are those females that have reached menarche and until becoming postmenopausal unless permanently sterile (defined as no menses for 12 months without an alternative medical cause).

Randomization may occur in IXRS the day prior to dosing for clinical logistics. Screening Visit and Randomization Visit may occur on the same day. The first dose of study treatment may occur on Day 1 or Day 2 (see Section 5.2.4)

The following activities should be done at the time of randomization.

NOTE: For therapeutic monitoring of SOC the Investigator will use discretion to decide when and how often to repeat INR or anti-FXa levels or aPTT measurements after randomization. These measurements will be taken and evaluated in the clinic, or alternatively, an optional site-specific local laboratory.

NOTE: For subjects randomized to the edoxaban arm, a blood sample will be collected before the first dose of edoxaban for PD analysis only if the subject did not receive any heparin (UFH or LMWH) or VKA 24 hours prior to randomization.

- PD blood sample for subjects randomized to edoxaban taken before dosing that day
- Discretionary anti-FXa level and/or aPTT measurement for subjects on SOC with heparin and INR assessment for the subjects on SOC with VKA
- Record any prior and/or concomitant medications used since the last visit.
- Record any AEs since screening visit, including any bleeding events.
- Urine pregnancy test (for post-menarchal females)
- Physical examination for body weight only
- Dispense study drug and record amount (number of tablets/bottles) dispensed. Prescription based, locally sourced SOC study therapy will need to be supported by a prescription identifying the type of SOC to be provided;
- Explain the study drugs and the proper daily dosing to the parent(s) or guardian(s) and subject (if applicable) using the study drug dosing calendar, and confirm that the subject understands the proper daily dosing of study drug.
- Instruct subject to bring all medications including study drug packaging and bottles to each visit (monthly visits even if there are no scheduled procedures).
- Complete the QOL Questionnaire. Note the QOL can be filled out by EITHER a parent or the study participant. The same person should complete the QOL at Month 3.

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

The following information may be provided to the parent(s), guardian(s) or subject (information booklet):

- The local medical contact person and emergency telephone number
- The visit schedule
- How to recognize and report signs and symptoms of possible bleeding and thromboembolic events (see Section 7.1 and Section 9.1).
- How to use the study drugs and instructions to keep empty medication packages

- Blood collections for assessing the INR will be dependent on the discretion of the Investigator.
- Provide subjects with a subject identification safety card and a prohibited medication card

6.4. Main Treatment Period

The Main Treatment Period is defined as the time from randomization until the end of Month 3 of treatment. All treatment comparative analyses will be made during this time period.

6.4.1. Subjects Randomized to the Edoxaban-Treatment Arm:

For subjects randomized to the edoxaban arm, a blood sample will be collected before the first dose of edoxaban for PD analysis only if the subject did not receive any heparin (UFH or LMWH) or VKA 24 hours prior to randomization.

6.4.2. Subjects Randomized to the SOC-Treatment Arm:

SOC will be provided by the Investigator. Alternatively, local supply depots within each country will provide SOC directly to the clinical sites. Subjects will be treated with heparin (UFH or LMWH) or VKA according to the site's SOC treatment procedure. However, if there are regulatory or clinical site hurdles providing the SOC, the Sponsor will provide SOC as enoxaparin 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 as a bridging therapy in combination with warfarin during the initial study treatment period.
- For subjects in whom clinicians prescribe warfarin, this will be started on Day 1. Heparin bridging prior to reaching therapeutic levels by INR with warfarin may be performed depending on the clinical site's practice. Bridging therapy will be provided by the Investigator for the short duration. 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. These measurements will be taken in the clinic, or alternatively, optional clinical site-specific local laboratory (Appendix 17.1).

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

Starting with Randomization, 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.

During study drug interruptions and after study drug discontinuation, subjects will be followed for the protocol-specified study procedures to assess the efficacy and safety endpoints and SAEs until the Month 3 visit (Visit 5). If a subject discontinues study drug prior to The Main Treatment

Period completion, the subject will continue to follow the protocol procedures to Month 3 visit and have a 30-day Follow-Up Visit (Visit 9).

At these monthly on-site visits, discretionary anti-FXa levels assessments and/or aPTT measurements will be performed for the subjects on SOC with heparin 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 and/or aPTT and INR monitoring. All therapeutic monitoring of SOC will be performed locally.

6.4.3.1. 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 9.9 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]).

  Height and body weight (may be performed by an Investigator or other healthcare provider designated by the Investigator).
- Urine pregnancy test in females of child bearing potential.
- Take blood samples for the following laboratory tests:

  LFTs (ALT, AST, TBL, and ALP)

  Serum creatinine and eGFR assessment

  PK only (pre-dose)

  PK/ PD blood samples (one time point between 1 and 3 hours post-dose for edoxaban-treated subjects)
- Discretionary anti-FXa level and/or aPTT measurement for subjects on SOC with heparin and INR assessment for the subjects on SOC with VKA.
- Safety review for AEs/SAEs
- Review for symptomatic endpoint events (bleeding, symptomatic TE with supporting imaging)

6.4.3.2. 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 (Section 9.9) 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.])

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

- Urine pregnancy test for females of child bearing potential
- Discretionary anti-FXa level and/or aPTT measurement for subjects on SOC with heparin and INR assessment for the subjects on SOC with VKA.
- Safety review for AEs/SAEs
- Review for symptomatic endpoint events (bleeding, symptomatic TE with supporting imaging)

6.4.4. Month 3 (Visit 5; End of Main Treatment Period) Procedures

All randomized subjects including those that have discontinued treatment prior to Month 3 will have an EOT assessment at Month 3.

Note: if there was a symptomatic thrombotic event experienced by the subject prior to Month 3 documented by the appropriate imaging, a Month 3 echocardiogram is not necessary since the subject has met an event endpoint.

The following will be performed at this visit:

- Perform physical examination (Section 9.9) 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.])

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

- Review concomitant medications
- Count unused study drug tablets/bottles/syringe and calculate compliance
- Safety review for AEs/SAEs
- Review for symptomatic endpoint events (bleeding, symptomatic TE with appropriate imaging)
- Complete the QOL Questionnaire. Note: the QOL can be filled out by EITHER a parent or the study participant. The same person should complete the QOL at Month 3.
- Take samples for the following:

  LFTs (ALT, AST, TBL, and ALP)

Serum creatinine and eGFR assessment

Hematology

Urine pregnancy test (for females of childbearing potential)

- Discretionary anti-FXa level and/or aPTT measurement for subjects on SOC with heparin and INR assessment for the subjects on SOC with VKA
- At the Investigator's discretion to extend the study, dispense edoxaban study drug medication and review dosing instructions per subject/parent(s)/guardian(s)'s request.
- Perform echocardiogram to evaluate presence of asymptomatic thrombosis. Note: if there was a symptomatic event experience by the subject prior to Month 3 documented by the appropriate imaging, a Month 3 echocardiogram is not necessary since the subject has meet an event endpoint.

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

At the Investigator's discretion, study treatment can be extended up to 12 months. All subjects will be offered edoxaban treatment for the duration of the Extension Period based on the Investigator's judgment of the subject's potential thrombotic burden.

For those subjects switching over from SOC to edoxaban in the extension period, the Principal Investigator may use discretion to schedule a visit if necessary and the visit should be documented on the designated Unscheduled page in eCRF.

At any time during the Extension 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 Follow-Up Visit (see Table 17.1).

The subjects on extended treatment will be followed for safety and efficacy assessment including bleeding events, TE occurrence, and AEs/SAEs at visit for Months 6 (Visit 6), 9 (Visit 7), and 12/Discontinuation Visit (Visit 8). Additionally, the subject will have a Follow-Up Visit (Visit 9) for safety assessment 30 days after treatment cessation or following Month 12, whichever is first. At Month 12/Discontinuation Visit, or at any time the subject 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 17.2. The visits will occur every 3 months.

Edoxaban dispensing will occur monthly during the Extended Treatment Period even though protocol study procedures have not been scheduled to ensure dosing compliance and drug accountability. In cases where clinical visit are not possible every month, a 3-month supply of edoxaban may be offered.

6.5.1. Month 6 (Visit 6) Procedures

- Record concomitant medications
- Count unused study drug tablets/bottles to assess compliance
- Dispense study drug medication and review dosing instructions
- Perform physical examination (Section 9.9) 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.])

  Height and body weight (may be performed by an Investigator or other healthcare provider designated by the Investigator).
- Urine pregnancy test for females of child bearing potential
- Review for symptomatic endpoint events (bleeding, symptomatic TE with appropriate imaging)
- Safety review for AEs/SAEs
- Collect blood samples for the following laboratory tests:

  Serum creatinine test

  eGFR assessment

6.5.2. Month 9 (Visit 7) Procedures

- Record concomitant medications
- Count unused study drug tablets/bottles and calculate compliance
- Dispense study drug medication and review dosing instructions
- Perform physical examination (Section 9.9) 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.]

