CLINICAL STUDY PROTOCOL

A PHASE 1, OPEN-LABEL, SINGLE-DOSE, NON-RANDOMIZED STUDY TO EVALUATE PHARMACOKINETICS AND PHARMACODYNAMICS OF EDOXABAN IN PEDIATRIC PATIENTS

DU176b-A-U157

IND NUMBERS 77,254 AND 63,266

EUDRACT NUMBER 2015-005732-18

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INVESTIGATOR AGREEMENT

A PHASE 1, OPEN-LABEL, SINGLE-DOSE, NON-RANDOMIZED STUDY TO EVALUATE PHARMACOKINETICS AND PHARMACODYNAMICS OF EDOXABAN IN PEDIATRIC PATIENTS

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the DSI representative listed below.

PPD	
Print Name	**Signature**
Senior Director, Specialty Medicine	
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 patient in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonization (ICH) 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 patients' 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**
Principal Investigator	
Title	**Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

EudraCT:	2015-005732-18
IND Numbers:	IND 77,254 for Stroke, IND 63,266 for Deep Vein Thrombosis/Venous Thromboembolism
Protocol Number:	DU176b-A-U157
Investigational Product:	Edoxaban (free base of edoxaban tosylate)
Active Ingredient(s)/INN:	Edoxaban tosylate: *N*-(5-Chloropyridin-2-yl)-*N*'-[(1*S*,2*R*,4*S*)-4-(*N*,*N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-*c*]pyridine-2-carboxamido)cyclohexyl] oxamide mono (4-methylbenzenesulfonate) monohydrate
Study Title:	A Phase 1, Open-label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients
Study Phase:	Phase 1
Indication Under Investigation:	Not applicable.
Study Objectives:	<u>Primary:</u> • To characterize the PK of edoxaban in pediatric patients following single-dose oral administration <u>Secondary:</u> • To evaluate the PD effects of edoxaban in pediatric patients following single-dose oral administration • To evaluate the safety and tolerability of single-dose oral administration of edoxaban in pediatric patients • To assess metabolite exposure (D21-2393, D21-3231, D21-1402, and D21-2135) in pediatric patients • To evaluate the palatability (bitterness, sweetness, and overall taste or aroma) of the liquid oral suspension of edoxaban

Study Design:	This is a Phase 1, open-label, multiple-center study in pediatric patients from 38 weeks gestation to < 18 years of age. Patients from 5 age cohorts (12 evaluable patients per age cohort) will receive a single dose of edoxaban. Each age cohort will be divided into a low- and high-dose group (6 patients per dose group). Order of enrollment will be from the oldest age cohort to the youngest age cohort. Within each age cohort, enrollment will first start in the lower dose group (to achieve exposures comparable to a 30 mg adult dose). After evaluation of PK and safety data from at least half the patients in the lower dose group, enrollment may then start in the higher dose group (to achieve exposures comparable to a 60 mg adult dose). If the observed exposures are higher than expected in the lower dose group and exceed the projected 60 mg adult exposure, then a lower dose may be investigated in the proposed "high-dose" group. Enrollment in the next younger age cohorts will begin when at least 50% of patients have completed the study in the older age cohort. Enrollment in the younger age cohorts will start only after PK and safety data have been evaluated from at least 6 patients (3 low-dose and 3 high-dose) in the older age cohort. Pharmacokinetic and safety data will be reviewed by a Data and Safety Monitoring Board (see Section 11.9) who will approve the start of the next younger age cohort. However, enrollment initiation of Cohort 5 may be considered without PK and safety data from at least 50% of patients in the preceding older dose group. Age cohorts and dose groups: • 12 to < 18 years of age on the day of dosing (12 evaluable total patients) – Cohort 1a: Low-dose group (6 patients) – Cohort 1b: High-dose group (6 patients) • 6 to < 12 years of age on the day of dosing (12 evaluable total patients) – Cohort 2a: Low-dose group (6 patients) – Cohort 2b: High-dose group (6 patients)

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

In Cohort 1, the oldest age group (12 to < 18 years), doses have been selected on the basis of modeling of adult data to target comparable exposures to 30 mg (low-dose) and 60 mg (high-dose). In this cohort, fixed dosing will be used. In Cohorts 2, 3, 4, and 5, the younger age groups (38 weeks gestation to < 12 years), appropriated doses will be selected to elicit target exposures comparable to those achieved from adult doses of 30 mg (low-dose) or 60 mg (high-dose). Patients in Cohort 1 will receive multiples of edoxaban tablets of 30 mg strength. Patients in Cohorts 2, 3, 4, and 5 will receive the edoxaban granule for oral suspension. The dose that each dose group receives will be determined by Daiichi Sankyo based on emerging PK data and modeled doses needed to achieve target exposures.

For patients in Cohort 1, 7 serial blood samples (2 mL per sample) will be collected for PK analysis based on a sampling windows approach: 0.25 to 1 hour, 1.5 to 3 hours, 3.5 to 6 hours, 6.5 to 8 hours, 8.5 to 14 hours, 24 to 36 hours, and 48 to 54 hours postdose. Additionally, 6 serial PD blood samples (1.8 mL per sample) will be collected for estimation of biomarkers of coagulation (prothrombin time [PT], activated partial thromboplastin time [aPTT], and anti-activated factor X [FXa]) at predose and immediately after simultaneously scheduled PK blood samples at 0.25 to 1 hour, 1.5 to 3 hours, 3.5 to 6 hours, 6.5 to 8 hours, and 24 to 36 hours postdose.

For patients in Cohorts 2 and 3, 5 serial blood samples (patients 6 to < 12 years of age: 2 mL per sample and

patients < 6 years of age: 1 mL per sample) will be collected for PK analysis based on a sampling windows approach: 0.25 to 1 hour, 1.5 to 3 hours, 4 to 8 hours, 9 to 14 hours, and 24 to 36 hours postdose. Additionally, 6 serial PD blood samples (patients 6 to < 12 years of age: 1.8 mL per sample and patients < 6 years of age: 1 mL per sample) will be collected for estimation of biomarkers of coagulation (PT, aPTT, and anti-FXa) at predose and immediately after simultaneously scheduled PK blood samples at 0.25 to 1 hour, 1.5 to 3 hours, 4 to 8 hours, 9 to 14 hours, and 24 to 36 hours postdose.

For patients in Cohort 4, 4 serial blood samples (600 µL per sample) will be collected for PK analysis based on a sampling windows approach: 0.5 to 2 hours, 3 to 8 hours, 9 to 14 hours, and 24 to 36 hours postdose. Additionally, 2 PD blood samples (1 mL per sample) will be collected for estimation of biomarkers of coagulation (PT, aPTT, and anti-FXa): once at the Screening Visit and once immediately after simultaneously scheduled PK blood sample at 0.5 to 2 hours postdose.

For patients in Cohort 5, blood samples (600 µL per sample) will be collected for PK analysis at a total of 3 of the 4 possible timepoints postdose: 0.5 to 2 hours (mandatory), 3 to 8 hours, 9 to 14 hours, and 24 to 36 hours. The timepoints will be assigned by the Sponsor once the subject is approved to be randomized. The Investigator will be informed of the PK timepoints to be collected for Cohort 5. Additionally, 2 PD blood samples (1 mL per sample) will be collected for estimation of biomarkers of coagulation (PT, aPTT, and anti-FXa): once at the Screening Visit and once immediately after simultaneously scheduled PK blood sample at 0.5 to 2 hours postdose.

Although windows for sample collection are allowed, the exact time and date of each blood sample will be recorded in the patient's Case Report Form.

Study Duration:	The study will last approximately 4 weeks for each patient, which will include a screening period (within 21 days of dosing), a treatment period, and a follow-up visit conducted within 10 days after dosing. However, a patient will be considered to have completed the study if they provide the last scheduled PK sample. The treatment period will consist of predose procedures occurring on Day -1 or 1, dosing on Day 1, and postdose procedures occurring postdose on Days 1, 2 (all cohorts) and Day 3 (all patients enrolled prior to Version 5.0 of the protocol may have had Day 3 PK samples obtained). The treatment period days may occur as in-patient or out-patient based on the clinic's ability/discretion. The overnight stays are not mandatory. Check-out procedures will be performed after the last PK/PD blood samples are collected (Day 2 or Day 3). The first patient is expected to be enrolled in June 2014.
Study Sites and Location:	Multiple sites in North America, Europe, and other regions
Planned Sample Size:	A total of 60 patients will be enrolled to obtain 12 evaluable patients in each age cohort (6 patients in each dose group).
Patient Eligibility Criteria:	Male and female pediatric patients who may require or are currently on anticoagulant therapy may be enrolled. These may include: • Patients who have a recently acquired or Investigator determined ongoing risk of thromboembolic events (e.g., patients with thrombophilia, congenital heart disease, presence of a central venous catheter and prior venous thromboembolic event [VTE]). • Patients who are completing their standard-of-care anticoagulant therapy. Edoxaban can be initiated 12 hours after cessation of enoxaparin, dabigatran, or apixaban therapy (A-U136, A-U151, and A-E152) and 24 hours after cessation of rivaroxaban therapy (A-U151). Note: that the dose of edoxaban should be at the time of the next scheduled standard-of-care anticoagulant administration: – At least 4 hours after last dose of unfractionated heparin.

  - At least 12 hours after last dose of twice daily (bid) low molecular weight heparin (LMWH).
  - At least 24 hours after last dose of once daily (qd) LMWH and synthetic pentasaccharide (SP) Xa inhibitors.
  - For patients who were on a prior vitamin K antagonist (e.g., warfarin [C-U122] and any other anticoagulants) therapy, international normalization ratio (INR) value should be ≤ 2.5 prior to edoxaban dosing. If the patient's INR is > 2.5, the patient's INR should be monitored until it is ≤ 2.5.

- Patients who are currently treated for VTE with at least 5 days of heparin may interrupt their standard-of-care anticoagulant therapy for edoxaban administration. The dose of edoxaban should be:
  - At least 12 hours from last dose of bid LMWH, with a restart of LMWH 24 hours after edoxaban dose.
  - At least 24 hours from last dose of qd LMWH, with a restart of LMWH 24 hours after edoxaban dose.
- Patients with cardiac conditions who may require anticoagulant therapy.
- Patients with sickle cell disease who may require anticoagulant therapy.

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

Dosage Form, Dose, and Route of Administration:	Edoxaban tablets (30 mg) or edoxaban granules for oral suspension (60 mg reconstituted with 8 mL water to provide a 6 mg/mL suspension for oral administration). In each age cohort, patients will receive appropriated single oral dose selected to target exposures comparable to adult doses of 30 mg (low-dose) or 60 mg (high-dose). If the observed exposure from the 30 mg dose in adolescents is higher than predicted and is comparable to the 60 mg adult dose exposures, then, the next cohort will receive a lower dose, instead of a higher dose. To allow for this flexibility, patients in the 12 to < 18 years of age cohort will receive edoxaban tablets of 30 mg strength. Patients younger than 12 years of age will receive the edoxaban granule for oral suspension. The dose amount given to each patient will be determined based on emerging data. The dose given may be updated based on emerging data. The PK model will be refined based on emerging data, modeling of a target age and weight range will establish dosing paradigms. The PK modeling will account for the range of weights. If a patient is unable or unwilling to ingest the assigned dosing form (tablet or suspension formulation), the patient will not be enrolled and will be replaced. Patients will be administered edoxaban in the morning with water. • Cohorts 1a/1b: 120 mL water; • Cohorts 2a/2b: 60 mL water; • Cohorts 3a/3b: 40 mL water; • Cohorts 4a/4b: 10 mL water; • Cohorts 5a/5b: 10 mL water. Patients will be asked to fast for at least 4 hours before dosing and for an additional 2 hours after dosing. If this is not feasible because of the patient's age or other needs, (unflavored) milk, or an equivalent substitute liquid (but not fruit juices), will be allowed until 1 hour before and starting at 1 hour postdose. During this period, the total volume of liquids should not exceed 240 mL, excluding the volume of water utilized for dosing.

Study Endpoints:	Pharmacokinetics: The PK endpoints will include modeled PK parameters such as apparent systemic clearance (CL/F), apparent volume of distribution (V/F), and area under the concentration-time curve (AUC) for edoxaban and metabolites, and metabolite/parent ratios for AUC. Pharmacodynamics: The PD endpoints will include observed, change-from-baseline, and percent-change-from-baseline PT, aPTT, and anti-FXa. Safety: Safety assessments will include: adverse events (AEs), physical examination findings, vital signs, standard hematology, clinical chemistry, and urinalysis laboratory tests. Note: urinalysis will be performed with plastic bags with a sticky strip from neonates and infants with diapers. Other: Palatability of the liquid formulation will be assessed using visual analog scale (VAS) scores.
Pharmacokinetics/ Pharmacodynamics/ Statistical Analyses:	Plasma concentration-time data for edoxaban and metabolites (if data are available) will be listed by patient, age cohort and/or dose group, and measurement time interval, and will be plotted and summarized using descriptive statistics, as appropriate. Plasma concentration-time data for edoxaban and metabolites will be analyzed using model-based approaches such as nonlinear mixed effects modeling, where data from other studies may be pooled with pediatric data, and PK parameters will be calculated. Estimated PK parameters will be assessed for age dependencies using graphical and/or modeling methods. Estimated PK parameters will be listed and summarized by age cohort and/or dose group using descriptive statistics. An exploratory analysis of variance model will be applied to natural log-transformed CL/F, V/F, and AUC with age cohort, dose, and age cohort by dose interaction as fixed factors. Appropriate adjustments on parameters, e.g., dose-normalization on AUC, or body weight-normalization on CL/F and V/F, might also be explored. The least-squares mean differences between age cohorts with age cohort of 12 to < 18 years as the reference and the corresponding 95%

	confidence intervals (CIs) will be exponentiated to obtain point estimates of ratios of geometric means and the corresponding 95% CIs by dose level and/or overall (as appropriate). For PD biomarkers (PT, aPTT, and anti-FXa), observed, change-from-baseline, and percent-change-from-baseline data will be listed by patient, age cohort and/or dose group, and measurement time interval, and will be plotted and summarized using descriptive statistics, as appropriate. The PK/PD relationships will be examined graphically to assess age dependencies. Additional PK/PD modeling may be conducted, if necessary, to understand age dependencies. The VAS scores for palatability will be listed and summarized by age cohort and/or dose group using descriptive statistics, if data permit.

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ABBREVIATION	DEFINITION
AE	Adverse event
AF	Atrial fibrillation
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{tau}	Area under the concentration-time curve over the dosing interval
bid	Twice daily
BMI	Body mass index
CES1	Carboxylesterase 1
CFR	Code of Federal Regulations
CHL/IU	Chinese hamster lung cells
CI	Confidence interval
CL/F	Apparent systemic clearance
CRF	Case Report Form (electronic or paper)
CRO	Contract Research Organization
CSPV	Clinical Safety Pharmacovigilance
CV%	Coefficient of variation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DSI	Daiichi Sankyo, Inc.
DSMB	Data and Safety Monitoring Board
EIU	Exposure in utero
FXa	Activated factor X
GCP	Good Clinical Practice (refers to ICH and CFR)
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalization ratio
IP	Investigational product
IRB	Institutional Review Board
LC-MS/MS	Liquid chromatography with tandem mass spectroscopy
LMWH	Low molecular weight heparin

ABBREVIATION	DEFINITION
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observed-adverse-effect level
OAT	Organic anion transporters
OCT	Organic cation transporters
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PopPK	Population based pharmacokinetic modeling
PT	Prothrombin time
qd	Once daily
RBC	Red blood cell
SAE	Serious adverse event
SAVER	Serious Adverse Event Report
SD	Standard deviation
SOP	Standard operating procedure
SP	Synthetic pentasaccharide
SUSAR	Serious adverse event reactions
TEAE	Treatment-emergent adverse event
TG	Thrombin generation
VAS	Visual analog scale
VTE	Venous thromboembolic event
V/F	Apparent volume of distribution
WBC	White blood cell

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Data Summary

A brief summary of relevant information from nonclinical and clinical studies included in the edoxaban (DU-176, free base of DU-176b) Investigator's Brochure is included below. Detailed information can be found in the Investigator's Brochure.[1]

1.1.1. Investigational Product

1.1.1.1. Name

Edoxaban tosylate (DU-176b): *N*-(5-Chloropyridin-2-yl)-*N'*-[(1*S*,2*R*,4*S*)-4-(*N,N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-*c*]pyridine-2-carboxamido)cyclohexyl] oxamide mono(4-methylbenzenesulfonate) monohydrate.