  Height and body weight (may be performed by an Investigator or other healthcare provider designated by the Investigator).
- Urine pregnancy test for females of child bearing potential
- Review for symptomatic endpoint events (bleeding and TE)
- Safety review for AEs/SAEs
- Collect blood samples for the following laboratory tests:

  Serum creatinine

  eGFR assessment

6.5.3. Month 12/Discontinuation Visit (Visit 8; Appropriate for subjects completing Month 12 or treated beyond Month 3 and discontinuing study prior to Month 12)

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

Procedures for subjects who withdraw consent 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.

The following will be performed at this visit:

- Record concomitant medications
- Count unused study drug tablets/bottles and calculate compliance
- Perform physical examination (Section 9.9) 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.])
- Safety review for AEs/SAEs
- Review for symptomatic endpoint events (bleeding and TE)
- Collect blood samples for the following laboratory tests:

  LFTs (ALT, AST, TBL, and ALP)

  Serum creatinine

  eGFR assessment

  Hematology
- Urine pregnancy test for females of child-bearing potential
- Optional echocardiogram to evaluate presence of asymptomatic intracardiac thrombosis based on Investigator's discretion.

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

Follow-Up Visits may be conducted by phone, however, if the subject experienced an AE of concern (Serious) or a symptomatic endpoint event since the Discontinuation Visit (ie symptomatic thrombosis), an office visit is highly recommended. A 30-day Follow-Up Visit will be required for all subjects who:

- Complete the study through Month 3, or
- Have a discontinuation from study any time after Month 3 prior to Month 12, or
- Complete Month 12 visit.

The following will be recorded or collected at the Follow-Up Visit:

- AEs/SAEs
- Review for symptomatic endpoint events (bleeding, symptomatic TE with imaging)
- Concomitant medications

6.7. Required Month 3 Follow-Up Phone Call for Withdrawal Subject Prior to Month 3.

In the Main Treatment Period a Month 3 Follow-Up phone call will be required for all subjects who withdrawal from the study because the assumption is that no additional visit will be conducted. The Follow-Up phone call will occur 3 months after the randomization of the subject (Month 3).

The following will be recorded on the Follow-Up phone call:

- Any symptomatic TE and/or bleeding events during the period of time from withdrawal to the phone call Follow-Up.
- Any AE or serious AE
- Concomitant medications taken.

7. EFFICACY ASSESSMENTS

Details regarding the definitions of the efficacy endpoints and how they will be assessed can be found in the CEC charter. The CEC will adjudicate events in a blinded manner. This adjudication will be independent of the Investigators. The CEC will complete assessments on an ongoing basis, and all information will be recorded in the clinical database.

Subjects with suspected recurrent TE will undergo objective testing to assess the current episode. If possible, a blood sample will be obtained for PD analysis. The following documentation should be sent for adjudication:

- Copies of all diagnostic imaging,
- The TE adjudication worksheets,
- eCRFs documents,
- Source documents including but not limited to hospital discharge summaries, autopsy reports, consultation reports, X-rays/scanning reports, and clinical laboratory reports

7.1. Assessments for Efficacy Endpoint(s)

The efficacy related endpoints are any TE including thrombi in the systemic arterial or venous pathways, intracardiac thrombi, DVT, PE, MI, SEE, and stroke which occurred during the study. This includes symptomatic TE and/or asymptomatic intracardiac thrombus.

Diagnosis of TE should be performed per the clinical site's existing protocol but should include at minimum 1 of the following:

- Asymptomatic intracardiac TE: The presence of an intra-luminal or mural thrombi within the cardiac chambers or surgical pathways on any cross-Sectional imaging modality. Mild laminar thickening of the internal surface of the Fontan pathway is not included. Echocardiography is the preferred modality in this setting.
- Symptomatic SEE (except stroke) which includes: retinal, upper limb and lower limb, mesenteric.
- The presence of cerebral infarction on computed tomography (CT) or magnetic resonance imagining (MRI) (performed after symptoms)
- The presence of symptomatic pulmonary embolism requires meeting 1 or more of the following criteria:

  An intraluminal filling defect in segmental or more proximal branches of the pulmonary artery on multislice CT scan

  A mismatched defect on a nuclear ventilation/perfusion scan compared to the prior imaging,

  A non-diagnostic lung scan accompanied by documentation of new DVT by (Doppler) ultrasonography or venography.

- Symptomatic DVT requires meeting 1 of the following criteria:

A non-compressible venous segment of the peripheral veins on ultrasonography

The presence of an echogenic intra-luminal thrombus or absence of flow in the central venous system on Doppler ultrasonography

An intraluminal filling defect or venous obstruction on venography

An intraluminal filling defect or venous obstruction on CT angiography.

An intraluminal filling defect or venous obstruction on MR venography.

- Death as a result of a thromboembolic event, including pulmonary embolism. All deaths will be adjudicated by the CEC.

  Diagnosis of fatal TE 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 TE cannot be ruled out.

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

Table 7.1: Symptoms of Thrombotic Disorders

Locations	Symptoms
Cardiac embolic stroke/ischemic stroke	• Hemiparesis or focal central nervous system deficit • Change in mental status (lethargy, depressed level of consciousness and coma) • Headache • Seizures (focal, generalized) • Speech disorder, including aphasia and mutism • Nausea, vomiting • Visual impairment (transient obscurations, reduced acuity, blindness) • Neck pain • Fever • Respiratory failure (in neonates) • Jittery movements (in neonates)

Table 7.1: Symptoms of Thrombotic Disorders (Continued)

Locations	Symptoms
Intracardiac thrombus	• Cardiac failure • Fatigue • Embolic event (Stroke, coronary emboli)
Myocardial infarction	• Dyspnea • Palpitations • Chest pain • Pallor • Poor feeding • Cardiac arrest
SEE (except Stroke) Retinal Upper limb and Lower limb Mesenteric	• Vision loss • Pain, pallor, paralysis, pulse deficit, paresthesia, cold limb, intermittent claudication • Acute severe abdominal pain, diarrhea, vomiting
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)

Table 7.1: Symptoms of Thrombotic Disorders (Continued)

Locations	Symptoms
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 • Acute psychiatric symptoms • Respiratory failure (in neonates) • Jittery movements (in neonates) • Hydrocephalus

Table 7.1: Symptoms of Thrombotic Disorders (Continued)

Locations	Symptoms
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 thrombosis	• Palpable flank mass • Macro or micro hematuria • Thrombocytopenia

Abbreviations: CVL = central venous line; VTE = venous thromboembolism

Table 7.2: Recommended Diagnostic Imaging Methods

Locations	Recommended Diagnostic methods
Cardiac embolic stroke/ischemic stroke	• **Magnetic resonance imaging (MRI) with diffusion-weighted imaging** Alternative Imaging Techniques: Magnetic resonance angiography (MRA) Computed tomography angiography (CTA) In case of suspected cardiac embolic stroke, an echocardiogram imaging should be performed
Intracardiac thrombus	• **Echocardiography** Alternative Imaging Techniques MRI Transesophageal echocardiography

Table 7.2: Recommended Diagnostic Imaging Methods (Continued)

Locations	Recommended Diagnostic methods
Myocardial infarction	• **Echocardiography** • **Angiography**
SEE (except Stroke	• **CTA** • **US/Doppler** • **Echography**
VTE in upper limb (CVL or non-CVL related)	• **Ultrasonography (US) for peripheral upper limb as axillary, subclavian and jugular veins** Alternative Imaging Techniques: MRI with venography (MRV) for central intra-thoracic veins Multi-detector CT venography (MDCT venography)
VTE in lower extremity (CVL or non-CVL related)	• **Doppler US (± repeated 1 week)** Alternative Imaging Techniques: MRV
Catheter-related thrombosis	• **Doppler US** • **Echocardiography** Alternative Imaging Techniques: Conventional venography MRV
Pulmonary embolism	• **V/Q scanning** • **Spiral CT pulmonary angiography (CTPA)** Alternative Imaging Techniques: Cardiac angiography Conventional pulmonary angiography Echocardiography/ transesophageal Magnetic resonance pulmonary angiography

Table 7.2: Recommended Diagnostic Imaging Methods (Continued)

Locations	Recommended Diagnostic methods
Sinovenous thrombosis	• **Brain MRI including T2 imaging and MRI with venography (MRV)** Alternative Imaging Techniques: Pre and post-contrast CT scan with venography (CTV) Doppler flow US; if fontanelle open
Renal vein thrombosis	• **Doppler/US**
Splanchnic and hepatic veins and vena cava	• **Doppler/US** Alternative Imaging Techniques: CT Scan

Abbreviations: CT = computed tomography; CTV = CT scan with venography; CVL = central venous line; MDCT = Multi-detector CT; MRI = magnetic resonance imaging; MRV = MRI with venography; VTE = venous thromboembolism

7.2. Appropriateness of Selected Efficacy Assessment(s)

The primary and secondary safety and efficacy endpoints respectively, were selected based on the current Food and Drug Administration/EMA's Pediatric Committee (PDCO) guidance on anticoagulant indications. The guidance recommends that adjudicated events for bleeds and TEs be assessed as outcomes as a consequence of treatment with anticoagulants.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

The timing and handling of blood samples for edoxaban-treated subjects for PK assessments and PD biomarkers are defined in Appendix 17.1. Plasma levels of edoxaban and its metabolite, D21-2393, will be measured from subjects in the edoxaban-treatment arm. The primary PD biomarkers, anti-FXa activity will be assayed from all edoxaban-treated subjects. For all sample collections, the study staff will record the date and time of last dose of study drug before sample collection and the date and time of the sample collection on the CRF. In addition, for PK samples, the date and time of the last meal before sample collection must be recorded onto both the eCRF and the laboratory accession form.