1.1.1.2. Description

Edoxaban is a potent and direct inhibitor of activated factor X (FXa) that prolongs clotting time of plasma. Edoxaban has been approved in the United States and European Union for adults as a clinically useful anticoagulant. In rat thrombosis models, this compound prevents thrombus formation and suppresses the hypercoagulable state.

1.1.1.3. Intended Use Under Investigation

Efficacy will not be studied in the protocol. The goal of this study is to identify pediatric doses that provide comparable exposure to adult efficacious doses to guide dose selection for Phase 3 studies in pediatrics.

1.1.1.4. Nonclinical Studies

Pharmacology

Pharmacological studies demonstrate that edoxaban is a potent and selective inhibitor of activated FXa in vitro. The in vitro anticoagulant effect of edoxaban is consistent with in vivo data. Edoxaban does not impair platelet aggregation induced by collagen, U46619 (a thromboxane A2 agonist), or adenosine diphosphate in human platelet-rich plasma.

The anticoagulant properties of edoxaban in vivo have been established in several rat thrombosis models: venous thrombus, disseminated intravascular coagulation, arterial-venous shunt, and venous stasis. The minimal effective single oral doses in the in vivo models were 0.1 to 2.5 mg/kg in rats yielding plasma edoxaban concentrations of about 5 to 170 ng/mL. Plasma concentrations were generally proportional to the administered doses.

There were no major safety pharmacology concerns with edoxaban.

Absorption, Distribution, Metabolism, and Excretion

In vitro protein binding of ^{14}C-edoxaban was assessed in human plasma obtained from healthy volunteers (N = 3/concentration). At concentrations of 0.2, 1, and 5 µg/mL, 54.3%, 54.4%, and 56.6% of ^{14}C-edoxaban, respectively, were bound to plasma protein.

In vitro distribution of ^{14}C-edoxaban was assessed in human blood cells from plasma of healthy volunteers (N = 3/concentration). At concentrations of 0.2, 1, and 5 µg/mL of ^{14}C-edoxaban, 45.7%, 45.9, and 47.4%, respectively, were distributed into the blood cells.

In human liver microsomes, 6 edoxaban metabolites were identified: D21-1402, D21-3231, D103-2684, D21-2393, D21-2135, and a hydroxylated metabolite at the *N, N*-dimethylcarbamoyl group of edoxaban. Cytochrome P450 (CYP) 3A4 was the major enzyme involved in the formation of D21-1402, D103-2684, and M-3a. D21-3231 and D21-2393 were formed independent of the reduced form of nicotinamide-adenine dinucleotide phosphate, indicating that they were not metabolized via CYP450 isozymes, but rather by a hydrolysis reaction. D21-2135 was considered a minor metabolite in this testing system.

The enzymes involved in the hydrolysis of edoxaban to D21-2393 were characterized using pooled human liver microsomes, cytosolic, and recombinant human carboxylesterase 1 (CES1). The results demonstrated that edoxaban is metabolized to D21-2393 in the liver by human CES1.

The P-glycoprotein (P-gp)-mediated transcellular transport of edoxaban and inhibitory effects of typical P-gp inhibitors on the vectorial transport of edoxaban were investigated using Caco-2 cell monolayers. The results indicated that edoxaban is a substrate of the efflux transporter, P-gp. The uptake of ^{14}C-edoxaban to S2 cells expressing transporter genes comprising human organic anion transporters (OAT) 1, OAT3, and human organic cation transporters (OCT) 2 was measured to elucidate the transport of edoxaban by human renal transporters. These results suggest that edoxaban is not a substrate for OAT1, OAT3, and OCT2.

The ontogeny of renal function, biliary secretion, P-gp, drug metabolizing enzymes CES 1 and CYP3A4, and gastric emptying and pH are likely to affect the pharmacokinetics (PK) of edoxaban for various pediatric age groups. However, the ontogeny of all the enzymes and transporters is not very well characterized. The kidneys are not fully mature at birth. The glomerular filtration rate in neonates is 4 mL/1.73 m^2, increasing rapidly to reach adult values by the end of first year. The glomerular filtration rate continues to increase and overshoot adult levels until prepubescent age, resulting in higher renal clearance in children compared to adults. The tubular function also matures slowly and reaches adult levels by 1 year of age.[2]

CYP3A4 has very low expression before birth, but increases rapidly, achieving 60% of adult levels between the ages of 6 and 12 months. The CYP3A4 activity is slightly higher in infants than in adults. The activity of CYP3A4 undergoes profound changes during all stages of development and is likely to affect drug metabolism in pediatrics.[3,4] The ontogeny of P-gp is complicated, and there are conflicting literature reports, which suggest both developmental differences as well as differences in expression and function in various organs.

Edoxaban absorption is likely to be affected by the gastric pH. In neonates and at birth, the gastric pH values are close to neutral; within first 48 hours, pH decreases to 3 and by 3 months of age, the gastric pH is decreased further, closer to adult levels. The gastric pH levels reach adult levels only by 2 years of age. Gastrointestinal physiology also changes during development and may affect the absorption of drug.[5]

The PK of edoxaban were investigated in rats and cynomolgus monkeys by measuring radioactivity following single oral doses of 3 and 1 mg/kg of ^{14}C-edoxaban (as edoxaban) to rats and monkeys, respectively. Wide-spread distribution of radioactivity following oral

administration of ^{14}C-edoxaban occurred in the rat (albino) with the highest concentrations found in the gastrointestinal and bladder contents, followed by the kidney, preputial gland, liver, intestine, Harderian gland, pituitary gland, and nasal cavity. In a tissue distribution study in pigmented rats, binding of edoxaban-related material occurred in ocular tissue and pigmented skin. This suggests that edoxaban can bind to melanin. In the monkey (pigmented), residual radioactivity at 336 hours was noted in the eyeball and skin, and trace amounts were present in the liver and kidney.

Following oral administration of edoxaban, parent compound edoxaban was the predominant form found in monkey and rat plasma. D21-3231 was the major metabolite found in rat plasma. Part of the D21-3231 found in the plasma may be from hydrolysis of edoxaban after sample collection, as edoxaban is unstable in rat plasma. The assessment of metabolites in the urine and feces of rats and monkeys administered ^{14}C-edoxaban by high-pressure liquid chromatography radio-chromatograms, and liquid chromatography with tandem mass spectroscopy (LC-MS/MS) assays showed that edoxaban was excreted largely unchanged. Edoxaban and its metabolites do not undergo conjugation prior to elimination. A plasma metabolite (D21-2393) found in humans was not detected radiometrically in rats and monkeys but trace amounts could be detected in excreta by LC-MS/MS. Because D21-2393 is found in human plasma at higher concentrations than the trace amounts in animal excreta, D21-2393 is considered to be a human-specific metabolite.

Toxicology

The single oral dose toxicity studies in rats and monkeys indicate a relatively low acute toxicity potential for edoxaban. Numerous chronic toxicology studies have been conducted in rats and cynomolgus monkeys with edoxaban dosing up to 52 weeks. The data from these studies are described in detail in the Investigator's Brochure.[1]

In these studies, edoxaban treatment did not produce any remarkable or otherwise notable changes in body weight, electrocardiogram, ophthalmology, physical examination, and macroscopic and histopathologic examinations. In the 52-week oral dosing study in cynomolgus monkeys, the no-observed-adverse-effect level (NOAEL) was estimated to be 5 mg/kg/day for males and females.

Edoxaban did not show genotoxic potential in bacterial reverse mutagenic assays, but chromosomal (numerical) aberrations were noted in other in vitro studies after exposure to very high concentrations (at which the drug precipitates) of edoxaban. Edoxaban did not show any genotoxic potential in bone marrow micronucleus tests in rats and cynomolgus monkeys, liver micronucleus test in rats, and unscheduled deoxyribonucleic acid (DNA) synthesis in rat liver. Since there was no damage to chromosomes or DNA in these in vivo studies, edoxaban is not considered to have genotoxic risk.

In a rat fertility and early embryonic development study, there were no effects on male or female reproduction or early embryonic development at edoxaban doses up to 1,000 mg/kg/day. In an embryo-fetal development study in rats given 30, 100, and 300 mg/kg/day, vaginal hemorrhage in dams and increased post-implantation loss occurred at 300 mg/kg/day. The NOAEL was estimated to be 100 mg/kg/day.

In an embryo-fetal development study in rabbits given 60, 200, and 600 mg/kg/day, maternal toxicity (vaginal hemorrhage, abortion, and death) and fetotoxicity (post-implantation loss and decreased fetal weight) occurred at 200 and 600 mg/kg/day. There were also increases in absent or small gall bladder of the fetuses at ≥ 200 mg/kg/day and an increase in 13th full ribs and 27th presacral vertebra at 600 mg/kg/day. The NOAEL was estimated to be 60 mg/kg/day for dams, embryos, and fetuses.

In the pre- and post-natal development study in rats given 3, 10, and 30 mg/kg/day, maternal toxicity (vaginal hemorrhage) and lower avoidance response rate in learning tests in the female offspring were observed on the first day of examination at 30 mg/kg/day, but not the second day of examination or in males. The NOAEL was estimated to be 30 mg/kg/day for general toxicity in dams and 10 mg/kg/day for reproduction in dams and the development of next generation.

Photosafety and eye function studies were performed because edoxaban distributed to ocular and skin tissues and bound to melanin in pigmented rats, as well as showed some absorption for light wavelengths greater than 290 nm. Phototoxic potential was evaluated in an in vitro photochromosomal aberration test in Chinese hamster lung cells (CHL/IU) and in an in vitro phototoxicity test in BALB/3T3 cells. Edoxaban did not show any phototoxic potential in either study. In a 9-month eye function test in male and female cynomolgus monkeys given 150 mg/kg/day, edoxaban did not affect any eye function parameter.

To assess the toxicity of the human-specific metabolite D21-2393, a 14-day repeated oral dose toxicity study in rats and in vitro and in vivo genotoxicity studies were performed. In the 14-day oral dose toxicity study, male and female rats were given D21-2393 at doses of 200, 600, and 2,000 mg/kg/day and there was no treatment-related toxicity. The NOAEL was estimated to be 2,000 mg/kg/day for rats. D21-2393 did not show any mutagenic potential in the bacterial reverse mutation test. D21-2393 induced numerical chromosomal aberrations in CHL/IU cells at high concentrations (1,250 μg/mL or higher) but did not show any such aberrations in human lymphocytes. Therefore, the observed polyploid induction in CHL/IU cells was not considered to be clinically relevant. In addition, D21-2393 did not show any genotoxic potential in the bone marrow of rats given either a single dose or repeated doses up to 2,000 mg/kg/day in the 14-day repeated oral dose toxicity study. Based on these results, D21-2393 is not considered to pose any genotoxic risk to humans. In a juvenile toxicity study in rats, edoxaban tosylate hydrate did not show any effects on postnatal development and growth, organ development, skeletal development, or sexual maturation at doses up to 20 mg/kg/day.

An ex vivo study (TMCP-Peds-001) evaluated the concentration-coagulation response relationship for edoxaban in neonatal (cord blood) and adult blood samples, using rivaroxaban as a positive control for establishing experimental conditions. The range of edoxaban concentrations tested in this study was 12.5 to 500 ng/mL, which spans the therapeutic range of edoxaban. Edoxaban induced dose-dependent inhibition of all coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [aPTT], anti-FXa, Intrinsic factor X, and thrombin generation [TG]) (Table 1.1).

Table 1.1: Ex-vivo Inhibition of Coagulation Biomarkers by Edoxaban and Rivaroxaban (TMCP-Peds-001)

	PT	aPTT	Anti-FXa	Intrinsic FX	TGA-Thrombin	TGA-Lag	TGA-Time to Peak	TGA-VI	TGA-ETP
Edoxaban: Cord vs Adult	NS 102%	NS 97%	N/A[1]	NS 99%	NS 109%	NS 111%	NS 105%	NS 115%	NS 94%
Rivaroxaban: Cord vs Adult	< 0.05 114%	NS 112%	NS 87%	NS 114%	< 0.05 145%	NS 97%	NS 87%	NS 129%	NS 112%

aPTT = activated partial thromboplastin time; ETP = endogenous thrombin potential; FXa = activated factor X; FX = factor X; N/A = not applicable; NS = non-statistically significant; PT = prothrombin time; TGA = thrombin generation assay; VI = velocity index.

1. Due to 0 value at baseline, change from baseline could not be calculated.

Ex vivo, there were no significant differences in inhibition of plasma biomarkers between adult and cord blood. The pharmacodynamic (PD) effects of edoxaban in plasma from ex vivo-treated cord blood were not significantly different from that in plasma from ex vivo-treated adult blood for any parameter (see Table 1.1). Differences fell within ± 10% for aPTT, Intrinsic FX, and 2 out of the 5 TG parameters and ± 23% of the remaining endpoints (PT and 3 TG parameters). Thus, anticoagulant effects of edoxaban are found to be similar between adult plasma and cord blood. These results concurred with previously published findings with rivaroxaban.[6] Despite a difference in the baseline activity of various biomarkers, the potency of drug effects was similar between adults and cord blood.

1.1.1.5. Clinical Experience

Edoxaban is currently marketed in Japan (since 22 April 2011) for prevention of venous thromboembolic events (VTE) in patients with lower extremity orthopedic surgery (total hip replacement, total knee replacement, and hip fracture surgery). It was further investigated worldwide in two Phase 3 clinical trials for reduction of stroke and systemic embolic events in patients with non-valvular atrial fibrillation and for treatment of acute VTE and prevention of recurrence in patients with symptomatic deep vein thrombosis and/or pulmonary embolism. Edoxaban has recently been approved in the United States, European Union, and Japan for stroke and systemic embolism prevention in atrial fibrillation (AF), and for treatment of VTE. In the European Union, edoxaban is also approved for the prevention VTE. It is also approved in Japan for VTE prophylaxis following orthopedic surgery.

In the Phase 3 trial in AF patients, DU176b-C-U301 (ENGAGE AF-TIMI 48), a total of 21,105 patients were randomized in the study. Of these, 14,069 were randomized to edoxaban (7,034 to 30 mg once daily [qd] edoxaban; 7,035 to 60 mg qd edoxaban). In the Phase 3 study in VTE patients, DU176b-D-U305 (Hokusai VTE), a total of 8,292 patients were randomized in the study. A total of 4,143 patients were assigned to 60 mg qd edoxaban arm and 4,118 patients treated with edoxaban completed the study (8,250 patients completed the study). Approximately, 1,400 patients have received edoxaban in 45 Phase 1 studies.