8.1. Pharmacokinetic (PK) Assessment(s)

Up to 3 samples will be collected from subjects in the edoxaban-treatment arm over the course of the study for edoxaban and D21-2393 analysis. Samples should be collected tubes with lithium heparin as anticoagulant.

The following blood samples for PK will be collected at Month 1 Visit:

- 1 sample before the dose,
- 1 sample between 1 to 3 hours after the dose at the Month 1 visit,
- If applicable, 1 sample at an event classified as TE or major or CRNM bleeding

Note: It is critical to record the date/time of the last dose as well as the date/time of the last meal prior to each PK sample collection. Collection information will be guided by the case report forms and guidelines.

8.2. Pharmacodynamic (PD) Assessment(s)

If blood volume restriction allows, blood samples will be collected from edoxaban-treated subjects for assessment of PD biomarkers at the following time points:

- Day 1 (at Randomization): one sample prior to first dose of edoxaban in tubes with citrate sodium as anticoagulant
- Month 1 Visit: one sample between 1 to 3 hours after the edoxaban dose at the Month 1 Visit at the time of PK specimen
- If applicable, 1 sample at an event classified as TE or major or CRNM bleeding

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

8.3. Biomarker Assessment(s)

Additional testing from the above of other biomarkers related to coagulation and/or of the mechanism of action of edoxaban may be done in the future.

8.4. Immunogenicity

Not applicable.

8.5. Pharmacogenomic Analysis

Not applicable.

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoint(s)

The safety endpoints related to safety objectives are bleeding events, including major, clinical relevant non-major and minor bleeding. All potential bleeding events 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.

Bleeding definitions are based on the ISTH modified recommendations[1],

- 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 cells.

- A CRNM bleed is an 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, or

  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 any other overt bleeding event that does not meet criteria for either major bleeding or clinically relevant, non-major bleeding.

Minimal criteria defining a significant bleeding per ISTH[10] 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 (gastrointestinal 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.

9.2. Adverse Event Collection and Reporting

In the event of a medical emergency, the Investigator at the clinical 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 ICF 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, lead to 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. 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.

The Investigator must 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 SAE (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 ICF) 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.

9.3. Adverse 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 and/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 clinical 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 Serious Adverse Events Reporting 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.

An Independent Data Monitoring Committee (IDMC) may recommend termination of the study. Termination may be made for any of the following reasons:

- Concerns about significantly higher bleeding risk relative to 1 of the study arms,
- Concerns about drug-induced liver injury,
- Any other safety concerns based on benefit/risk evaluation by the IDMC.

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 SAE 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 ICF) 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 subject/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 or drugs if a combination is administered 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 over-the-counter 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, and adverse events of special interest 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 clinical 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.

Fatal or life-threatening serious events that are also efficacy or safety endpoints will be reported as an expedited report to the regulatory agencies. Events such as MI, SEE, stroke, VTE, and PE and/or safety endpoints such as bleeding events (which are not life-threatening or fatal) will be exempted from SAE processing and expedited reporting. 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 Event Report 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 for SAE or hepatic events meeting the criteria, summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. 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 clinical site 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 Inc. 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 clinical sites or other studies of the study drug, as appropriate per local reporting requirements. Daiichi Sankyo Inc. and/or CRO will comply with any additional local safety reporting requirements.

In the United States, 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 states, it is the Sponsor's responsibility to report SUSARs to all ECs.

9.7. Exposure In Utero During Clinical Studies

Daiichi Sankyo Inc. must be notified of any subject who becomes pregnant while receiving or 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

To expedite qualification and randomization for subjects living a distance from the Investigator site, the site may choose to use their local laboratory for screening eligibility labs. The sample should be split with analysis at both the central laboratory as well as the local laboratory. For the purpose of eligibility, the local laboratory results will be utilized and entered into the eCRF.

Blood and urine samples (if abnormal by dipstick) 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.

9.8.1. Hematology

The ethylenediaminetetraacetic acid tube of blood will be drawn for the hematology assessments listed in. 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 and performed at the Screening Visit.

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

Table 9.2: Serum Chemistry

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

[a] Serum creatinine will be measured at Screening and On-Treatment Study Visits (Months 1, 3, 6, 9 and Month 12/Discontinuation)

9.8.3. Liver Function Test

The LFT will include alanine aminotransferase (ALT), aspartate aminotransferase (AST), TBL, and ALP. The LFT will be measured at Screening and on-treatment study visits at Months 1 (Visit 3), 3 (Visit 5), and 12 (Visit 8).

9.8.4. Estimated Glomerular Filtration Rate (eGFR) Assessment

Estimated glomerular filtration rate (eGFR) will be estimated from serum creatinine (Appendix 17.9). The eGFR assessment will be done at Screening (Visit 1), Month 1 (Visit 3), 3 (Visit 5), 6 (Visit 6), 9 (Visit 7), and 12/Discontinuation (Visit 8). Samples taken at the Screening Visit should be split to allow for central laboratory analysis and local laboratory analysis for qualification.

9.8.5. Urinalysis

Standard urinalysis using a dipstick will be conducted for all subjects at the Screening /Qualification Visit (Visit 1) (Table 9.3). The urinalysis will only be done at Screening (Visit 1).

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 positive findings on macroscopic analysis (dipstick), urine microscopic examination for red blood cells, white blood cells, bacteria, and casts should be performed at the central laboratory.

9.8.6. Hepatitis Serology

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),
- Antinuclear antibody (ANA) and anti-SmAb,
- Cytomegalovirus (CMV) and Epstein-Barr virus (EBV)

9.8.7. Urine Pregnancy Testing

All female subjects must have a negative urine pregnancy test at randomization and each of the specified visits. A highly sensitive urine pregnancy test will be performed at the Randomization Visit (Day 1), On-Treatment Study Visits (Month 1 [Visit 3], Month 2 [Visit 4], Month 3 [Visit 5], Month 6 [Visit 6], Month 9 [Visit 7] and Month 12 [Visit 8])/ Discontinuation Visit.

9.8.8 Monitoring of SOC Therapeutic Level

Routine monitoring of subjects on VKA (INR) or heparin based therapy (Anti-FXa, aPTT) after randomization is performed locally and up through Month 3.

9.9. Physical Examination

Physical examination will be conducted for all scheduled visits except Randomization Visit and includes:

- Height and body weight

  This may be performed by an Investigator or other healthcare provider designated by the Investigator.

- Vital signs including blood pressure, 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.

- An assessment of each of the relevant major body systems.

Information will be entered in the case report form, date of measurement, and measurement results for systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, height, body weight, and body mass index (BMI).

9.10. Electrocardiograms

Not applicable.

9.11. Other Examinations

Not applicable.

10. OTHER ASSESSMENTS

A pediatric QOL questionnaire will be issued at randomization and at the end of the treatment period (Month 3, Visit 5) to assess such categories as: health and activities, feelings about themselves, relationships with others, and school behavior. Note the QOL can be filled out by EITHER a parent or the study participant. The same person should complete the QOL at Month 3.

PedsQL version 4.0, generic core scale will be used in the study. The Sponsor will provide a hard copy of the questionnaire. Data will be entered into the EDC.

The following questionnaires will be used:

- Adolescent (13-18) Self report
- Adolescent (13-18) Parent report
- Child (8-12) Self report
- Child (8-12) Parent report
- Young child (5-7) Self report
- Young child (5-7) Parent report
- Toddler (2-4) Parent report

11. STATISTICAL METHODS

11.1. General Statistical Considerations

All efficacy analyses will be based on the modified intention-to-treat (mITT) Analysis Set and will be performed based on the treatment group assigned at randomization.

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

All analyses for the Extension Period will be based on subjects who participate in the Extension Period and take only edoxaban in the Extension Period, in the specified analysis set, and will be summarized for the edoxaban treatment group. Data listings will be prepared for subjects who are randomized to the SOC arm, participate in the Extension Period, and do not switch to edoxaban right after the Month 3 Visit.