Approximately 1,300 human patients have been exposed to edoxaban in 45 completed Phase 1 studies, as of 30 June 2012. In healthy male patients, edoxaban was well tolerated with no evidence of major bleeding or clinically relevant liver function abnormality at repeated doses up

to 120 mg qd and 60 mg twice daily (bid) for 10 days and as single doses up to 180 mg. Consistent with the anticoagulant effect of edoxaban, minor, transient bleeding events were observed.

In healthy adults, a 60 mg oral dose of edoxaban results in peak concentrations of 309 ± 97 ng/mL. Peak concentrations are achieved within 1 to 2 hours (Study A-U151 and Study A-U147). The apparent terminal elimination half-life following oral administration is about 10 to 14 hours. Following intravenous administration, the mean terminal elimination half-life was about 7 hours (Study A-U139). The total clearance (arithmetic mean ± standard deviation [SD]) of edoxaban is estimated to be 21.8 ± 3.03 L/h with a steady-state volume of distribution of 107 ± 19.9 L (Study A-U139). The absolute bioavailability of edoxaban is estimated to be about 62% (Study A-U139). The PK profile of edoxaban is similar for single and multiple dosing. Steady-state is achieved within 3 days of dosing, with minimal accumulation upon qd dosing (less than 2-fold). The mean accumulation ratio at steady-state for C_{max} is 1.07 and for area under the concentration-time curve over the dosing interval (AUC_{tau}) (over 24 hours), is 1.14 (Study A-U151). At steady-state, a 60 mg dose results in peak concentrations of 303 ± 88 ng/mL at median (range) time to maximum concentration values of 1.5 hour (0.5, 4.00 hour). The steady-state exposure (AUC_{tau}) is 1,990 ± 403 ng·h/mL, with trough concentrations of 15.5 ± 3.98 ng/mL (Study A-U151).

Edoxaban is the active moiety and is the predominant circulating drug-related moiety. In healthy adults, edoxaban undergoes both Phase 1 and 2 metabolism. Phase 1 metabolism is predominantly mediated by CYP3A4 and CES1. Metabolism by CES1 results in the formation of a human-specific metabolite D21-2393, which accounts for less than 10% of total edoxaban exposure in healthy adults. Phase 2 metabolism is mediated by glucuronidation (Study PRT019). Seven metabolites have been identified. Three of the metabolites (D21-2393, D21-2135, and D21-1402) are pharmacologically active with anticoagulant activity (BG11-H0026-R01). However, due to low abundance (< 10% for D21-2393 and < 5% for D21-2135 and D21-1402, each), the metabolites are not expected to contribute significantly to overall pharmacological activity of edoxaban in adults.

Edoxaban is primarily eliminated unchanged in urine and through biliary secretion; with metabolism contributing to a lesser extent towards total clearance of edoxaban. In healthy volunteers, edoxaban is the predominant excreted component in urine, accounting for 24% of the administered dose. In feces, it accounts for 49% of administered dose (Study PRT019). In healthy volunteers, renal and nonrenal clearances contribute equally (approximately 50% each) to the total clearance of edoxaban. The human-specific metabolite, D21-2393, is not detected in urine and only about 2% is detected in feces (A-U139 and PRT019).

In drug interaction studies with P-gp inhibitors (erythromycin, ketoconazole, cyclosporine, and verapamil), exposure of edoxaban increased, but the increase was generally less than 2-fold.

Other drug interaction studies with inhibitors of P-gp and/or other CYPs (quinidine, amiodarone, and dronedarone) also resulted in less than 2-fold increase in edoxaban exposure.

When edoxaban is dosed with a high-fat meal, there is no change in total exposure, but peak exposure increases by about 40%.

Concomitant administration of anti-platelet drugs (aspirin [100 and 325 mg qd × 5 days] and naproxen [500 mg bid × 2 days]) was assessed by investigating PK and bleeding times. Edoxaban exposure was either not affected or minimally affected by concomitant aspirin and naproxen. In all 3 studies, bleeding times increased after administration of edoxaban, but to a lesser extent than those observed with either of the anti-platelet agents alone. Administration of edoxaban in combination with the anti-platelet agents resulted in longer bleeding times than observed for any of the drugs alone. The inter-study comparisons of edoxaban coadministered with either 100 or 325 mg aspirin indicated no significant difference in bleeding times by aspirin dose in these short-term studies. Patients who received edoxaban and aspirin 325 mg had more bleeding adverse events (AEs) than those treated with edoxaban alone or aspirin alone. However, the data are limited and until there is further experience, the dose of aspirin coadministered with edoxaban should be limited to 100 mg in the absence of a compelling indication (e.g., acute myocardial infarction to reduce the risk of bleeding).

Switching to edoxaban from other drugs has been studied in healthy adults. Edoxaban can be initiated 12 hours after cessation of enoxaparin, dabigatran, or apixaban therapy (A-U136, A-U151, and A-E152) and 24 hours after cessation of warfarin or rivaroxaban therapy (C-U122 and A-U151).

The PD responses, specifically activated aPTT, PT, and anti-FXa activity, closely parallel the time course of plasma edoxaban concentrations. On the basis of these biomarkers and others measuring thrombin generation, the onset of action for the anticoagulant effects of edoxaban is observed immediately after the first dose and maximum activity corresponds with maximum concentration (C_{max}).

Clinical (90 mg) and supra-therapeutic (180 mg) doses of edoxaban had no effect upon QT_cI interval in the thorough QT_c study, which was confirmed to have adequate sensitivity based on the QT_cI effect of the positive control (moxifloxacin 400 mg). Moreover, QT_cF and QT_cB methods yielded the same conclusion. Systemic exposure (as defined by C_{max} and area under the concentration-time curve [AUC] parameters) to edoxaban and its metabolite D21-2393 from the 90 mg edoxaban dose was consistent with results from previous studies.

Beriplex P/N, a 4-factor prothrombin complex concentrate has been evaluated as a potential reversal agent in a study in healthy volunteers. In this study, bleeding duration (BD) prolongation after a punch biopsy was the primary end point. Beriplex P/N dose-dependently reversed the effects of edoxaban on BD. Complete reversal was observed following 50 IU/kg dose, partial reversal was observed following 25 IU/kg and no reversal was observed following 10 IU/kg. This treatment, however, has not been tested in patient populations with bleeding.

Details of these and additional clinical studies are provided in the Investigator's Brochure.[1]

1.2. Study Rationale

Edoxaban is an orally active, selective, reversible FXa inhibitor that is being developed as an anticoagulant for the treatment of venous thromboembolism including deep vein thrombosis, pulmonary embolism, and prevention of recurrent VTE. The pivotal Phase 3 study (C-U305) was completed in 2012. This is the first study in pediatric patients, ages 38 weeks gestation to < 18 years, in which, the PK/PD profile of edoxaban will be evaluated following a single-dose administration of oral edoxaban. The goal of this study is to identify pediatric doses that provide

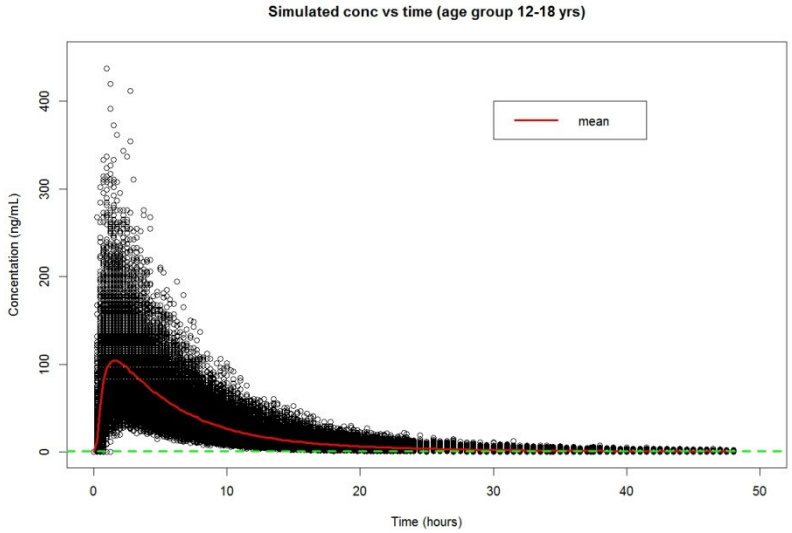
comparable exposure to adult efficacious doses to guide dose selection for Phase 3 studies in pediatrics. Additional PK data will be obtained from Phase 3 studies in pediatrics.

1.3. Dose Selection Rationale

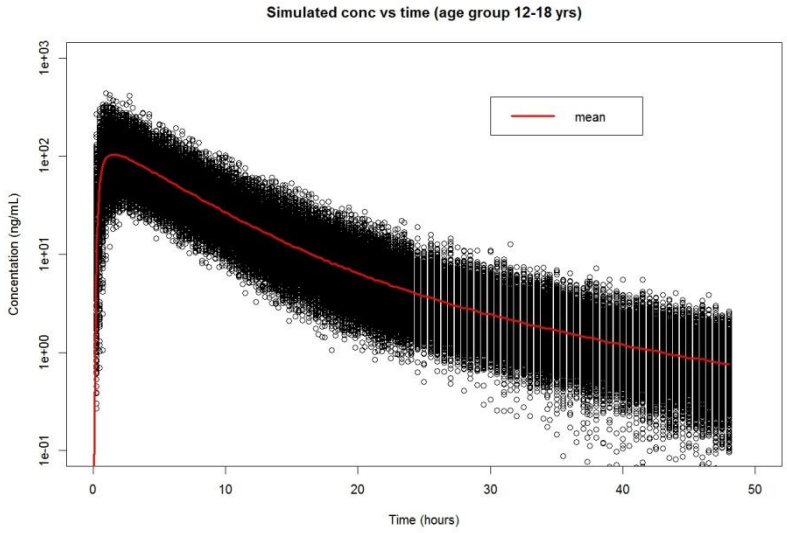
A 60 mg qd dosing regimen in adults was found to be safe and effective in the pivotal Phase 3 trial in VTE patients. Based on in vitro data, it appears that edoxaban has similar activity in adults and neonatal cord blood. Hence, it is expected that doses that achieve similar exposures to the adult dose of 60 mg may be most effective in pediatric populations. This study is designed to safely evaluate exposures of a low- and high-dose in each pediatric cohort, in order to guide dosing in a Phase 3 study in pediatrics. The ex vivo study (TMCP-Peds-001) showed the anticoagulant effects of edoxaban are found to be similar between adult plasma and cord blood. Despite a difference in the baseline activity of various biomarkers, the potency of drug effects was similar between adults and cord blood. The current study is targeting to have similar plasma exposure as in the adult Phase 3 VTE study with low (30 mg) and high exposure (60 mg). For the younger age groups, it is planned to adjust the dose based on anticipated ontogeny differences and available data in the older pediatric age cohorts. The starting dose for adolescents low-dose group was selected on the basis of population PK modeling (PopPK) and simulations (Figure 1.1). The PopPK model was based on adult data (median age [range] 33 [18 to 85] years; median body weight [range] 75.8 [42 to 165 kg]). The basic structural model was a 2-compartment model with first-order absorption and lag time. The simulation dataset consisted of 12 typical male patients from 12 to 18 years. Body weight and height estimates were from the 2000 CDC (Centers for Disease Control and Prevention) Growth charts.[7] Creatinine clearance values were calculated using the Schwartz equation.[8] A total of 1,200 individuals were simulated. A simulated 30 mg dose appears to provide similar or slightly lower mean exposure in the adolescent population.

Figure 1.1: Simulated Plasma Concentration Time Profiles for Ages 12 to 18 Years (30 mg Dose)

Linear



Semi-logarithmic



1.4. Risks and Benefits for Study Patients

As described in United States regulations, this study is considered to fall into Title 21 Code of Federal Regulation (CFR) Part 50.53 as "Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition."

The goal of this study is to identify pediatric doses that provide comparable exposure to adult efficacious doses in order to guide dose selection for Phase 3 studies in pediatrics.

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

In U157 study, the risk is considered as minimal for patients who already took anticoagulant therapy due to their health conditions. U157 is a single dose study with a sequential enrolment (from older to younger) and with two tested doses ("low" dose to achieve exposures comparable to a 30 mg adult dose and "high" dose to achieve exposures comparable to a 60 mg adult dose). U157 patients are NOT healthy children; their health conditions already exposed them to procedures necessary to address their health problems related to thromboembolism. In patients with no history of thromboembolic events, the risk is considered as a minor increase over minimal risk. U157 risk was estimated based on experience with similar treatments and procedures in the pediatric population[12] and from the well-known edoxaban effects in adults (Hokusai VTE Study). U157 is a dose finding study with safety as a secondary objective. The benefit to participate in U157 can be considered as direct for patients with health conditions exposing them to occurrence and/or recurrence of a thromboembolic event.

U157 study also presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children with thromboembolic disease. The data derived from this study could potentially benefit pediatric patients when the study data is disclosed and becomes publically available or if it should lead to a possible update of the edoxaban label. In addition, doses derived from this study will be implemented in Phase 3 studies; in particular, patients with diagnosed VTE or cardiac diseases that may predispose them to venous or arterial thromboembolism.

The research will be conducted in accordance with sound ethical principles, and adequate provisions are made for soliciting the assent of the children and the permission of their parents or legal guardians.

The safety monitoring practices employed by this protocol (i.e., physical examinations, vital signs, AEs, and clinical laboratory assessments) in addition to periodic data review by a Data and Safety Monitoring Board (DSMB) are considered adequate to protect the patients' safety.

Please refer to the Investigator's Brochure[1] for the summary of clinical experience including side effects associated with edoxaban treatment.

1.5. Population, Route, Dosage, Dosage Regimen, and Treatment Period

The study population will include patients 38 weeks gestation to < 18 years of age of both sexes, who may require, or are currently on anticoagulant therapy.

These may include:

- Patients who have a recently acquired or Investigator determined ongoing risk of thromboembolic events (e.g., patients with thrombophilia, congenital heart disease, presence of a central venous catheter and prior venous thromboembolic event [VTE]).
- Patients who are completing their standard-of-care anticoagulant therapy. Note: that the dose of edoxaban should be at the time of the next scheduled standard-of-care anticoagulant administration:
  - At least 4 hours after last dose of unfractionated heparin.
  - At least 12 hours after last dose of bid low molecular weight heparin (LMWH).
  - At least 24 hours after last dose of qd LMWH and synthetic pentasaccharide (SP) Xa inhibitors.
  - For patients who were on a prior vitamin K antagonist (e.g., warfarin [C-U122] and any other anticoagulants) therapy, international normalization ratio (INR) value should be ≤ 2.5 prior to edoxaban dosing. If the patient's INR is > 2.5, the patient's INR should be monitored until it is ≤ 2.5.
- Patients who are currently treated for VTE with at least 5 days of heparin may interrupt their standard-of-care anticoagulant therapy for edoxaban administration. The dose of edoxaban should be:
  - At least 12 hours from last dose of bid LMWH, with a restart of LMWH 24 hours after edoxaban dose.
  - At least 24 hours from last dose of qd LMWH, with a restart of LMWH 24 hours after edoxaban dose.
- Patients with cardiac conditions who may require anticoagulant therapy.
- Patients with sickle cell disease who may require anticoagulant therapy.

For any condition, anticoagulant treatment interruption or discontinuation should not take place if the patient is at increased risk and should be appropriate as per standard care of practices.

The following dosage forms will be provided for this study:

- Edoxaban 30 mg oral tablets for patients 12 and < 18 years of age.
- Edoxaban granules for oral suspension (60 mg reconstituted with 8-mL water) to provide a 6 mg/mL suspension for oral administration for patients < 12 years of age.

In each age cohort, appropriated doses will be selected to achieve exposures comparable to adult doses of 30 mg (low-dose) or 60 mg (high-dose). If the observed exposure from the 30 mg dose in adolescents is higher than predicted and is comparable to the 60 mg adult dose exposures, then, the next cohort will receive a lower dose, instead of a higher dose. To allow for this

flexibility, patients in the 12 to < 18 years of age cohort will receive edoxaban tablets of 30 mg strength. Patients younger than 12 years of age will receive the edoxaban granule for oral suspension. The dose amount given to each patient will be determined based on emerging data. The dose given may be updated based on emerging data.

The PK model will be refined based on emerging data, modeling of a target age and weight range will establish dosing paradigms. The PK modeling will account for the range of weights.

1.6. Compliance Statement, Ethics, and Regulatory Compliance

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

- European Commission Directive (2001/20/EC Apr 2001)
- European Commission Directive (2005/28/EC Apr 2005)
- Food and Drug Administration GCP Regulations: CFR Title 21, parts 11, 50, 54, 56, and 312
- The Health Insurance Portability and Accountability Act as appropriate and/or
- Other applicable local regulations

1.6.1. Patient Confidentiality

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

The Investigator must ensure that the patient's anonymity is maintained. On the Case Report Form (CRF) or other documents submitted to Daiichi Sankyo, Inc. (DSI), patients should be identified by a unique patient identifier as designated by the Sponsor. Documents that are not for submission to DSI (e.g., signed Informed Consent Forms [ICF]) should be kept in strict confidence by the Investigator.

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

1.6.2. Informed Consent Procedure

Before a patient's participation in the study, it is the Investigator's responsibility to obtain freely given consent and assent (generally, this age averages at 7 years of age), in writing, from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a

prospective patient, to the patient's participation in the clinical study. The written ICF should be prepared in the local language(s) of the potential patient 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 IEC or IRB prior to being provided to potential patients.

The patient's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the patient's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the patient or a legally acceptable representative, 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 patient or legal representative. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

If the patient or legally acceptable representative cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the patient or the legally acceptable representative has orally consented to the patient's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the patient or the legally acceptable representative and that informed consent was freely given by the patient or the legally acceptable representative.

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

According to 21 CRF 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 CRF 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 (i.e., separate assent forms for patients 7 to 12 years and for patients 13 to 17 years) to ensure the assents maintain their "maturity levels and understandability."

1.6.3. Regulatory Compliance

The study protocol, patient information and consent form, the Investigator's Brochure, or written instructions to be given to the patient, available safety information, patient recruitment procedures (e.g., advertisements), information about payments and compensation available to the

patients, and documentation evidencing the Investigator's qualifications should be submitted to the IEC 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 Statistical Analysis Plan.

The Investigator must submit and, where necessary, obtain approval from the IEC or IRB for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IEC or IRB of deviations from the protocol or serious AEs (SAEs) occurring at the site and other AE reports received from DSI or Contract Research Organization (CRO), in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will ensure all legal aspects are covered, and approval of 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 the appropriate notification of or approval by the relevant regulatory bodies.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective of this study is to characterize the PK of edoxaban in pediatric patients following single-dose oral administration.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

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

2.1.3. Exploratory Objectives

No exploratory objectives are planned for this study.

2.2. Study Hypothesis

This is the first edoxaban pediatric study and is not intended to test a hypothesis, but rather to generate information that will allow dose selection for subsequent clinical efficacy/safety studies in pediatrics.

3. STUDY DESIGN

3.1. Overall Plan

3.1.1. Study Type

This is a Phase 1, open-label, single-dose, non-randomized, multiple-center PK and PD study in pediatric patients. The study will include 5 pediatric age cohorts with evaluation of 2 different doses within each age cohort (low- and high-dose).

Age cohorts and dose groups:

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

A total of 60 patients will be enrolled such that 12 evaluable patients will be in each age cohort and 6 patients will be within each dose group. Dropouts or patients with unusable data (for reasons other than AEs) may be replaced.

3.1.2. Treatment Groups

Patients will be dosed orally with a single dose of edoxaban on Day 1. Patients in the 12 to < 18 years of age cohort will be dosed with multiples of edoxaban tablets of 30 mg strength. Patients younger than 12 years of age will receive the edoxaban granule for oral suspension. The dosing amount and formulation type may change based on emerging data.

If a patient is unable or unwilling to ingest the assigned dosing form (tablet or suspension formulation), the patient will not be enrolled and will be replaced.

Patients will be administered edoxaban in the morning with water.

- Cohorts 1a/1b: 120 mL water;
- Cohorts 2a/2b: 60 mL water;
- Cohorts 3a/3b: 40 mL water;
- Cohorts 4a/4b: 10 mL water;
- Cohorts 5a/5b: 10 mL water.

Patients will be asked to fast for at least 4 hours before dosing and for an additional 2 hours after dosing. If this is not feasible because of the patient's age or other needs, (unflavored) milk, or an equivalent substitute liquid (but not fruit juices), will be allowed until 1 hour before and starting at 1 hour postdose. During this period, the total volume of liquids should not exceed 240 mL, excluding the volume of water utilized for dosing.

Order of enrollment will be from the oldest age cohort to the youngest age cohort. Within each age cohort, enrollment will first start in the lower dose group (to achieve exposures comparable to a 30 mg adult dose). After evaluation of PK and safety data from at least half the patients in the lower dose group, enrollment may then start in the higher dose group (to achieve exposures comparable to a 60 mg adult dose). If the observed exposures are higher than expected in the lower dose group and exceed the projected 60 mg adult exposure, then a lower dose may be investigated in the proposed "high-dose" group. Enrollment in the next younger age cohorts will begin when at least 50% of patients have completed the study in the older age cohort. Enrollment in the younger age cohorts will start only after PK and safety data have been evaluated from at least 6 patients (3 low-dose and 3 high-dose) in the older age cohort. Pharmacokinetic and safety data will be reviewed by a DSMB (see Section 11.9) who will approve the start of the next younger age cohort. However, enrollment initiation of Cohort 5 may be considered without PK and safety data from at least 50% of patients in the preceding older dose group.

In Cohort 1, the oldest age group (12 to < 18 years), doses have been selected on the basis of modeling of adult data to target comparable exposures to 30 mg (low-dose) and 60 mg (high-dose). In this cohort, fixed dosing will be used. In Cohorts 2, 3, 4, and 5, the younger age groups (38 weeks gestation to < 12 years), appropriated doses will be selected to elicit target exposures comparable to those achieved from adult doses of 30 mg (low-dose) or 60 mg (high-dose). Patients in Cohort 1 will receive multiples of edoxaban tablets of 30 mg strength. Patients in Cohorts 2, 3, 4, and 5 will receive the edoxaban granule for oral suspension. The dose that each dose group receives will be determined by Daiichi Sankyo based on emerging PK data and modeled doses needed to achieve target exposures.

Study duration will be approximately 4 weeks for each patient, which will include a screening period (within 21 days of dosing), a treatment period, and a follow-up visit conducted within 10 days after dosing. However, a patient will be considered to have completed the study if they provide the last scheduled PK sample. The treatment period will consist of predose procedures occurring on Day -1 or 1, dosing on Day 1, and postdose procedures occurring postdose on Days 1, 2 (all cohorts) and Day 3 (all patients enrolled prior to Version 5.0 of the protocol may have had Day 3 PK samples obtained). The treatment period days may occur as in-patient or

out-patient based on the clinic's ability/discretion. The overnight stays are not mandatory. Check-out procedures will be performed after the last PK/PD blood samples are collected (Day 2 or Day 3).

An attempt will be made to have a balanced distribution of ages in each age cohort and dose group to provide maximum information regarding PK/PD and safety/tolerability.

In each age cohort, appropriated doses will be selected to target exposures comparable to adult doses of 30 mg (low-dose) or 60 mg (high-dose). This will be done on an ongoing basis, whereby emerging PK concentration-time data from completed patients will be analyzed on an ongoing basis and used to predict the doses required to obtain targeted exposures in upcoming age cohorts and dose groups. Additionally, this ongoing PK analysis will be used to refine and optimize the PK blood sampling scheme (number of samples and timing) in upcoming age cohorts and dose groups.

Refer to the Schedule of Events (Appendix 17.7) and study procedures (Section 6).

3.1.3. Study Endpoints

The PK endpoints will include modeled PK parameters such as apparent systemic clearance (CL/F), apparent volume of distribution (V/F), and area under the concentration-time curve (AUC) for edoxaban and metabolites, and metabolite/parent ratios for AUC.

The PD endpoints will include observed, change-from-baseline, and percent-change-from-baseline PT, aPTT, and anti-FXa.

Safety assessments will include: AEs, physical examination findings, vital signs, standard hematology, clinical chemistry, and urinalysis laboratory tests. Note: urinalysis will be performed with plastic bags with a sticky strip from neonates and infants with diapers.

Palatability of the liquid formulation will be assessed using visual analog scale (VAS) scores.

3.1.4. Duration of the Study

The first patient is expected to be enrolled in June 2014.

3.1.5. Duration of Patient Participation

Approximately 4 weeks for each patient, which will include a screening period (within 21 days of dosing), a treatment period, and a follow-up visit conducted within 10 days after dosing. However, a patient will be considered to have completed the study if they provide the last scheduled PK sample. The treatment period will consist of predose procedures occurring on Day -1 or 1, dosing on Day 1, and postdose procedures occurring postdose on Days 1, 2 (all cohorts) and Day 3 (all patients enrolled prior to Version 5.0 of the protocol may have had Day 3 PK samples obtained). The treatment period days may occur as in-patient or out-patient based on the clinic's ability/discretion. The overnight stays are not mandatory. Check-out procedures will be performed after the last PK/PD blood samples are collected.

3.1.6. Stopping Rules

Due to potential tolerability differences among age cohorts, stopping criteria will be applied independently to each age cohort. The minimum intolerable dose will be defined as (1) the dose

at which a minimum of 60% of evaluable patients in an age cohort experiences more than 1 occurrence of moderate or severe AEs, related to edoxaban or (2) the dose at which at least 1 patient in an age cohort experiences an SAE judged to be medically serious and related to edoxaban as assessed by an independent DSMB. The DSMB will be responsible for reviewing and assessing the available safety data as set forth in the DSMB Charter.

3.1.7. Steering Committee

A steering committee consisting of a panel of study Investigators or therapeutic area experts will be convened to provide clinical and scientific expertise to Daiichi-Sankyo on the design, execution, and analysis of this Phase 1 pediatric study. Responsibilities of the Steering Committee are set forth in the Steering Committee Charter.

3.2. Selection of Doses

3.2.1. Experimental Treatments

Not applicable.

3.2.1.1. For the Study

Edoxaban will be evaluated in all patients in 1 treatment period. Each patient will receive a single oral dose on Day 1. In each age cohort, appropriated doses will be selected to achieve exposures comparable to adult doses of 30 mg (low-dose groups) and 60 mg (high-dose groups). The doses given to each age cohort and dose group will be adjusted based on emerging data.

3.2.1.2. For Individual Patients

The dose given to individual patients will be based on age cohort, body weight and targeted exposure as described in Section 3.2.1.1.

3.2.2. Control Treatments

Not applicable.

4. STUDY POPULATION

4.1. Enrollment

The Investigator will maintain a confidential screening log of all potential study candidates that includes limited information of the patients (initials, age [derived], and sex), date, and outcome of the screening process (e.g., enroll in the study, reason for ineligibility, and refused to participate).

The Investigator will be expected to maintain an enrollment log of all patients enrolled in the study indicating their assigned study number.

The Investigator will maintain a confidential patient identification code list. This confidential list of names of all patients allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any patient, when necessary.

Patients will be considered enrolled upon obtaining informed consent (assent, when applicable) at randomization.

Each patient or legally acceptable representative will sign an ICF and assent, if applicable, as required by country-specific regulatory authorities. For additional information on informed consent, see Section 1.6.2.

4.1.1. Inclusion Criteria

Male and female pediatric patients who may require or are currently on anticoagulant therapy may be enrolled.

These may include:

- Patients who have a recently acquired or Investigator determined ongoing risk of thromboembolic events (e.g., patients with thrombophilia, congenital heart disease, presence of a central venous catheter and prior VTE).
- Patients who are completing their standard-of-care anticoagulant therapy. Edoxaban can be initiated 12 hours after cessation of enoxaparin, dabigatran, or apixaban therapy (A-U136, A-U151, and A-E152) and 24 hours after cessation of rivaroxaban therapy (A-U151). Note: that the dose of edoxaban should be at the time of the next scheduled standard-of-care anticoagulant administration:
  - At least 4 hours after last dose of unfractionated heparin.
  - At least 12 hours after last dose of bid LMWH.
  - At least 24 hours after last dose of qd LMWH and SP Xa inhibitors.
  - For patients who were on a prior vitamin K antagonist (e.g., warfarin [C-U122] and any other anticoagulants) therapy, INR value should be ≤ 2.5 prior to edoxaban dosing. If the patient's INR is > 2.5, the patient's INR should be monitored until it is ≤ 2.5.

- Patients who are currently treated for VTE with at least 5 days of heparin may interrupt their standard-of-care anticoagulant therapy for edoxaban administration. The dose of edoxaban should be:
  - At least 12 hours from last dose of bid LMWH, with a restart of LMWH 24 hours after edoxaban dose.
  - At least 24 hours from last dose of qd LMWH, with a restart of LMWH 24 hours after edoxaban dose.
- Patients with cardiac conditions who may require anticoagulant therapy.
- Patients with sickle cell disease who may require anticoagulant therapy.

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

Patients must satisfy all of the following criteria to be included in the study. Any temporal changes in the following criteria that may prohibit patient consideration, but should normalize for future eligibility, should be reassessed for the patient's future participation in the study:

1. Patients/legal guardian(s) must be able to provide written informed assent (patient, when applicable) and ICFs (signed by parent/legal guardian) prior to participating in the study.
2. Male or female patients 38 weeks gestation to < 18 years of age on the day of dosing.
3. Patients 2 to < 18 years of age must have a body mass index (BMI) between the 5th and 95th percentile based on the 2000 CDC Growth Charts[7] (the maximum number of patients in each dose group that have a BMI between the 85th and 95th percentile should not be more than 2 patients). Patients < 2 years of age must have a body weight between the 5th and 90th percentile based on the 2000 CDC Growth Charts.[7]
4. Female patients who have had menarche must test negative for pregnancy, as per local practice, at screening and check-in.
5. Female patients who have had menarche and are sexually active must agree to use an effective contraception method, per local practice, for at least 30 days prior to edoxaban dose.
6. Patients/legal guardian(s) must agree to food and drug restrictions during the study.
   - Patients must agree to abstain from and/or legal guardians must agree not to give the patient cola, tea, coffee, chocolate, and other caffeinated drinks and food from 48 hours before dose administration to until after the last PK sample collection (see Section 5.3 for a complete list). Mothers who are breastfeeding study patients should maintain this same dietary restriction for 24 hours prior to edoxaban dosing.
   - Patients must agree to abstain from and/or legal guardian(s) must agree not to give the patient St. John's Wort and food/supplement and beverages containing grapefruit, grapefruit juice, and Seville oranges from 14 days before the first dose through to until after the last PK sample collection (see Section 5.3).

- Patients must agree to abstain from CYP3A4 inhibitors/inducers and P-gp inhibitors/inducers for 14 days prior to the edoxaban dose to until after the last PK sample collection (see Section 5.2).