All confidence intervals will be descriptive and will be two-sided 95% confidence interval (CI), unless otherwise specified.

Unless otherwise specified, the baseline value of an efficacy variable for a subject is the last non-missing measurement before the randomization, 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 group.

There is no formal statistical interim analysis planned. However, after the first 50 subjects enrolled in the edoxaban treatment group and 25 subjects enrolled in the SOC treatment group complete the first 3-month treatment period, an interim assessments by IDMC of safety endpoints will be performed to allow for enrollment of subjects <1 year of age into study.

11.2. Analysis Sets

Randomized Analysis Set will include all subjects who sign the ICF and are randomized.

Safety Analysis Set will include all subjects in the Randomized Analysis Set who received at least 1 dose of study drug. Analysis will be based on the study drug the subject actually received.

mITT Analysis Set will include all subjects in the Randomized Analysis Set who received at least 1 dose of study drug. Analysis will be based on the study drug the subject was randomized to receive.

PK Analysis Set will include all subjects in the Safety Analysis Set who had at least 1 PK sample with measurable concentration.

PD Analysis Set will include all subjects in the Safety Analysis Set who had at least 1 measurable PD sample.

11.3. Study Population Data

Subject disposition will be summarized by treatment group and in total for the Main Treatment Period and for the edoxaban treatment group for the Extension Period, respectively, for the Randomized Analysis Set. The number and percentage of randomized subjects who discontinued treatment prematurely will be tabulated by the main reason for discontinuation by treatment group for the Main Treatment Period and for the Extension Period.

The number of subjects for each defined analysis set will also be tabulated by treatment group as well as in total for the Main Treatment Period and for the Extension Period, respectively.

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

The demographic and baseline characteristics such as age, sex, race, height, weight, calculated BMI, type of underlying disease, taking concomitant aspirin or not at baseline, and primary and secondary prevention will be summarized descriptively for the mITT and Safety Analysis Sets. The demographic and baseline characteristics will also be summarized for subjects who participate in the Extension Period.

Study drug exposure and study duration will be summarized using descriptive statistics for the Safety Analysis Set by treatment group for the Main Treatment Period and the Extension Period. Edoxaban compliance will also be summarized using counts of tablets/ bottles. SOC compliance will be summarized by Percent time in therapeutic INR range for subjects who receive VKA or anti-FXa level for subjects who receive heparin.

Medical history will be summarized for the Safety Analysis Set. Prior medication will be summarized by treatment for the Safety Analysis Set. Concomitant medication will be summarized by treatment for the Safety Analysis Set for the Main Treatment Period and for the Extension Period.

11.4. Statistical Analysis

11.4.1. Efficacy Analysis

All confidence intervals will be two-sided 95% confidence intervals, unless stated otherwise.

11.4.1.1. Secondary Efficacy Analysis

The TE stated in this Section, include symptomatic thrombi in the systemic arterial or venous pathways (DVT, PE, stroke, SEE, intracardiac thrombus, and MI), and asymptomatic intracardiac thrombus identified by cardiac imaging.

The following secondary efficacy endpoints will be summarized by treatment group using incidence, and annualized event rate for both the Main Treatment Period and the Extension Period, as well the rate difference between edoxaban and the comparator with the corresponding 95% CI for the Main Treatment Period. The incidence of each component will also be summarized by treatment group. This analysis will be based on CEC adjudicated results.

- The combination of symptomatic TE in the systemic arterial or venous pathways including DVT, PE, stroke, SEE, intracardiac thrombus, MI, and asymptomatic intracardiac thrombus identified by cardiac imaging that occur from randomization to the Month 3 Visit.
- Deaths as a result of TE that occurs from randomization to the Month 3 Visit.
- All-cause mortality occurring from randomization to the Month 3 Visit.
- The combination of symptomatic TE in the systemic arterial or venous pathways including DVT, PE, stroke, SEE, intracardiac thrombus, and MI, and asymptomatic intracardiac thrombus identified by cardiac imaging, which occur from the day after the Month 3 Visit to the date of last dose of study drug plus 30 days for subjects who participate in the Extension Period.
- Deaths as a result of TE that occurs from the day after the Month 3 Visit to the date of last dose of study drug plus 30 days for subjects who participate in the Extension Period.
- All-cause mortality which occur from the day after the Month 3 Visit to the date of last dose of study drug plus 30 days for subjects who participate in the Extension Period.

11.4.1.2. Exploratory Efficacy Analysis

The combination of symptomatic TE and asymptomatic intracardiac thrombus, deaths as a result of TE, and all-cause mortality will also be analyzed for periods and subjects below:

- Events from randomization to the date of last dose of study drug plus 30 days for subjects who do not participate in the Extension Period
- Events from the day after the Month 3 Visit to the data of last dose of study drug for subjects who participate in the Extension Period
- Events occurring from randomization to the Month 3 Visit or to the date of last dose of study drug plus 3 days if study treatment is discontinued in the Main Treatment Period, whichever is earlier.

To assess the efficacy for intra-patient between the Main Treatment Period and previous anticoagulant regimen, TE history since diagnosis of underlying disease and within the prior 3 months to randomization will be collected. The incidence of TE and annualized event rate in the 3 months prior to randomization and during the Main Treatment Period will be calculated for subjects who have both pre-randomization and post-randomization data available. This analysis will be based on Investigator-reported events.

To compare edoxaban regimen with available existing historical control data, a literature review and a search for registered clinical trials with similar endpoints will be conducted. The available results of control data will be extracted and tabulated together with the results of the Main Treatment Period from this study.

TE will also be classified as primary prevention events and secondary prevention events based on thrombosis history, and summarized by treatment group for events occurring during the Main

Treatment Period and from the day after the Month 3 Visit to the date of last dose of study treatment plus 30 days, respectively. Due to the small sample size of the study, further stratification by primary and secondary prevention is not feasible. Hence, caution is needed in the interpretation of the result, especially when imbalance occurred between two groups.

11.4.2. Pharmacokinetic/Pharmacodynamic/Biomarker Analyses (Edoxaban Subjects Only)

Plasma concentration and biomarker data will be summarized by age, dose and time point using descriptive statistics. The plasma concentration data will be pooled with data from other studies for a population PK analysis using nonlinear mixed effects modeling.

Exposure-response relationships will be evaluated for the safety and efficacy endpoints through a model based approach, if data allow, and will be reported separately.

Pharmacokinetic and pharmacodynamics data will be analyzed separately and reported separately. The plasma concentrations of edoxaban and its metabolite, D21-2393, as well as the PD measures will be listed and summarized by age, dose and time point.

11.4.3. Safety Analysis

11.4.3.1. Analysis of Bleeding Events

The primary safety endpoint is the composite of major and CRNM bleeding events that occur during the Main Treatment Period: from the date of first dose of study drug to the Month 3 Visit, or to the date of last dose of study drug plus 3 days if study treatment is discontinued, whichever is earlier. This analysis will be based on CEC adjudication results.

The time to major or CRNM bleeding occurring during the Main Treatment Period will be compared between treatment groups for subjects in the Safety Analysis Set, using the Cox proportional hazards regression model with treatment group, concomitant usage of aspirin at baseline, and underlying disease (Kawasaki disease, Fontan surgery, heart failure or Other) as covariates. Hazard ratio between edoxaban and SOC treatment group will be calculated with corresponding 95% CI. The incidence, annualized event rate, and rate difference between edoxaban and SOC treatment groups will also be calculated.

In addition, incidence, annualized event rate and rate difference between edoxaban and SOC treatment groups with corresponding 95% CI will be calculated for following endpoints for Safety Analysis Set for the Main Treatment Period. Incidence and annualized event rate will also be calculated for the following endpoints occurring from the day after Month 3 Visit to date of last dose of study drug plus 30 days in the Extension Period.

- Major and CRNM bleeding event combined
- Major bleeding event
- All bleeding event (major, CRNM, and minor bleeding combined)

The above 3 categories of bleeding endpoints will also be summarized for the periods and subjects below:

- Incidence, annualized event rate, and rate difference will be calculated for events occurring from the date of first dose of study drug to the date of last dose of study drug plus 30 days for subjects who do not participate in the Extension Period.
- Incidence and annualized event rate will be calculated for events occurring from the day after Month 3 Visit to the data of last dose of study drug for subjects who participate in the Extension Period.

To assess the safety for intra-patient between the Main Treatment Period and previous anticoagulant regimen, bleeding history since diagnosis of underlying disease and within the past 3 months of randomization will be collected. The incidence of bleeding events and annualized event rate in the 3 months prior to randomization and during the Main Treatment Period will be calculated for the subjects who have both pre-randomization and post-randomization data available. This analysis will be based on Investigator reported events.

To compare edoxaban regimen with available existing historical control data for bleeding, a literature review and a search for registered clinical trials with similar endpoints will be conducted. The available results of control data will be extracted and tabulated together with the results of the Main Treatment Period from this study.