7. Patients must agree to abstain from the use of nonsteroidal anti-inflammatory drugs (such as ibuprofen) and antiplatelet (except for low-dose aspirin) from 14 days prior to edoxaban dose until after the last PK sample is collected. Patients on low-dose aspirin treatment (1 to 5 mg/kg/day, maximum of 100 mg/day) are permitted to participate in the study per the Investigator's judgment that this does not place the patients at risk. Low-dose aspirin on Day 1 should be withheld until 4 hours post edoxaban dose.
8. Other than signs and symptoms characteristic to their disease state, patients are to be in good health as determined by the absence of clinically significant deviations from normal, with respect to medical and surgical history, physical examination, vital signs, and laboratory reports, as deemed by the Investigator prior to enrollment.

4.1.2. Exclusion Criteria

Patients who meet any of the following criteria will be disqualified from entering the study. Any temporal changes in the following criteria that may prohibit patient consideration, but should normalize for future eligibility, should be reassessed for the patient's future participation in the study:

1. Patients with abnormal coagulation tests during screening, as defined by local laboratory reference ranges, which are not explained by anticoagulant therapy or temporary concomitant affections.
2. Patients with stroke where anticoagulant therapy is contraindicated.
3. Patients with stage 2 hypertension defined as blood pressure confirmed > 99th percentile + 5 mmHg.
4. Patients with renal function less than 50% of normal for age and size as determined by the National Kidney Disease Education Program version of the Schwartz formula (see Appendix 17.5).[8]
5. Actively bleeding, has a high risk of bleeding, or has a history of major bleeding.
6. Has a currently active gastrointestinal ulceration or a known history of peptic ulcer or gastrointestinal bleeding (including hematemesis, melena, or rectal bleeding including bleeding from hemorrhoids) within the previous 3 months.
7. Has known diabetic retinopathy.
8. Has thrombocytopenia at screening (< 20 × 10^9/L).
9. Patients with history of major trauma, major or invasive procedures within the last month prior to screening. Otherwise, shorter time may be permitted depending on the surgery and based on the Investigator's judgment of bleeding risk.
10. Patients with known malabsorption disorders (e.g., cystic fibrosis or short bowel syndrome). Otherwise, shorter time may be permitted depending on the surgery and based on the Investigator's judgment.

11. Hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk, alanine transaminase (ALT) > 5 times the upper limit of normal (ULN), or total bilirubin > 2 times the ULN with direct bilirubin > 20% of the total.
12. Patient is currently enrolled in another investigational device or drug study or is receiving other investigational agents. Patients must have completed the prior clinical study at least 30 days prior to dosing.
13. Patients of childbearing potential (post-menarche) who are sexually active and are not using approved contraception, per local practice; who are pregnant (as based on test results); or are breastfeeding.
14. Females with history of abnormal menses, including history of menorrhagia (heavy menstrual bleeding), metrorrhagia, or polymenorrhea.
15. Patient has known hypersensitivity to the active ingredient or any of the excipients of any compounds of the investigational product (IP) (see Appendix 17.1).
16. Positive drug or alcohol screen (excluding cotinine) at screening for patients 12 years of age or older, neonates (0 to 28 days old), and for patients who are being breastfed. Exception to this is if patients are on prescription drug(s). The window to potentially hold and/or resume the prescription drug will need to be determined by DSI based on the information of the prescription drug.
17. Patients who have received a transfusion or any blood products within 30 days prior to the first dose.
18. Patients with any condition that, as judged by the Investigator, would place the patient at increased risk of harm if he/she participated in the study or would interfere with the conduct of the study or the interpretation of the data.
19. Patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome and are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies).

4.2. Removal of Patients from Therapy

4.2.1. Reasons for Withdrawal/Early Discontinuation

Any patient who discontinues from the study treatment for any reason will have their study treatment discontinuation recorded. A patient will be considered to have completed the study if they provide the last scheduled PK sample.

Patients may be withdrawn from the study after signing informed consent for the following reasons:

- AE.
- Physician decision.
- Withdrawal of consent by the following:
  - Child,

  - Parent, or
  - Legal guardian.
- Protocol violation.
- Death.
- Pregnancy.
- Termination of all or part of the study by the Sponsor.
- Other.

If a patient withdraws 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 treatment and the reason for withdrawal.

If the patient is withdrawn due to an AE, the Investigator will follow the patient until the AE has resolved or stabilized.

All patients who are withdrawn from the study should complete protocol-specified withdrawal procedures (Section 4.2.2).

4.2.2. Withdrawal Procedures

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason without penalty. Every effort will be made to determine why any patient withdraws from the study prematurely. This information should be recorded. All patients who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. If a patient withdraws prematurely after dosing, all data normally collected prior to study discharge should be collected at the time of premature discontinuation, or at the scheduled end-of-study visit. A genuine effort must be made to determine the reason(s) why a patient fails to return for the necessary visits. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the clinic.

4.2.3. Patient Replacement

Dropouts (for reasons other than AEs) may be replaced, if deemed necessary, upon written approval by the Sponsor. A replacement patient will be within the same age cohort range and will receive the same dose and formulation of IP as the patient being replaced. Any replacements will be made only after receiving the Sponsor's written prior authorization.

4.2.4. Patient Re-screening

Re-screening of patients that fail to meet the Inclusion and Exclusion criteria is allowed if the reason for failure to meet the criteria has resolved and is no longer considered a risk to the patient (e.g., temporal laboratory deviations meeting exclusion criteria, treatment with contraindicated medications, non-chronic diagnoses). Re-screening of patients for this reason will be reviewed on a case-by-case basis and is dependent upon approval from the Medpace and Daiichi Sankyo Medical Monitors. However, if a patient is screened but cannot dose for

personal/logistic reasons within 21 days of screening, they will need to be re-screened. The exception is, patients that were previously on warfarin therapy and need to be within the acceptable range of INR values. This will not be considered rescreening, and only INR values will be monitored at subsequent testing to ensure that prior to edoxaban dosing, the patient meets inclusion with INR ≤ 2.5.

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

The Investigator must ensure that the IP will be used only in accordance with the protocol.

According to ICH GCP 1.33, an IP is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study. This includes products with marketing authorizations when used or assembled (formulated or packaged) in a way different from the approved form or when used for an unapproved indication, or when used to gain further information about an approved use.

The IP for this study is edoxaban (DU-176b) in any of the following formulations:

- Edoxaban 30 mg oral tablets.
- Edoxaban granules for oral suspension (60 mg reconstituted with water to provide a 6 mg/mL suspension for oral administration).

Edoxaban doses will be appropriated to achieve exposures comparable to adult doses of 30 mg (low-dose) and 60 mg (high-dose). Patients in the 12 to < 18 years of age cohort will receive multiples of edoxaban tablets of 30 mg strength. Patients < 12 years will receive the liquid oral suspension formulation.

5.1.1. Method of Assigning Patients to Treatments and Blinding

This will be an open-label study. This study is not randomized. Patients will receive edoxaban on 1 occasion. Enrollment will first start in the lower dose group of the oldest age cohort (to achieve exposures comparable to a 30 mg adult dose). After evaluation of PK and safety data from at least half the patients in the lower dose group, enrollment will start in the higher dose group (to achieve exposures comparable to a 60 mg adult dose). If the observed exposures are higher than expected in the lower dose group and exceed the projected 60 mg adult exposure then a lower dose may be investigated in the proposed "high-dose" group. Enrollment in the next younger age cohorts will begin when PK and safety data from at least 50% (N = 6) of patients in the preceding older dose group have been reviewed. Pharmacokinetic and safety data will be reviewed by a DSMB (see Section 11.9) who will approve the start of the next younger age cohort. However, enrollment initiation of Cohort 5 may be considered without PK and safety data from at least 50% of patients in the preceding older dose group. An attempt will be made to enroll patients spanning the entire age range for each age cohort.

5.1.2. Method of Assessing Treatment Compliance

The following measures will be employed to ensure treatment compliance. The single dose of IP should be administered under the supervision of clinical study personnel. For patients receiving the tablet formulation, a mouth and hand check of all patients should be carried out to ensure that all tablets have been swallowed, if applicable. For patients receiving the liquid oral suspension the clinic personnel will check and record whether any of the liquid is spit out or lost to drooling.

5.1.3. Labeling and Packaging

Investigational products will be packaged and labeled in an open-label format. Clinical study labels will include study number, contents, quantity, lot number, directions, storage conditions, CAUTION statement as required by country/region, and Sponsor information. In addition, oral syringes for dosing of reconstituted suspension will be provided by the Sponsor.

Edoxaban 30 mg tablets, expressed as the anhydrous free base, will be supplied by the Sponsor in blister cards containing 30 tablets, in an open-label format. The 60 mg edoxaban granules for reconstitution, will be packaged in amber glass bottles (wide neck) with white polypropylene caps, and supplied by the Sponsor.

5.1.4. Preparation

The IP will be provided as tablets and as a granule for oral suspension formulation.

No special preparation will be required for the tablet formulation.

For edoxaban (DU-176b) granule for oral suspension 60 mg, investigational product will be supplied in amber glass bottles (wide neck) with white polypropylene caps. The medication requires reconstitution with water and must be freshly prepared just prior to administration (within 30 minutes). The total amount of diluent (non-carbonated water) to be added is 8 mL, and added in 1 part. After reconstitution, the resultant drug concentration will be 6 mg/mL. The maximum amount of medication will be 10 mL. Aliquots appropriate to provide the required dose will be withdrawn from this 10 mL suspension. Before aliquoting, the bottle must be shaken. The edoxaban suspension is a single-use preparation for immediate use and is not intended to be stored.

5.1.5. Storage

Investigational products (edoxaban tablets and granules for reconstitution) must be stored at 20° to 25°C (68° to 77°F), with excursions permitted to 15° to 30°C (59° to 86°F). Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions. If storage conditions go outside of the specified range, DSI should be contacted. The excursions will be discussed with the Sponsor to determine what action is necessary.

5.1.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition and temperature recording of the drug, check for appropriate local language in the label, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed as instructed on the form. The original will be retained at the 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 resolution is obtained from the Sponsor.

A Drug Accountability Record will be used for the IP, and can be provided by the Sponsor/Sponsor representative, or the site can use a Sponsor Approved Form. The record must be kept current and should contain the dates and quantities of drug received, patients for whom the IP was dispensed (identification number and/or initials or supply number as applicable), the date and quantity of IP dispensed and remaining, if from individual patient drug units, as well as the initials of the dispenser.

At the end of the study, or as directed, all IP, including unused, partially used, or empty containers, will be destroyed at the clinic. The IP will only be returned to a designee as instructed by the Sponsor if the clinic is unable to perform the IP destruction. Dosage form (ie, tablet, granule bottle) site level accountability documentation is required as part of the disposition records of the investigational product. The dosage form site level accountability documentation should be appended to the Certificate of Destruction.

Investigational product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return/destruction of IP must be documented. Dosage form (ie, tablet, granule bottle) site level accountability documentation must 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.

At the end of the study, a final IP reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition standard operating procedures (SOPs).

All IP 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 site.

5.1.7. Retention Samples

Retention samples will be collected and stored in countries where required by regulations.

5.2. Concomitant Medications

For the below specified number of days through study completion or upon early withdrawal, the following medications are not allowed:

- Use of P-gp inhibitors or inducers (see Appendix 17.4) within 14 days prior to the edoxaban dose until after the last PK sample is collected.
- Use of any CYP3A4 inhibitors/inducers (see Appendix 17.3) for 14 days prior to edoxaban dose to until after the last PK sample is collected.

- Use of nonsteroidal anti-inflammatory drugs (such as ibuprofen), and antiplatelet (except low-dose aspirin [1 to 5 mg/kg/day, maximum of 100 mg/day]) from 14 days prior to edoxaban dose to until after the last PK sample is collected. Patients on low-dose aspirin treatment (1 to 5 mg/kg/day, maximum of 100 mg/day) are permitted to participate in the study per the Investigator's judgment that this does not place the patients at an unacceptable bleeding risk. Low-dose aspirin on Day 1 should be withheld until 4 hours post edoxaban dose.

During the study, concomitant mediations required for care of treatment-emergent AEs (TEAEs) will be permitted; although, where possible, the Investigator should speak with the DSI Medical Monitor and Study Director before prescribing such medication. For treatment of pain or for analgesic use, if needed, acetaminophen is recommended.

Any medication (other than study drug) taken by patients during the course of the study will be recorded and coded using the World Health Organization drug dictionary. If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the patient.

5.3. Lifestyle Guidelines

At screening, patients/legal guardians will be informed that if accepted for the study, no St. John's Wort or foods/supplements or beverages containing grapefruit, grapefruit juice, or Seville oranges are allowed for 14 days prior to dosing to until after the last PK specimen collection. Patients must agree to abstain from and/or legal guardians must agree not to give the patient cola, tea, coffee, chocolate, and other caffeinated drinks and food from 48 hours before dose administration through the end of the last PK specimen collection. Mothers who are breastfeeding study patients should maintain this same dietary restriction for 24 hours prior to edoxaban dosing.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Appendix 17.7. To minimize pain and distress for pediatric patients, the following measures are allowed:

- Use of topical anesthetics
- Use of indwelling cannula

However, heparin should not be used for flushing the cannula.

6.1. Screening

Screening will take place within a 3-week window (Days -21 to -2) before dosing. Informed consent will be obtained from the patient/guardian prior to performing any of the screening assessments. For information regarding re-screening, see Section 4.2.4.

The following activities and/or assessments will be performed at/during screening:

- Informed consent (for parent/legal guardian/patient) and depending on the age of the patient, an assent form may also be signed by the patient.
- Inclusion/exclusion criteria.
- Record demographic information (date of birth/age, sex, ethnicity, and race).
- Medical and surgical history, including medication history.
- AE monitoring.
- Concomitant medication monitoring.
- Physical examination, including height, weight, and BMI (derived).
- Pregnancy test based on local practice (for post-menarchal females).
- Patients of childbearing potential (post-menarche) who are sexually active must agree to use an effective contraception method, per local practice, for the duration of the study.
- Blood samples for:
  - Clinical laboratory tests (hematology and serum chemistry) if not performed within 2 weeks prior to screening (refer to Section 9.6).
  - Coagulation (PT, INR, and aPTT).
  - Serology (human immunodeficiency virus [HIV] and hepatitis B and C testing) if not performed within 2 weeks prior to screening.
  - PD blood samples for Cohorts 4 and 5.

- Urine sample for:
  - Urine drug screen for the presence of the following controlled substances: opiates, benzodiazepines, amphetamines, cannabinoids, cocaine, barbiturates, phencyclidine, cotinine levels (non-exclusionary), and alcohol will be performed on patients 12 years of age and older, for newborns, and for patients who are being breastfed.
  - Urine sample for dipstick analysis. Microscopic analysis may be required if dipstick is positive for blood, RBC, or WBC.
- Vital signs including blood pressure, pulse rate, and body temperature after resting at least 5 minutes in a sitting or supine position. (Note: the appropriate cuff size based on arm circumference will be used).

6.2. Randomization

This is not a randomized study. In each age group, patients will be assigned to a particular treatment in a manner that allows for an even distribution of ages across doses (this decision will be made in consultation with clinical study lead).

6.3. Treatment Period

6.3.1. Check-in and Treatment

The following procedures apply to check-in and treatment, as appropriate.

Patients will be asked to fast for at least 4 hours before dosing and for an additional 2 hours after dosing. If this is not feasible because of the patient's age or other needs, (unflavored) milk, or an equivalent substitute liquid (but not fruit juices), will be allowed until 1 hour before dosing and starting at 1 hour postdose. During this period, the total volume of liquids should not exceed 240 mL, excluding the volume of water utilized for dosing.

6.3.2. Check-in (Day -1/1 Predose)

Check-in is scheduled for Day -1; however, check-in may also occur on Day 1 prior to dosing at the clinic's discretion. Patients may be confined from time of check-in until after the last assessment is made on Day 2 (or Day 3 for patients enrolled prior to Version 5.0 of the protocol); however, overnight stays are not required.

The following activities and/or assessments will be performed at/during check-in:

- Reassessment of eligibility.
- Medical and surgical history, including medication history.
- Physical examination, including height, weight, and BMI (derived).
- Pregnancy test based on local practice (for post-menarchal females).

- Urine sample for:
  - Urine drug screen for the presence of the following controlled substances: opiates, benzodiazepines, amphetamines, cannabinoids, cocaine, barbiturates, phencyclidine, cotinine levels (non-exclusionary), and alcohol will be performed on patients 12 years of age and older, for newborns, and for patients who are being breastfed.
  - Urine sample for dipstick analysis. Microscopic analysis may be required if dipstick is positive for blood, RBC, or WBC.
- Vital signs including blood pressure, pulse rate, and body temperature after resting at least 5 minutes in a sitting or supine position. (Note: the appropriate cuff size based on arm circumference will be used.)
- AE monitoring.
- Concomitant medication monitoring.

6.3.3. Treatment Period (Days 1 to 3)

6.3.3.1. Day 1

On Day 1, the following procedures will be performed after the patient has fasted for at least 4 hours (patients will continue to fast until 2 hours postdose). Patients who have not fasted must return on a subsequent day for Day 1 treatment. Any procedure occurring after hour 8 on Day 1 may be performed using a home healthcare service, depending on the availability of the service in the patient's country:

- **All Cohorts:**
  - Edoxaban administration.
  - Assessment of palatability for patients or guardians of patients receiving the edoxaban granule for oral suspension formulation (including bitterness, sweetness, overall taste, and aroma) using 100 mm VAS.
  - AE monitoring.
  - Concomitant medication monitoring.
- **Cohort 1:**
  - Vital signs (including, blood pressure, pulse rate, and body temperature) will be taken before dose administration and within the following windows: 0.25 to 1 hour, 1.5 to 3 hours, and 8.5 to 14 hours postdose. All vital sign assessments will be performed before the scheduled blood sampling for edoxaban and after at least a 5-minute rest in a sitting or supine position. The position is which the vital signs are taken (i.e., sitting or supine) will be recorded in the CRF.

- Serial PK blood samples will be collected after edoxaban administration using a window approach at 0.25 to 1 hour, 1.5 to 3 hours, 3.5 to 6 hours, 6.5 to 8 hours, and 8.5 to 14 hours postdose.
- Serial PD blood samples for estimation of biomarkers of coagulation (aPTT, PT, and anti-FXa) will be collected at predose and immediately after simultaneously scheduled PK sample collections at 0.25 to 1 hour, 1.5 to 3 hours, 3.5 to 6 hours, and 6.5 to 8 hours.

- **Cohorts 2 and 3:**
  - Vital signs (including, blood pressure, pulse rate, and body temperature) will be taken before dose administration and within the following windows: 0.25 to 1 hour, 1.5 to 3 hours, and 9 to 14 hours postdose. All vital sign assessments will be performed before the scheduled blood sampling for edoxaban and after at least a 5-minute rest in a sitting or supine position. The position is which the vital signs are taken (i.e., sitting or supine) will be recorded in the CRF.
  - Serial PK blood samples will be collected after edoxaban administration using a window approach at 0.25 to 1 hour, 1.5 to 3 hours, 4 to 8 hours, and 9 to 14 hours postdose.
  - Serial PD blood samples for estimation of biomarkers of coagulation (aPTT, PT, and anti-FXa) will be collected at predose and immediately after simultaneously scheduled PK sample collections at 0.25 to 1 hour, 1.5 to 3 hours, 4 to 8 hours, and 9 to 14 hours postdose.
- **Cohort 4:**
  - Vital signs (including, blood pressure, pulse rate, and body temperature) will be taken before dose administration and within the following windows: 0.5 to 2 hours, 3 to 8 hours, and 9 to 14 hours postdose. All vital sign assessments will be performed before the scheduled blood sampling for edoxaban and after at least a 5-minute rest in a sitting or supine position. The position is which the vital signs are taken (i.e., sitting or supine) will be recorded in the CRF.
  - Serial PK blood samples will be collected after edoxaban administration using a window approach at 0.5 to 2 hours, 3 to 8 hours, and 9 to 14 hours postdose.
  - PD blood samples for estimation of biomarkers of coagulation (aPTT, PT, and anti-FXa) will be collected immediately after simultaneously scheduled PK sample collection at 0.5 to 2 hours postdose.

- **Cohort 5:**
  - Vital signs (including, blood pressure, pulse rate, and body temperature) will be taken before dose administration and within the following windows: 0.5 to 2 hours, 3 to 8 hours, and 9 to 14 hours postdose. All vital sign assessments will be performed before the scheduled blood sampling for edoxaban and after at least a 5-minute rest in a sitting or supine position. The position is which the vital signs are taken (i.e., sitting or supine) will be recorded in the CRF. Note: Patients will receive either 2 or 3 of these vital signs recordings depending on which PK blood sample timepoints they are assigned.
  - PK blood samples will be collected after edoxaban administration at a total of 3 of the 4 possible timepoints postdose: 0.5 to 2 hours (mandatory), 3 to 8 hours, 9 to 14 hours, and 24 to 36 hours (on Day 2). The timepoints will be assigned by the Sponsor once the subject is approved to be randomized.
  - PD blood samples for estimation of biomarkers of coagulation (aPTT, PT, and anti-FXa) will be collected immediately after simultaneously scheduled PK sample collection at 0.5 to 2 hours postdose.

Exact dates and times of dosing and sample collection will be recorded in the patients' CRFs and used for analyses. At time points when PK, and PD blood samplings occur at the same time, the PK blood samples will be collected first and then PD blood samples will be collected. An overnight stay on Day 1 is not mandatory.

6.3.3.2. Day 2

On Day 2, the following procedures will be performed:

- **All Cohorts:**
  - AE monitoring.
  - Concomitant medication monitoring.
- **Cohort 1, 2, and 3:**
  - PK blood samples will be collected using a window approach at 24 to 36 hours postdose.
  - PD blood samples for estimation of biomarkers of coagulation (aPTT, PT, and anti-FXa) immediately after collection of the simultaneously scheduled PK samples at 24 to 36 hours postdose.
- **Cohort 4:**
  - PK blood samples will be collected using a window approach at 24 to 36 hours postdose.
- **Cohort 5:**
  - Note: For this cohort, only 3 of 4 possible PK timepoints will provide a blood specimen. For patients who provided only 2 PK blood samples on Day 1, a 3rd PK

blood sample will be collected at 24 to 36 hours. No PK blood samples will be collected for patients who provided 3 PK blood samples on Day 1.

Note: the overnight stay on Day 1 is not required; however, the above procedures will occur on Day 2. Some patients may be given the option to have a home healthcare service conduct the Day 2 procedures in the patient's home, depending on the availability of the service in the patient's country. Exact dates and times of dosing and sample collection will be recorded in the patients' CRFs and used for analyses. At time points when PK and PD blood samplings occur at the same time, the PK blood samples will be collected first and then PD blood samples will be collected.

6.3.3.3. Day 3

On Day 3, the following procedures will be performed:

- **PK blood samples for Cohort 1:** will be collected using a window approach at 48 to 54 hours postdose.
- Vital signs (including blood pressure, pulse rate, and body temperature) will be taken 48 to 54 hours postdose. All vital sign assessments will be performed before the scheduled blood sampling for edoxaban and after at least a 5-minute rest in a sitting or supine position. The position is which the vital signs are taken (i.e., sitting or supine) will be recorded in the CRF.
- AE monitoring.
- Concomitant medication monitoring.

Note: the overnight stay on Day 2 is not required; however, the above procedures will occur on Day 3. Some patients may be given the option to have a home healthcare service conduct the Day 3 procedures in the patient's home, depending on the availability of the service in the patient's country. Exact dates and times of dosing and sample collection will be recorded in the patients' CRFs, and used for analyses.

6.4. Follow-up

Patients will participate in a follow-up visit. The visit will occur within 10 days after the edoxaban dosing. It will include the following:

- **All Cohorts:**
  - Physical examination, including weight, BMI, and height.
  - Vital signs including blood pressure, pulse rate, and body temperature after resting at least 5 minutes in a sitting or supine position (Note: the appropriate cuff size based on arm circumference will be used.)
  - AE monitoring.
  - Concomitant medication monitoring.
  - Coagulation (PT, INR, and aPTT).
  - Blood samples for clinical laboratory tests (hematology) (refer to Section 9.6).

- **Cohorts 1, 2, and 3:**
  - Blood samples for clinical laboratory tests (serum chemistry) (refer to Section 9.6).

Some patients may be given the option to have a home healthcare service conduct follow-up procedures in the patient's home, depending on the availability of the service in the patient's country.

6.5. 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 IRB/IEC.

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 patient. Sponsor must be notified of all intended or unintended deviations to the protocol (e.g., 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 patient was ineligible or received the incorrect dose or investigational treatment, and had at least 1 administration of IP, data should be collected for safety purposes.

The Investigator should notify the IEC or IRB of deviations from the protocol in accordance with local procedures.

7. EFFICACY ASSESSMENTS

Not applicable.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Variable(s)

8.1.1. Collection of Samples

PK blood samples will be collected for measurement of plasma concentrations of edoxaban and its metabolites (D21-2393, D21-3231, D21-1402, and D21-2135).

PK blood samples for patients in Cohort 1: Serial PK blood samples (2 mL per sample) will be collected over the following time windows:

- 0.25 to 1 hour postdose (1 sample)
- 1.5 to 3 hours postdose (1 sample)
- 3.5 to 6 hours postdose (1 sample)
- 6.5 to 8 hours postdose (1 sample)
- 8.5 to 14 hours postdose (1 sample)
- 24 to 36 hours postdose (1 sample)
- 48 to 54 hours postdose (1 sample)

PK blood samples for patients in Cohort 2 and 3: Serial PK blood samples (patients 6 to < 12 years of age: 2 mL per sample and patients < 6 years of age: 1 mL per sample) will be collected over the following time windows:

- 0.25 to 1 hour postdose (1 sample)
- 1.5 to 3 hours postdose (1 sample)
- 4 to 8 hours postdose (1 sample)
- 9 to 14 hours postdose (1 sample)
- 24 to 36 hours postdose (1 sample)

PK blood samples for patients in Cohort 4: Serial PK blood samples (600 µL per sample) will be collected over the following time windows:

- 0.5 to 2 hours postdose (1 sample)
- 3 to 8 hours postdose (1 sample)
- 9 to 14 hours postdose (1 sample)
- 24 to 36 hours postdose (1 sample)

PK blood samples for patients in Cohort 5: PK blood samples (600 µL per sample) will be collected after edoxaban administration at a total of 3 of the 4 possible timepoints postdose (timepoints will be assigned by the Sponsor once the subject is approved to be randomized):

- 0.5 to 2 hours postdose (mandatory) (1 sample)
- 3 to 8 hours postdose (1 sample)
- 9 to 14 hours postdose (1 sample)
- 24 to 36 hours postdose (1 sample)

Emerging PK concentration-time data from completing patients will be analyzed on an ongoing basis and used to refine and optimize the PK blood sampling scheme (i.e., both the number of samples and the sampling windows) if necessary.

The total blood volume collected for each age cohort will not exceed the guidelines for pediatrics research for each age cohort.[9] Blood loss must not exceed 1% of total blood volume at any time, 3% during 4 weeks. Blood sampling from patients for bioanalytical assessment will use the local methods appropriate for the patient's age to minimize associated blood volume, invasiveness, and pain.

Exact dates and times of dosing and sample collection will be recorded in the patients' CRFs and used for analyses.

Samples will be collected, labeled, stored, and shipped as detailed in Appendix 17.2.

8.1.2. Determination of Drug Concentrations

The plasma samples will be assayed for edoxaban and metabolites using a validated LC-MS/MS assay.

Edoxaban and D21-2393 will be evaluated for each time point, and if sufficient sample volume is available, then the following metabolites will also be assessed at each time point: D21-3231, D21-1402, and D21-2135. If sufficient blood volume is not available, then blood samples for a patient will be analyzed for edoxaban and D21-2393 for each time point but pooled to analyze the pooled sample for analysis of other metabolites. The pooled sample will also be analyzed for edoxaban and D21-2393, so relative abundance of metabolites to edoxaban can be calculated.

8.1.3. Rationale for Sample Collection Scheme

Blood sampling times specified in Section 8.1.1 have been optimized based on PopPK and simulations, as described in Section 1.3.

8.2. Pharmacodynamic Variable(s)

8.2.1. Coagulation

PD blood samples for patients in Cohort 1: Serial PD blood samples (1.8 mL per sample [Aliquots 1 and 2 will have approximately 0.25 mL and Aliquot 3 will hold the remaining portion of the sample]) will be collected (concurrent with the PK blood samples, if applicable) for measurement of biomarkers of coagulation (aPTT, PT, and anti-FXa) over the following time windows:

- Predose (1 sample)
- 0.25 to 1 hour postdose (1 sample)
- 1.5 to 3 hours postdose (1 sample)
- 3.5 to 6 hours postdose (1 sample)
- 6.5 to 8 hours postdose (1 sample)
- 24 to 36 hours postdose (1 sample)

PD blood samples for patients in Cohort 2 and 3: Serial PD blood samples (patients 6 to < 12 years of age: 1.8 mL per sample and patients < 6 years of age: 1 mL per sample [Aliquots 1 and 2 will have approximately 0.25 mL and Aliquot 3 will hold the remaining portion of the sample]) will be collected (concurrent with the PK blood samples, if applicable) for measurement of biomarkers of coagulation (aPTT, PT, and anti-FXa) over the following time windows:

- Predose (1 sample)
- 0.25 to 1 hour postdose (1 sample)
- 1.5 to 3 hours postdose (1 sample)
- 4 to 8 hours postdose (1 sample)
- 9 to 14 hours postdose (1 sample)
- 24 to 36 hours postdose (1 sample)

PD blood samples for patients in Cohort 4 and 5: PD blood samples (1 mL per sample [Aliquots 1 and 2 will have approximately 0.25 mL and Aliquot 3 will hold the remaining portion of the sample]) will be collected (concurrent with the PK blood samples, if applicable) for measurement of biomarkers of coagulation (aPTT, PT, and anti-FXa) over the following time windows:

- Screening Visit (1 sample)
- 0.5 to 2 hours postdose (1 sample)

The total blood volume collected for each age cohort will not exceed the guidelines for pediatrics research for each age cohort.[9] Blood loss must not exceed 1% of total blood volume at any time, 3% during 4 weeks. For younger age cohorts, microsampling assays may be employed. Blood sampling from patients for PD assessment will use the local methods appropriate for the patient's age to minimize associated blood volume, invasiveness, and pain.

Exact dates and times of dosing and sample collection will be recorded in the patients' CRFs and used for analyses.

Samples will be collected, labeled, stored, and shipped as detailed in Appendix 17.2.

8.3. Biomarker and Exploratory Variable(s)

Not applicable.