11.4.3.2. Analysis of Hepatic Events

The analysis of hepatic events will be based on CEC adjudication results. All CEC adjudication confirmed hepatic events will be summarized for the characteristics of the hepatic events by treatment group for the Main Treatment Period and for the Extension Period.

11.4.3.3. Adverse Event Analyses

Treatment-emergent AEs (TEAEs) are defined as AEs that occur, having been absent before the study treatment administration, or worsen in severity after the initiation of study treatment administration.

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

The number and percentage of subjects reporting TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment group for the Main Treatment Period and for the Extension Period. TEAEs will be further summarized by severity and relationship to study drug. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs leading to discontinuation from study treatments and death events.

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

11.4.3.4. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation and by treatment group for the Safety Analysis Set, as well as for the change from baseline for the parameters which planned to collect both at baseline and post-baseline in the Main Treatment Period. The baseline value is defined as the last non-missing value before the

initial administration of study treatment. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the Month 3 Visit.

Similar summaries will also be provided for clinical laboratory results by scheduled time of evaluation during the Extension Period, as well as for the change from Month 3 Visit to the visits after Month 3.

Abnormal clinical laboratory results will be included a by-subject data listing.

11.4.3.5. Vital Sign Analyses

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

Similar summaries will also be provided for vital signs by scheduled time of evaluation during the Extension Period, as well as for the change from Month 3 Visit to the visits after Month 3.

11.4.4. Other Endpoint Analysis

Descriptive statistics for QOL score at baseline and Month 3 will be summarized for each question, each dimension, and overall by treatment group and QOL specified age group for Safety Analysis Set.

11.5. Interim Assessment

No formal statistical interim analysis is planned. However, an interim assessment by the IDMC of safety endpoints of the study will take place after the first 50 subjects in the edoxaban treatment group and 25 subjects in the SOC arm from 1 to <18 year of age complete the first 3 months of treatment. This will allow for enrollment of subjects <1 year of age.

11.6. Sample Size Determination

A sample size of 150 subjects was chosen for this study. This study is not a powered study intended to draw conclusions based on statistically significant differences between edoxaban and SOC. An adequately powered study would be unachievable due to the significantly large sample size required and the enormous challenge to enroll these pediatric patients. Although the sample size is not based on statistical consideration, assuming major and CRNM bleeding event rates (which are the primary endpoints for this study) are the same as observed in adult Hokusai-VTE Study, (ie, 8.5% and 10.3% in edoxaban and SOC arms, respectively); with 100 subjects in edoxaban arm and 50 subjects in standard of care arm, the 95% CI around the point estimate of the risk difference between edoxaban and SOC is -11.8%, 8.2%..

11.7. Statistical Analysis Process

The clinical study will be analyzed by the Sponsor or its agent/CRO.

The statistical analysis plan (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 (SAS Institute, Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURANCE

12.1. Monitoring and Inspections

The Sponsor or designee's Medical 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 International Council for Harmonization (ICH) Good Clinical Practice (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 clinical 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 clinical site 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 EDC. 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 EDC 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 clinical sites, 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.

SAEs 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 Medical Dictionary for Regulatory Activities. All prior and concomitant medications will be coded using World Health Organization 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 ICFs, 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 clinical site (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 clinical site 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, ICFs, 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 IRB/EC and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at clinical site, 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 ICH consolidated Guideline E6 for 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 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 IRB/EC 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 clinical site. 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.

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's 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 clinical site 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 authority 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(ies), 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 IRBs/ECs 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 IRB/EC. 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 Inc. 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 clinical sites in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments are documented in a Summary of Changes section in the protocol amendment. 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 clinical site(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 Independent Data Monitoring Committee (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

An Independent Data Monitoring Committee (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 cardiovascular mortality, and all-cause mortality etc.

Further details concerning the IDMC responsibilities, structure, and the frequency of committee meetings are elaborated in the IDMC charter. Briefly the IDMC will meet to review the study safety data when 10%, 25%, 50%, and 75% of subjects complete Month 3 of any study treatment. In addition, the IDMC will review the edoxaban exposure analysis from the U157 study in addition to the safety data from each age cohort to approve the proposed dose for the same age cohort in the U313 study.

Additionally subjects less than 1 year of age will be admitted to the study after the review by the IDMC of safety data of 50% subjects in 1 to <18 years of age group who have completed the Main Treatment Period of 3 months (50 subjects in edoxaban arm and 25 subjects in SOC arm).

15.10. Clinical Events Committee

An independent study specific CEC will review and adjudicate key endpoint events (bleedings, all types of TE, stroke, MI, deaths, liver enzyme abnormalities requiring study drug discontinuation) without unblinding. Endpoints reported during telephone contacts will also be adjudicated.

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 academic and clinical guidance on study implementation and conduct of the study, and interpretation of results as specified in the Committee Charter. It may consist of Principal Investigator(s), and/or key opinion leaders, 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 regularly updated as necessary.

15.12.1. Sponsor's Responsible Medical Officer and Clinical Study Leader

PPD

Senior Medical Director, Clinical Development, Specialty Medicine

Daiichi Sankyo Inc.

211 Mount Airy Road

Basking Ridge, NJ 07920

PPD

15.12.2. Sponsor's Safety Contacts

PPD

Senior Director, Clinical Safety and Pharmacovigilance

Daiichi Sankyo UK Ltd.

Chiltern Place, Chalfont Park, Gerrards Cross, SL9 0BG • United Kingdom

PPD

15.12.3. CROs

IQVIA, Inc.

5927 South Miami Boulevard

Morrisville, NC 27560

Telephone No: PPD

15.12.4. EDC Partner

Chiltern International Inc.

3147 South 17th Street, Suite 300

Wilmington, North Carolina 28412

Telephone No: PPD

15.12.5. IXRS Partner

Suvoda

181 Washington Street, Suite 100

Conshohocken, PA 19428

Telephone No: PPD

PPD

15.12.6. Central Laboratory Partner

Q2 Solutions North America (a Quintiles Quest Joint Venture)

Q2 Solutions

27027 Tourney Road, Suite 2E

Valencia, CA 91355

15.12.7. PD Biomarkers

Medpace Reference Laboratories

5365 Medpace Way

Cincinnati, OH 45227

15.12.9 PK Samples All Countries

Q2 Solutions

19 Brown Road

Ithaca, NY 14850

USA

15.12.10 Sponsor's Biostatistician

PPD (Associate Director, Biostatistics, Biostatistics and Data Management)

Daiichi Sankyo Inc.

211 Mt. Airy Road

Basking Ridge, NJ

Telephone No: PPD

15.12.11 Drug Labeling, Packaging and Distribution

Fisher Clinical Services Inc.

7554 Schantz Road

Allentown, PA 18106

Telephone No: PPD

16. REFERENCES

1. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; (3)692 4.
2. Giglia TM, Bulas DI, Sell JE, et al. Thrombotic complications in a pediatric cardiovascular surgery population: a nine-year experience [abstract]. J Am Coll Cardiol. 2001;37:465A.
3. Manlhiot C, Menjak IB, Brandão LR, et al. Risk, clinical features, and outcomes of thrombosis associated with pediatric cardiac surgery. Circulation. 2011;124:1511 1519.
4. Monagle P, Cochrane A, Roberts R, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. J Am Coll Cardiol. 2011;58(6):645-51.
5. DU176b Investigator's Brochure Version 16.0. 13 June 2016.
6. Young G. Diagnosis and treatment of thrombosis in children: general principles. Pediatr Blood Cancer. 2006;46:540 546.
7. Chalmers EA. Epidemiology of venous thromboembolism in neonates and children. Thrombosis Research. 2006;118:3 12.
8. Nowak-Göttl U, Kosch A, Schlegel N, et al. Thromboembolism in children. Curr Opin Hematol. 2002;9:448 453.
9. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for industry: drug-induced liver injury: premarketing clinical evaluation. (October, 2007). Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072278.pdf.
10. Rodeghiero F, Tosetto A, Abshire T, Arnold DM, Coller B, James P, Neunert C, Lillicrap D, ISTH/SSC joint VWF and Perinatal/Pediatric Hemostasis Subcommittees Working Group. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. J Thromb Haemost 2010; 8: 2063 5.
11. CHEST 2012; 141(2)(Suppl):e737S e801S.

17. APPENDICES

17.1. Schedule of Events

Table 17.1: Schedule of Events

Study Period	Screening/ Qualification Visit[a]	Randomization[a]	On-Treatment Study Visits						Required 30-Day Follow-Up Visit[b]
			Main Treatment Period			Extension Period (Optional)			
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Day	**At least Day -30 to Day 1**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12/ Discontinuation Visit[c]**	**30 Days After Last Dose of Study Drug or Discontinuation Visit**
Visit Window[d]			**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
IXRS Transaction	X		X	X	X	X	X	X	
IXRS Randomization		X							
Study Informed Consent	X								
Review Inclusion/ Exclusion Criteria	X								
Record Demographic Information	X								
Record Medical/Surgical History	X								
Record Prior and Concomitant Medications	X[e]	X	X	X	X	X	X	X	X
Perform Physical Examination (Vital signs and Body Height/Weight Assessments)[f]	X		X	X	X	X	X	X	
Measure Body Weight Only		X							
Liver function assessment (ALT, AST, TBL, ALP)[g]	X		X		X			X	
Serum Creatinine/eGFR assessment	X		X		X	X	X	X	
Serum Chemistry Panel excluding creatinine	X								

Table 17.1: Schedule of Events (Continued)

Study Period	Screening/ Qualification Visit[a]	Randomization[a]	On-Treatment Study Visits						Required 30-Day Follow-Up Visit[b]
			Main Treatment Period			Extension Period (Optional)			
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Day	**At least Day 30 to Day 1**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12/ Discontinuation Visit[c]**	**30 Days After Last Dose of Study Drug or Discontinuation Visit**
Visit Window[d]			**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Screening: aPTT, INR[h]	X[h]								
Post-randomization: INR, Anti-FXa, aPTT, Assessment on SOC[i]		……. X ……..							
Echocardiogram[j]	X				X			Optional X	
Hematology	X				X			X	
Urinalysis	X								
Urine Pregnancy Test[k]		X	…….. X ……..						
QOL Questionnaire[l]		X			X				
AE/SAE Reporting[m]	**…….……..…… X ……..……**								
Endpoints Reporting (Bleeding, TE)[n]	**…….…… X ……...……**								
Study Drug Dispensing via IXRS		X	X	X	X	Dispense on a monthly basis after Month 3 visit or optional 3 month distribution of edoxaban to match visit interval			
Study Drug Compliance			X	X	X	Assess on a monthly basis after Month 3 visit or at the next scheduled visit if 3 month drug dispense is used			

Table 17.1: Schedule of Events (Continued)

Study Period	Screening/ Qualification Visit[a]	Randomization[a]	On-Treatment Study Visits						Required 30-Day Follow-Up Visit[b]
			Main Treatment Period			Extension Period (Optional)			
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Day	**At least Day 30 to Day 1**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12/ Discontinuation Visit[c]**	**30 Days After Last Dose of Study Drug or Discontinuation Visit**
Visit Window[d]			**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
PK Sampling[o]			X						
PD Sampling[p]		X[p]	X						

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; CRNM = clinically relevant non-major; eCRF = electronic case report form; FXa = activated Factor X; INR = international normalized ratio; IXRS = Interactive Web/Voice Response System; LIFT = liver function test; LMWH = low molecular weight heparin; PD = pharmacodynamics; PK = pharmacokinetics; QOL = Quality of Life; SAE = serious adverse event; SOC= standard of care; TBL = total bilirubin; TE = thromboembolic events; UFH = unfractionated heparin; ULN = upper limit of normal; VKA = vitamin K antagonist.

[a] Randomization may occur in IXRS the day prior to dosing for clinical logistics. Screening and Randomization may occur on the same day. The site may choose to use their local laboratory for screening eligibility labs. The sample should be split with analysis at both the central laboratory as well as the local laboratory. For the purpose of eligibility, the local laboratory results will be utilized and entered into the eCRF.

[b] Follow-Up Visit will be performed 1 month after the subject completes the study (Month 3 or Month 12) or 30 days after discontinuation from study in the Extension Period. If discontinuation occurs prior to Month 2 visit, Month 3 visit will be combined with 30-day Follow-Up Visit. Follow-Up Visits may be conducted by phone, however, if the subject experienced an adverse event of concern (Serious) or a symptomatic endpoint event since their Discontinuation Visit, an office visit is highly recommended.

[c] If a subject completes the Main Treatment Period and discontinues from the study after Month 3 but prior to Month 12, a study visit is required at that time and will be referred to as the Discontinuation Visit.

[d] Scheduling of visits within windows should be done with caution to the drug supply available in a dispensing unit. Randomization may be performed the same day as the Screening/Qualification Visit.

[e] Prior medications include 30 days prior to Screening/Qualification Visit. Record anticoagulant and/or antiplatelet therapy up to 3 months prior to Screening Visit.

[f] Targeted physical examination performed by an Investigator or other healthcare professional designated by the Investigator. Vital signs include blood pressure, 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).

[g] Hepatitis serology will be performed if a combination of LFT and TBL abnormalities which define Hy's Law cases as ALT and/or AST ≥3 × ULN with TBL ≥2 × ULN.

[h] aPTT and INR assessment will be done for all subjects at local laboratory.

[i] Discretionary anti-FXa levels assessments and/or aPTT measurements will be performed locally for the subjects on SOC with heparin (UFH or LMWH) and INR assessments will be performed locally for the subject on SOC with VKA. Additional interim unscheduled visits may be performed at the Investigator's discretion to assess VKA therapeutic levels (2-3) based on INR and to assess LMWH or UFH therapeutic blood levels based anti-FXa activity (and/or) aPTT.

[j] Note: Valid screening echocardiograms are images taken within 5 weeks prior to Randomization Visit. A Month 3 echocardiogram is optional if the subject experiences a symptomatic TE documented by an image. A reported post-Month 3 symptomatic TE should have a supporting appropriate image. If no symptomatic TE is reported during the Extension Period, the Investigator has the option to perform an echocardiogram at his/her discretion to rule out any asymptomatic TE event at study discontinuation.

[k] Highly sensitive urine pregnancy test to be performed for females of childbearing potential.

[l] Only the parent or study participant will fill out the form. The same person will fill out the QOL questionnaire at the Screening Visit and Month 3.

[m] AE/SAE reporting should occur throughout the study and not be restricted to specific visits.

[n] Symptomatic endpoint events should be reported as soon as site personnel learn of the event. Symptomatic endpoint event surveillance with supporting imaging should occur throughout the study and not be restricted to specific visits.

[o] Only for subjects receiving edoxaban. In addition, one sample will be taken at for every AE classified as a TE, or major or CRNM bleeding. PK samples will be collected pre-dose and 1 to 3 hours post-dose.

[p] At Day 1, Visit 2 (at Randomization), one PD sample will be collected prior to first dose of edoxaban in tubes with citrate sodium as anticoagulant and at Month 1 Visit 3, one sample will be collected between 1 to 3 hours after the edoxaban dose at the same time of PK specimen. For subjects randomized to the edoxaban arm, a PD blood sample will be collected only if the subject did not receive any heparin (UFH or LMWH) or VKA within a 24-hour wash-out period prior to randomization.

17.2. Recommendations per CHEST 2012 Guidelines[11]

Table 17.2 shows the initial treatment and prophylactic doses of LMWH that are used in pediatric subjects based on age.

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 q 12h
Enoxaparin has 110 anti-Factor Xa units/mg Recommended target anti-FXa range for LMWH is 0.5 to 1.0 IU/mL. Note: The anti-FXa assay detects heparin in subject's plasma based on inhibition of Factor Xa in the assay reagent.			

Table 17.3 shows the protocol for anticoagulation therapy to maintain an INR between 2 and 3 for pediatric subjects on warfarin therapy.

Table 17.3: Protocol for Anticoagulation Therapy to Maintain an INR Between 2 and 3 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

Abbreviations: INR = international normalized ratio

17.3. Effective Methods of Birth Control

Women of childbearing age are defined as those females that have reached menarche and until becoming postmenopausal unless permanently sterile (defined as no menses for 12 months without an alternative medical cause) and are eligible for the study based on the inclusion and exclusion criteria.

Female subjects of childbearing potential must test negative for pregnancy at Randomization (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.

Only in individual cases where the stable use of highly effective methods is medically contraindicated (investigator’s written documentation required), double barrier methods may be acceptable.

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. Contraindications for Standard of Care Therapy

Contraindications to warfarin (COUMADIN):

- Hypersensitivity to the active substance or to any of the excipients
- Hemorrhagic stroke
- Clinically significant bleeding
- Use within 72 hours of major surgery with risk of severe bleeding
- Use within 48 hours postpartum
- Pregnancy
- Drugs where interactions may lead to a significantly increased risk of bleeding

Contraindications to enoxaparin (LOVENOX):

- Hypersensitivity to either enoxaparin sodium, heparin or its derivatives including other LMWH
- Acute bacterial endocarditis
- Active major bleeding
- Conditions with a high risk of uncontrolled hemorrhage, including recent hemorrhagic stroke or thrombocytopenia in subjects with a positive in-vitro aggregation test in the presence of enoxaparin; active gastric or duodenal ulceration
- Subjects receiving heparin for treatment rather than prophylaxis

Note: Loco-regional anesthesia in elective surgical procedures is contraindicated.