9. SAFETY ASSESSMENTS

9.1. Adverse Events

All clinical AEs occurring after the patient (or parent/guardian) signs the ICF and through the follow-up visit (up to 10 days after the last dose), whether observed by the Investigator or reported by the patient or patient's parent/guardian, will be recorded on the AE 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 SAEs are to be reported according to the procedures in Section 9.4 SAE Reporting-Procedure for Investigators. Investigator diagnosis will be recorded. Always report a 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 which do not worsen in severity should not be reported as SAEs (see Section 9.3.2 for definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. In addition, 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.

Each day the Investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient (or parent/guardian) or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. All laboratory values must be appraised by the Investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the Investigator must be recorded as an AE on the CRF, and if serious, reported as an SAE following the procedures in Section 9.4.

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

9.2. Safety Endpoints

Not applicable.

9.3. Definitions

9.3.1. Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which 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 lab findings which should be considered AEs.

9.3.2. Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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 patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, blood dyscrasias, or development of drug dependency or drug abuse.

Note:

- 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 treatment requiring hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

9.3.3. Adverse Event Severity

The following definitions should be used to assess intensity of AEs:

- Mild: Awareness of sign or symptom, but easily tolerated, i.e., does not interfere with patient's usual function.
- Moderate: Discomfort enough to cause interference with usual activity.

- Severe: Incapacitating with inability to work or do usual activity, i.e., interferes significantly with patient's usual function.

9.3.4. Causality Assessment

The Investigator should assess causal relationship between an AE and the IP on the basis or his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

- 1 = Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
  - 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.
- 2 = Not Related:
  - The AE does not follow a reasonable sequence from study product administration or can be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

9.3.5. Action Taken Regarding the Study Product

- 1 = Dose Not Changed: No change in study drug dosage was made.
- 2 = Drug Withdrawn: The study product was permanently stopped.
- 3 = Dose Reduced: The dosage of study product was reduced.
- 4 = Drug Interrupted: The study product was temporarily stopped.
- 5 = Dose Increased: The dosage of study product was increased.

9.3.6. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The patient fully recovered from the AE with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - Include sequelae/residual effects.
- 3 = Not Recovered/Not Resolved
  - The AE itself is still present and observable.
- 4 = Fatal
- 5 = Unknown

9.3.7. Other Action Taken for Event

- 1 = None
  - No treatment was required.
- 2 = Medication required
  - Prescription and/or over-the-counter medication was required to treat the AE.
- 3 = Other

9.4. Serious Adverse Event Reporting – Procedure for Investigators

9.4.1. Initial Reports

Within 24 hours of receipt of an SAE report:

- Complete a Daiichi Sankyo SAVER form, sign it, and fax it to Medpace using the designated fax transmittal form. Medpace will review and forward the SAVER form to Daiichi Sankyo Clinical Safety and Pharmacovigilance (CSPV).
- Call the Medpace SAE hotline for any questions regarding SAE reporting.

  Medpace SAE hotline – USA

  PPD

  Medpace SAE hotline – Europe:

  PPD
- Place the initial version of SAVER in the patient's file.

9.4.2. Follow-up Reports

Within 24 hours of the receipt of new information for a reported SAE:

- Complete a Daiichi Sankyo SAVER form with the new information. Please complete Sections 1 through 3 even if they contain no new information. For Sections 4 through 10, provide only the new information. Sign and fax the form to Medpace using the fax transmittal form.
- For SAEs that resulted in death, provide the autopsy report, if available, via e-mail, fax, or express mail.
- The CRO designated above will review and forward the follow-up SAVER form and supporting documents to Daiichi Sankyo CSPV.
- Place the follow-up version of the SAVER form and all supporting documentation in the patient's file.

9.4.3. Notifying Regulatory Authorities, Investigators, and IRB/IEC

Daiichi Sankyo and/or Medpace will inform Investigators, IRBs/IECs, and regulatory authorities of any Suspected Unexpected SAE Reactions (SUSARs) occurring in other clinics or other Daiichi Sankyo studies of the IP, as appropriate per local reporting requirements.

In the United States, upon receipt of the Sponsor's notification of SUSARs that occurred with the IP, 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 IECs.

The Reference Safety Information for the study is found in Section 6.11 of the Investigator's Brochure.

9.5. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any patient who becomes pregnant while receiving the IP or during the follow-up period.

Although pregnancy is not technically an AE, 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 patient using the Exposure In Utero (EIU) Reporting form. Please make sure the patient does not receive any study drug after learning of the pregnancy and contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the patient until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., post-partum complications, spontaneous 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 9.4.

9.6. Clinical Laboratory Evaluations

Blood samples for the following hematology tests will be taken at screening (if not performed within 2 weeks prior to screening) and at the final follow-up visit (or early termination). Blood samples for the following serum chemistry tests will be taken at screening (if not performed within 2 weeks prior to screening) for all cohorts, and at the final follow-up visit (or early termination) for Cohorts 1, 2, and 3. Cohorts 4 and 5 will not have serum chemistry performed at the final follow-up (or early termination) visit. (See Appendix Section 17.7).

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count (with indices), reticulocyte count, white blood cell (WBC) count (with differential), and platelet count
- Serum chemistry: sodium, potassium, magnesium, bicarbonate, chloride, calcium, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase, glucose, creatinine, blood urea nitrogen, total protein, albumin, uric acid, creatine kinase, total cholesterol, and triglycerides

Urinalysis to include urine dipstick with specific gravity, pH, protein, glucose, ketones, blood, RBC, WBC, bilirubin, and urobilinogen at screening and check-in. Microscopic analysis is required if dipstick is positive for blood, RBC, or WBC.

At screening only, blood will be collected for hematology and serum chemistry (if not performed within 2 weeks prior to screening) to include blood volume for HIV and hepatitis B and C testing. A pregnancy test (based on local practice) will be performed at screening and at check-in (Day -1/1 predose) for all female patients who have had menarche. At screening, urine samples will also be used to check for the presence of the following controlled substances: opiates, benzodiazepines, amphetamines, cannabinoids, cocaine, barbiturates, phencyclidine, cotinine levels (non-exclusionary), and alcohol.

Coagulation tests (PT, INR, and aPTT) will be collected in citrated blood collection tubes during screening and at the follow-up visit. Blood samples will be treated for PT, INR, and aPTT estimation as per the SOPs of the local or central laboratory.

The blood volume for all scheduled clinical laboratory assessments will not exceed the guidelines for pediatrics research for each age cohort.[9] Blood loss must not exceed 1% of total blood volume at any time, 3% during 4 weeks.

9.7. Vital Signs

Vital signs (blood pressure, pulse rate, and body temperature) will be monitored at screening, at check-in (Day -1/Day 1 predose), Day 1 (and Day 3 for patients enrolled prior to Version 5.0 of the protocol) postdose, and at the final follow-up visit (or early termination). Heart rate and blood pressure will be measured after an at least 5-minute rest in a sitting or supine position. The position in which the vital signs are measured will be recorded in the patients' CRF.

9.8. Electrocardiograms

Not applicable.

9.9. Physical Findings

A complete physical examination will be performed on each patient at screening, at check-in (Day -1/Day 1 predose), on Day 3 (for patients enrolled prior to Version 5.0 of the protocol), and during the follow-up visit.

Body height and weight will be measured for all patients during the physical examinations to determine BMI.

9.10. Other Safety Assessments

Not applicable.

10. OTHER ASSESSMENTS

Formulation Palatability

Patients receiving the edoxaban granule for oral suspension formulation who are developmentally capable of providing an accurate response will be asked to rate several aspects of palatability (including bitterness, sweetness, overall taste, and aroma) using 100 mm VAS. The VAS questionnaire will be provided to the sites by Medpace.

Patients who are old enough will score the VAS themselves. For younger children, the parents will provide this information, if possible. For the youngest children, there will be free text input available, to provide information on whether the patient spit it out and may not have liked the flavor, etc.

VAS and text responses will be measured and/or recorded on the CRF. Refer to Appendix 17.6 for the VAS.

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Pharmacokinetic Analysis Set

The PK analysis set will comprise all patients who receive edoxaban as per protocol and have at least 1 postdose PK measurement with known collection times and date/time of dose administration and who do not have any clinically significant events or protocol deviations that may have compromised the integrity of the PK results.

11.1.2. Pharmacodynamic Analysis Set

The PD analysis set will comprise all patients who receive edoxaban as per protocol and have at least 1 postdose PD measurement with known collection time and date/time of dose administration and who do not have any clinically significant events or protocol deviations that may have compromised the integrity of the PD results.

11.1.3. Safety Analysis Set

The safety analysis set will include all patients who received edoxaban.

11.2. General Statistical Considerations

Complete details of the planned statistical analyses will be included in a separate Statistical Analysis Plan. The analyses for this study will be considered descriptive and exploratory. No visit windows will be used for analysis.

In general, all data will be summarized by age cohort and dose group, and all evaluable data will be included in the analyses. For qualitative variables, the population size (N for sample size and n for available data) and the percentage/incidence (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including the population size (N for sample size and n for available data), mean, SD, coefficient of variation (CV%), median, minimum, and maximum values.

11.3. Study Population Data

Patient disposition, demographics and baseline characteristics, prior and concomitant medications will be tabulated.

11.4. Efficacy Analyses

Not applicable.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

11.5.1. Pharmacokinetic Analyses

Plasma concentration-time data for edoxaban and metabolites (if data are available) will be listed by patient, age cohort and/or dose group, and measurement time interval, and will be plotted and summarized using descriptive statistics, as appropriate.

Plasma concentration-time data for edoxaban and metabolites will be analyzed using model-based approaches such as nonlinear mixed effects modeling, where data from other studies may be pooled with pediatric data, and PK parameters will be calculated. The goal of this approach will be to estimate PK parameters such as CL/F and V/F in pediatric patients. Derived PK parameters such as AUC and metabolite-to-parent ratios (if data permit) for AUC will also be estimated. Estimated PK parameters will be assessed for age dependencies using graphical and/or modeling methods. Estimated PK parameters will be listed and summarized by age cohort and/or dose group using descriptive statistics.

An exploratory analysis of variance model will be applied to natural log-transformed CL/F, V/F, and AUC with age cohort, dose, and age cohort by dose interaction as fixed factors. Appropriate adjustments on parameters, e.g., dose-normalization on AUC, or body weight-normalization on CL/F and V/F, might also be explored. The least-squares mean differences between age cohorts with age cohort of 12 to < 18 years as the reference and the corresponding 95% confidence intervals (CIs) will be exponentiated to obtain point estimates of ratios of geometric means and the corresponding 95% CIs by dose level and/or overall (as appropriate).

11.5.2. Pharmacodynamic Analyses

For PD biomarkers (PT, aPTT, and anti-FXa), observed, change-from-baseline, and percent-change-from-baseline data will be listed by patient, age cohort and/or dose group, and measurement time interval, and will be plotted and summarized using descriptive statistics, as appropriate.

The PK/PD relationships will be examined graphically to assess age dependencies. Additional PK/PD modeling may be conducted, if necessary, to understand age dependencies.

11.6. Safety Analyses

All analyses involving safety data (physical examination, vital signs, AEs, clinical laboratory tests [hematology, serum chemistry, and urinalysis]) will be based on the safety analysis set.

11.6.1. Adverse Event Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (latest version). All AEs, including SAEs, will be mapped to system organ class and preferred term and will be listed in the data listing. A TEAE is defined as an AE that emerges during treatment, having been absent pretreatment, or worsening relative to the pretreatment state. The number and percentage of patients reporting TEAEs will be tabulated for the safety analysis set by MedDRA preferred term and system organ class with a breakdown by dose, and further by relationship to study drug administered, and by severity. Listings of death events, SAEs, and AEs that lead to discontinuation of a patient will be presented.

11.6.2. Clinical Laboratory Evaluation Analyses

Standard hematology, serum chemistry, coagulation, and urinalysis at each planned assessment and change from baseline at each planned post-baseline assessment will be summarized for the safety analysis set by dose. Patients with abnormal values will be noted in the data listings.

11.6.3. Vital Sign Analyses

Vital signs will be summarized using descriptive statistics for baseline, each study evaluation, and change from baseline to each evaluation. Listings of all vital sign data will be provided.

11.6.4. Physical Finding Analyses

Results of physical examinations conducted throughout the study will be presented in listings. Patients with clinically significant abnormal findings will be noted in the data listings.

11.7. Other Analyses

11.7.1. Palatability Analyses

The VAS scores for palatability will be listed and summarized by age cohort and/or dose group using descriptive statistics, if data permit.

11.8. Interim Analyses

Emerging PK concentration-time data from completing patients will be analyzed using model-based approaches on an ongoing basis and used to predict and optimize the doses required to obtain targeted exposures in upcoming age cohorts and dose groups. Additionally, this ongoing PK analysis will be used to refine and optimize the PK blood sampling scheme (number of samples and timing) in upcoming age cohorts and dose groups.

11.9. Data and Safety Monitoring Board

An independent DSMB consisting of a panel of clinicians or therapeutic area experts will be convened to provide independent review to assure that patient safety and integrity of the trial are being upheld. Responsibilities of the DSMB are set forth in the DSMB Charter.

11.10. Sample Size Determination

A total of 60 patients will be enrolled, 12 evaluable per age cohort. Based on the assumptions of the inter-patient CV of 10.8% and 29.3% for CL/F and V/F respectively[10], and the ratio of a younger age cohort to the reference age cohort (12 to < 18 years) to be 1, a sample size of 12 evaluable per age cohort would provide > 95% power to assess that the 95% CI for cohort to reference cohort ratio is contained within the 60% to 140% range for CL/F. This sample size would provide about 76% power for the assessment on V/F. If emerging data suggest that the variability is much larger than anticipated, sample size may be increased.

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

The DSI 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 (e.g., CRFs, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action 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 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. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories, etc.) 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.

12.2. Data Collection

Completion of the CRFs should be kept current to enable the monitor to review the patient's status throughout the course of the study. The CRF will be completed, reviewed, and signed off or e-signed by the Investigator.

If the study employs paper CRFs, the Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the Investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

If the study employs Electronic Data Capture, the Investigator e-signs according to the study data flow.

12.3. Data Management

Each patient will be identified in the database by a unique patient identifier as defined by the Sponsor.

To ensure the quality of clinical data across all patients and sites, a Clinical Data Management review will be performed on patient data according to specifications given to DSI. Data will be vetted both electronically and manually. For electronic CRFs, 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 Electronic Data Capture application. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies.

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

Serious AEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using the most current version of MedDRA.

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 CRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the patient'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.

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:

- Patient files containing completed CRFs, informed consents, 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 IEC/IRB and the Sponsor.
- Records related to the IP(s) including acknowledgment of receipt at 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 Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an

agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

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.

12.5. Record Keeping

Records of patients, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, and distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. 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 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.

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 DSI. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

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

14. PUBLICATION POLICY

15. STUDY ADMINISTRATIVE INFORMATION

15.1. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days. The Sponsor will assure the timely submission of amendments to regulatory authorities.