Contraindications to UFH:

- History of heparin-induced thrombocytopenia (with or without thrombosis)
- Uncontrolled, active bleeding (except disseminated intravascular coagulation)
- Acute bacterial endocarditis
- When suitable, blood-coagulation tests (eg, the whole-blood clotting time, partial thromboplastin time, etc) cannot be performed at appropriate intervals
- Hypersensitivity to heparin
- Advanced renal or hepatic dysfunction
- Severe hypertension
- Major surgery involving the brain, spinal cord and eye.

17.5. Prohibited Concomitant Medications at Any Time during the Treatment Period with Edoxaban or SOC

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)

17.5.1. 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 to 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:

- Thienopyridines: 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®)
- P2Y12 Inhibitor: Cangrelor
- Dextran

17.5.2. 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.

17.5.3. Parenteral Anticoagulants

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

Examples of prohibited parenteral anticoagulant medications include the following:

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

17.5.4. Intravenous Fibrinolytics

Intravenous fibrinolytics are prohibited in both treatment arms. 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.

17.5.5. Non-Steroidal Anti-Inflammatory Drugs (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. Table 17.4 lists examples of NSAIDs.

Table 17.4: Thorough List of NSAIDs

Aceclofenac	Acemetacin	Alclofenac
Amtolmetin	Azapropazone	Benoxaprofen
Bromfenac	Bufexamac	Carprofen
Clonixin	Dexibuprofen	Dexketoprofen
Diclofenac	Diclofenac/Hyaluronic Acid	Diflunisal
Dipyrone	Droxicam	Etodolac
Etofenamate	Felbinac	Fenbufen
Fenoprofen	Fentiazac	Floctafenine
Flufenamic Acid	Flurbiprofen or Fluribuprofen	Hydrocodone/Ibuprofen
Ibuprofen	Indomethacin	Indoprofen
Isoxicam	Ketoprofen	Ketorolac
Lansoprazole/Naproxen	Lornoxicam	Loxoprofen
Meclofenamate	Mefenamic Acid	Meloxicam
Morniflumate	Nabumetone	Naproxen
Niflumic Acid	Nimesulide	Oxaprozin
Oxycodone/Ibuprofen	Phenylbutazone	Piketoprofen
Pirazolac	Piroxicam	Pirprofen
Prophenazone	Proquazone	Sulindac
Suprofen	Tenidap	Tenoxicam
Tiaprofenic Acid	Tolmetin	Zomepirac

17.5.6. P-gp Inducers (Prohibited Medication)

Rifampin is a P-gp inducer that has been shown to lower the edoxaban exposure Therefore, concomitant use of rifampin is contraindicated during the treatment period. Other P-gp induces may lead to a lower exposure of edoxaban than predicted for clinical efficacy. 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®)

17.6. Concomitant Medications that Require Edoxaban Dose Adjustment

17.6.1. P-gp Inhibitors List

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

Table 17.5 shows examples (not limited to) of 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, propafen

17.7. 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.

Subjects transitioning from edoxaban to any VKA will have their INR recorded at last study visit. Bridging with heparin may occur during VKA titration until the INR is at a therapeutic level of 2 to 3.

INR will need to be measured as frequently as necessary until the INR target of ≥2. 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 (e.g. 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 and have a 30-day Follow-Up Visit according to the Schedule of Events (Appendix 17.1).

For subjects who complete the Main Treatment Period but do not continue into the Extension Treatment Period, the subjects will receive a Discontinuation Visit and a Follow-Up Visit, 30 days after last dose of study drug.

For subjects who continue into the Extension Period, the Follow-Up Visit will occur 30 days after the Discontinuation Visit (Month 12, Visit 8).

17.8. Management of Serious/Life-Threatening Bleeding

The following steps are currently recommended for subjects with ongoing major bleeding (see Section 9.1):

- 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 UFH/LMWH:

The antidote for UFH/LMWH is protamine sulfate. The dose of protamine sulfate given is dependent upon the dose of UFH/LMWH administered and the time of administration.

Suggestions from the Sponsor:

- If protamine is given within 8 hours of the UFH/LMWH then a maximum neutralizing dose is 1 mg protamine/100 units (or 1 mg) of UFH/LMWH given in the last dose.
- If more than 8 hours have passed since the dose of UFH/LMWH was given, administer 0.5 mg protamine per 1 mg (100 units) of UFH/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 intensive care unit (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:

If a subject has significant but not life-threatening bleeding: Administer Vitamin K 0.5 mg to 2 mg SC (NOT intramuscularly) plus fresh frozen plasma (20 mL/kg IV) to a maximum of 4 units.

If a subject has major bleeding (any INR) or requires emergency surgery doses because their INR >8:

- Stop Warfarin
- Vitamin K (30 µg/kg) IV, consider higher doses if INR >8
- Prothrombin complex concentrate (PCC) replacement therapy (To note: fresh frozen plasma gives inferior correction and is not recommended):

  Beriplex® [4-factor Prothrombin Complex Concentrate approved in several European countries] (and Kcentra® approved in the United States) (Discuss with on call hematologist). Beriplex dosage is calculated based on the current INR and subject's weight (see Table 17.6)

  Repeat the INR following PCC

Further doses of Beriplex or Vitamin K may be required

Table 17.6: Dose Adjustments for INR Elevation

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 PCC, 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 (area under the curve 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®), activated PCC, 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 clinical 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.

17.9. Estimated Glomerular Filtration Rate (eGFR) Assessment

Table 17.7 shows the estimated glomerular filtration rate assessment, including the eGFR threshold for dose reduction.

Table 17.7: Estimated Glomerular Filtration Rate Based on Age

Age (Sex)	Normal eGFR (Mean eGFR±SD)	30% Minimal eGFR for Study Qualification[a] (Mean eGFR by Formula)	eGFR Threshold for Dose Reduction[b] (Mean eGFR by Formula)
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: S46-S75			

[a] Subject 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 < 1year): K=0.33
Infant (Term <1year): 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)

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

Figure 17.1: Blood Pressure Levels for Boys by Age and Height Percentile

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.

Figure 17.2: Blood Pressure Levels for Girls by Age and Height Percentile

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.

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

Figure 17.3: Growth Chart (Boys 2 to 20 Years of Age)

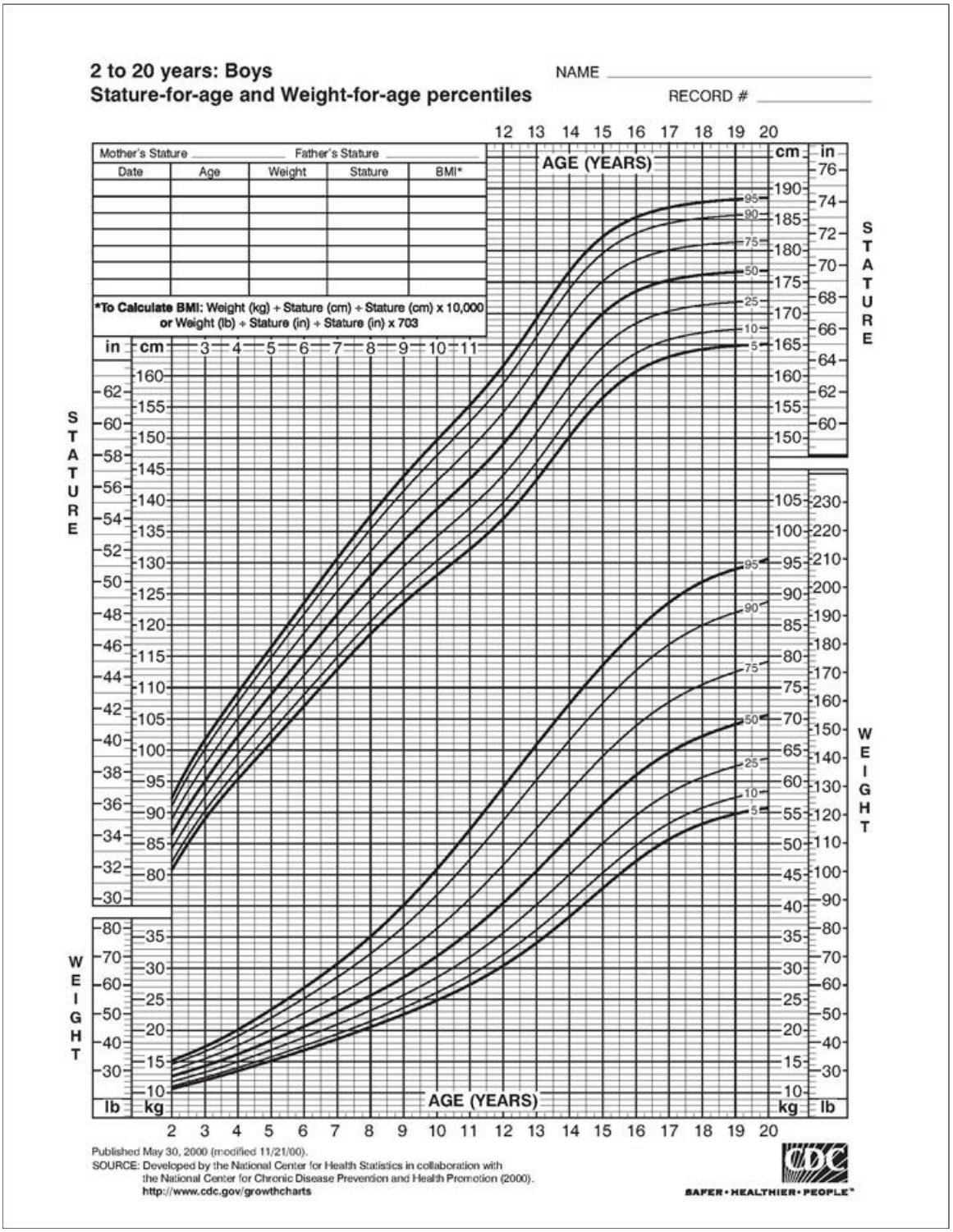


Figure 17.4: Growth Chart (Girls 2 to 20 Years of Age)

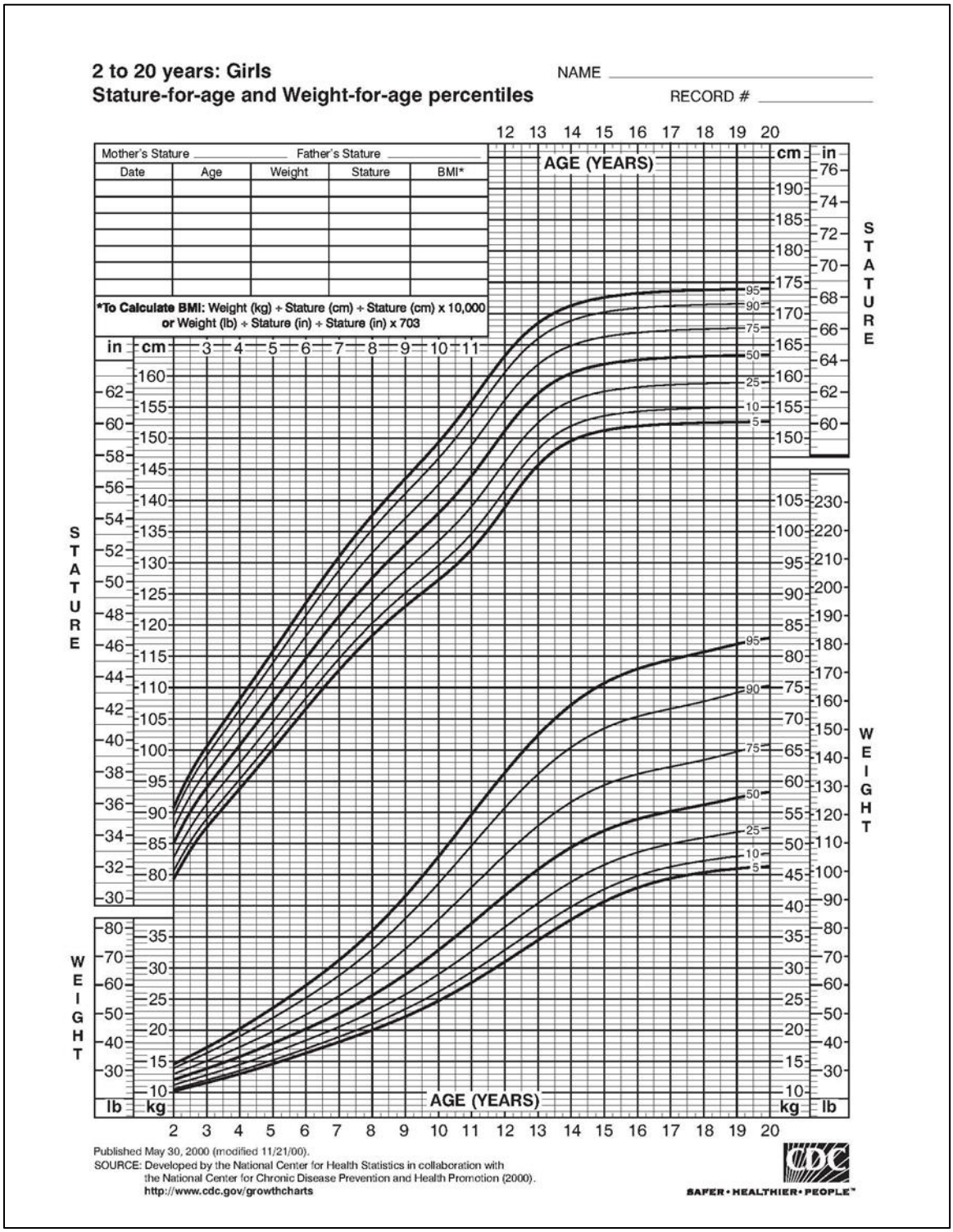


Figure 17.5: Growth Chart (Boys Birth to 24 Months of Age)

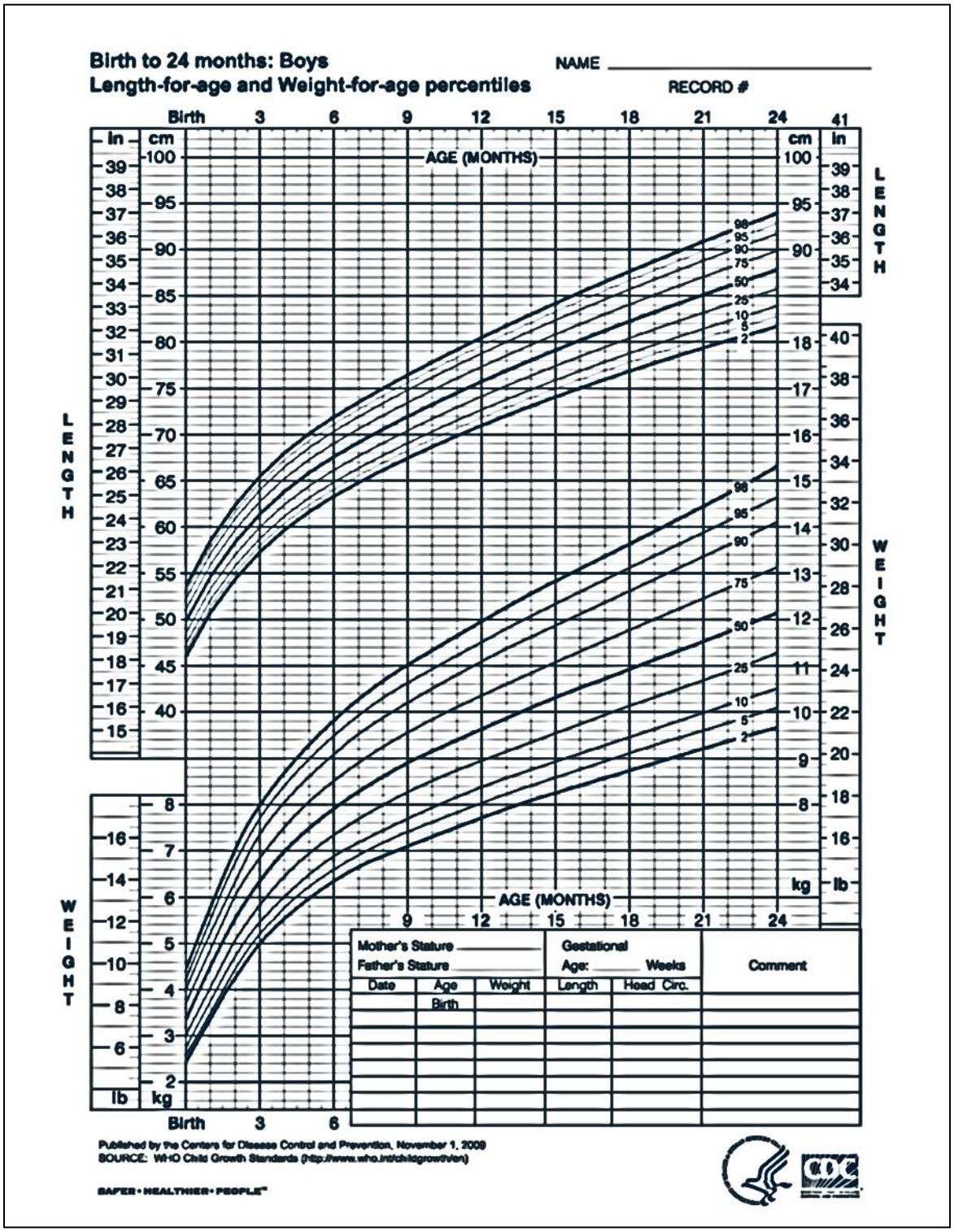


Figure 17.6: Growth Chart (Girls Birth to 24 Months of Age)