15.2. Address List

15.2.1. Sponsor

Daiichi Sankyo, Inc.
211 Mount Airy Rd
Basking Ridge NJ 07920

15.2.1.1. Daiichi Sankyo, Inc. Medical Monitor

PPD

Daiichi Sankyo, Inc.
211 Mount Airy Rd
Basking Ridge, NJ 07920
PPD

15.2.1.2. Clinical Study Leader

PPD

Daiichi Sankyo, Inc.
211 Mount Airy Rd
Basking Ridge, NJ 07920
PPD

15.2.1.3. Daiichi Sankyo, Inc. Clinical Study Manager

PPD

Clinical Development Operations
Daiichi Sankyo, Inc.
211 Mount Airy Rd
Basking Ridge, NJ 07920
PPD

PPD
Clinical Development Operations
Daiichi Sankyo, Inc.
211 Mount Airy Rd
Basking Ridge, NJ 07920
PPD

15.2.2. Clinical Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
PPD

15.2.2.1. Clinical Research Organization Medical Monitor

PPD
Senior Medical Director
Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
Home office:
Wester Bogaardstraat 2
2011 WX Haarlem
the Netherlands
PPD

15.2.2.2. Clinical Research Organization Project Manager

Global Clinical Trial Manager
PPD
Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
PPD

15.2.3. Drug Safety

15.2.3.1. Sponsor Serious Adverse Event Report Form General Contact

Daiichi Sankyo, Inc.
Clinical Safety and Pharmacovigilance
PPD

15.2.4. Data Management

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
PPD

15.2.5. Biological Pharmacokinetic Specimens

PPD or delegate
Q_2 Solutions
19 Brown Rd
Ithaca, NY 14850
PPD

15.2.6. Biological Pharmacodynamic Specimens

PPD
Project Coordinator
Medpace Reference Laboratories, United States
5365 Medpace Way
Cincinnati, OH 45227
PPD

15.2.7. Biological Specimens (Outside North America Only)

PPD
Project Manager
Medpace Reference Laboratories, Belgium
Technologielaan 19
3001 Leuven, Belgium
PPD

15.2.8. Clinical Safety Laboratory

Central or local laboratories.

16. REFERENCES

1. DU-176b Investigator's Brochure, November 2013.
2. Chen N, Aleksa K, Woodland C, Rieder M, Koren G. Ontogeny of drug elimination by the human kidney. *Pediatr Nephrol* 2006; 21: 160-168.
3. De Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Cytochrome P450 3A: ontogeny and drug disposition. *Clin Pharmacokinet* 1999; 37: 485-505.
4. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants. Part 1. *Clin Pharmacokinet* 2002; 41: 959-998.
5. Abdel-Rahman SM, Amidon GL, Kaul A, Lukacova V, Vinks AA, Knipp GT et al. Summary of the National Institute of Child Healthy and Human Development – Best Pharmaceuticals for Children Act pediatric formulation initiatives workshop – pediatric biopharmaceutics classification system working group. *Clin Therap* 2012; 34: S11-24.
6. Novak M, Schlagenhauf A, Bernhard H, Schweintzger S, Leschnik B, and Muntean W. Effect of rivaroxaban, in contrast to heparin, is similar in neonatal and adult plasma. *Blood Coag Fibrinolysis* 2011, 22:588-592.
7. 2000 CDC (Centers for Disease Control and Prevention) Growth charts for the United States: Methods and Development. [Internet]. May 2002 [cited 2013 Aug 28]; 11(246). Available from: http://www.cdc.gov/growthcharts/2000growthchart-us.pdf.
8. Schwartz GJ, Work DF. Measurement and Estimation of GFR in Children and Adolescents. *Clin J Am Soc Nephrol* 2009; 4: 1832-43.
9. Howie SRC. Blood sample volumes in child health research: review of safe limits. Bulletin of WHO. 2011; 89: 46-53.
10. TMPP 006, Edoxaban Population Pharmacokinetic Analysis Based on Phase 1 Data, 4 Feb 2013.
11. Young G, Albisetti M, Bonduel M et al. Impact of inherited thrombophilia on venous thromboembolism in children. *Circulation*. 2008;118:1373-82.
12. Young G. New anticoagulants in children. *Hematology Am Soc Hematol Educ Program*. 2008:245-50.

17. APPENDICES

17.1. Additional Information on Investigational Products

Edoxaban 15 mg, 30 mg, and 60 mg tablets contain mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, talc, polyethylene glycol, iron oxide yellow, iron oxide red (15 mg orange film-coated tablets only), and carnauba wax.

Edoxaban granules for oral suspension 60 mg contains mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, carboxymethylcellulose sodium, xylitol, and strawberry flavor.

17.2. Instructions for Specimen Collection, Storage, and Shipment

17.2.1. Collection, Storage, Handling, and Shipping for Sample Analysis of Plasma Edoxaban (DU-176b) and Metabolites

A blood volume not to exceed the guidelines for pediatrics research for each age cohort[9] will be taken from specified patients at the times detailed in Section Section 8. Blood loss must not exceed 1% of total blood volume at any time, 3% during 4 weeks. Blood sampling from patients for bioanalytical assessment will use the local methods appropriate for the patient's age to minimize associated blood volume, invasiveness, and pain.

- If 1.0 to 2.0 mL of blood, in accordance to volume guidance described above, can be collected for the specified time points, the following procedures can be applied: blood samples will be collected into pre-chilled 2 mL polyethylene Vacutainer tubes containing lithium heparin as anticoagulant for the preparation of plasma.
- For Cohorts 1 to 3, if less than 1.0 mL of blood can be collected following volume guidance described above, small volume blood collection procedures and devices, deemed age-appropriate locally for collecting lithium heparin plasma can be applied. It is important to ensure that such procedures should not introduce volume bias, i.e., no pre- or post-addition of any solution to the blood collection tube (which may affect the volume of harvested plasma). Recommended devices, and collection procedures, are described in lab manual.

The tube containing blood for plasma preparation will be gently inverted multiple times (≥ 8) to ensure thorough mixing of anticoagulant (lithium heparin) and blood, then placed in a cool box containing ice/water mixture. The samples should be centrifuged within 45 minutes of collection, at approximately 1,500 g for approximately 10 minutes. Immediately following centrifugation, the separated plasma should be pipetted (be careful not to touch the bottom layer), into sample storage vial(s) following the below suggestion:

- If more than approximately 0.3 mL of plasma is harvested, the plasma will be divided approximately equally into 2 polypropylene cryogenic sample storage vials (designated Aliquot 1 and 2) with screw-cap. The sample storage vial volume should not exceed 2.0 mL. Each storage vial should contain more than 100 µL of plasma.
- For Cohorts 1 to 3, if less than approximately 0.3 mL of plasma is harvested, then the plasma will be transferred into 1 polypropylene cryogenic sample storage vial (designated Aliquot 1) with screw-cap. The sample storage vial volume should not exceed 2.0 mL.

The cryogenic vials should be maintained by being chilled on ice before transferred to the freezer. Within 90 minutes after blood draw, the sample storage vials will be stored, still in upright position, in the dark in a **non-cycling freezer** at approximately -20ºC ± 10ºC.

Any sample anomalies should be recorded on the sampling forms.

Sample Transfer

Samples will be shipped to a central lab. For international shipment, a courier that can monitor and replenish dry ice should be used. Each country should establish its own process for

monitoring and replenishing dry ice. Shipments will be sent after PK samples are collected for each patient. Aliquots 1 and 2 should be shipped on different days. Samples will be packed in sufficient dry ice to last 3 or more days. Samples should only be shipped on Monday, Tuesday, or Wednesday.

Shipping Documentation

The shipping documentation should include, at minimum, the following information:

- Study protocol number
- Complete inventory of samples shipped
- Name of shipping site contact person

Sample Packing Suggestions

Package samples in appropriate boxes with covers (e.g., fiberboard storage boxes and dividers). Secure the covers with rubber bands or tape and identify the contents of each box. Place boxes in a moisture protective bag such as a "SAF-T-PAK" (http://www.saftpak.com) before placing in the main shipping carton. The main shipping carton should consist of a corrugated cardboard box with a separate polyfoam box with lid placed inside. Place the appropriate amount of dry ice in the polyfoam box surrounding the sample packages, such that dry ice will last approximately 3 days.

Sample Receiving Contact at Q_2 Solutions

PPD or delegate
Attn: Sample Receiving
Q2 Solutions
19 Brown Rd
Ithaca, NY 14850
PPD

17.2.2. Collection, Storage, Handling, and Shipping of Blood Samples for Pharmacodynamic Analysis

The following assays will be made for PD assessments: PT, aPTT, and anti-FXa.

Blood samples (volumes not to exceed the guidelines for pediatrics research for each age cohort[9]) will be collected in sodium citrated blood collection tubes from specified patients at the times detailed in Section 8. Blood loss must not exceed 1% of total blood volume at any time, 3% during 4 weeks. Blood sampling from patients for PD assessment will use the local methods appropriate for the patient's age to minimize associated blood volume, invasiveness, and pain.

For any blood draw, an adequate volume of waste will need to be drawn to clear all tubing of tissue debris or possible contaminants (i.e., heparin) as this may impact analyses. All waste may be returned to the patient per local hospital practices. Please refer to the Laboratory Manual for additional details.

Immediately after the collection, the samples will be mixed by gentle inversion 8 or more times and subsequently within 30 minutes of collection centrifuged at 1,500 × *g* for 15 minutes. Samples will then be kept on ice, and the resulting platelet poor plasma (being careful not to pipette or disturb cell layer) will then be divided into 3 aliquots (if possible) and transferred to clean screw-topped suitably labeled transfer tubes (cryo vials) as follows:

Aliquots 1 and 2: approximately 0.35 mL per tube

Aliquot 3: Remainder of the plasma sample into the third tube

Note – the volumes and the aliquoting scheme might need to be adjusted for each age cohort.

Aliquot 1 should be shipped first. After receiving confirmation of receipt, Aliquot 2 and 3 should be shipped. All aliquots should be stored at or below -70ºC until transferred to Medpace for analysis. Samples should be stored within 60 minutes of collection. Aliquot 1 will be stored in 1 freezer, and Aliquots 2 and 3 will be stored in a different freezer.

All samples must be packed in sufficient dry ice to last 3 days and will be shipped on a Monday, Tuesday, or Wednesday to ensure weekday overnight delivery.

Samples in North America will be shipped to:

PPD

Sample Management

Medpace Reference Laboratories USA

5365 Medpace Way

Cincinnati, OH 45227

PPD

Samples outside North America will be shipped to:

Medpace Reference Laboratories, Belgium
Technologielaan 19
3001 Leuven, Belgium
PPD

17.3. Cytochrome P450 Clinically Significant Drug Interaction Table

INHIBITORS
3A4,5,7
amiodarone NOT azithromycin cimetidine clarithromycin diltiazem erythromycin fluvoxamine itraconazole ketoconazole mibefradil nefazodone troleandomycin verapamil
INDUCERS
3A4,5,7
Carbamazepine pioglitazone rifabutin rifampin Troglitazone

List obtained from P450 Drug Interaction Table: Abbreviated “Clinically Relevant” Table, Version 5.0 released on January 12, 2009, last updated on January 31, 2012. Available at: http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx (last accessed 09 Feb 2012).

17.4. P-Glycoprotein Inhibitors and Inducers

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

17.4.1. P-gp Inhibitor Table

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

17.4.2. P-gp Inducers List (Prohibited Medication)

Rifamin is a P-gp inducer that has been shown to lower the edoxaban exposure. The example medications listed below (but not limited to) have not been tested with edoxaban but are also P-gp inducers. These should be avoided during the study as their use may lead to a lower exposure of edoxaban than predicted for clinical efficacy.
(http://www.straighthealthcare.com/p-glycoprotein.html#inducers)

- Rifampin
- Carbamazepin (Tegretol®)

17.5. Modified Schwartz Equation (Pediatric Patients < 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

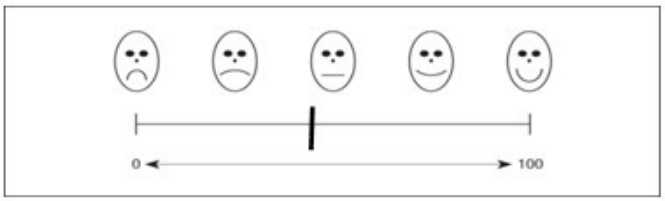
17.6. VAS Patient Questionnaire

Protocol:	Subject Number: _ _ _ _ _ _ _ _ _
Patient Initials: _ _ _	DATE: DAY MONTH YEAR

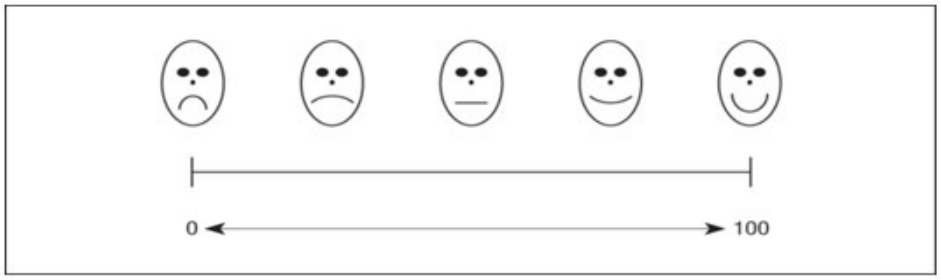
Palatability Visual Analog Scale

*Palatability is defined as the overall appreciation of an (often oral) medicinal product towards its **bitterness, sweetness, overall taste, and aroma.***

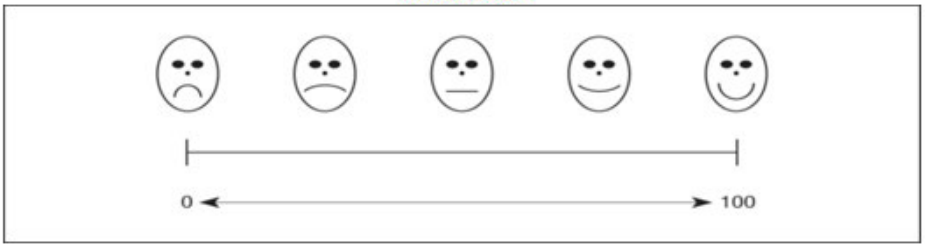
Place a mark on the corresponding lines below and on the next page as shown in the example.



Palatability

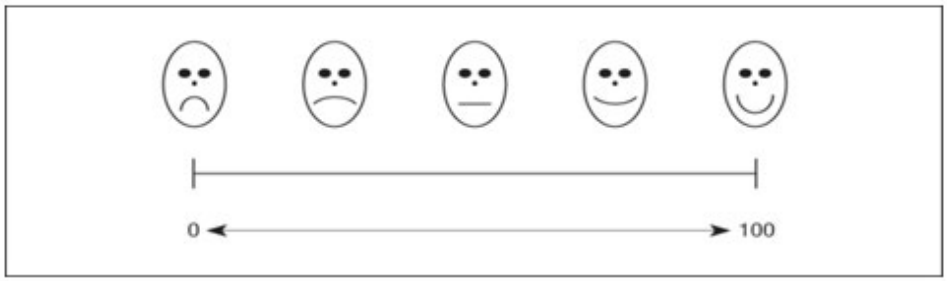


Bitterness

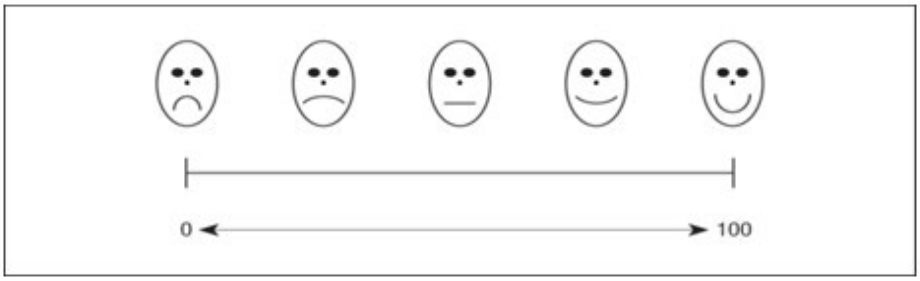


Protocol:	Subject Number: _ _ _ _ _ _ _ _ _
Patient Initials: _ _ _	DATE: DAY MONTH YEAR

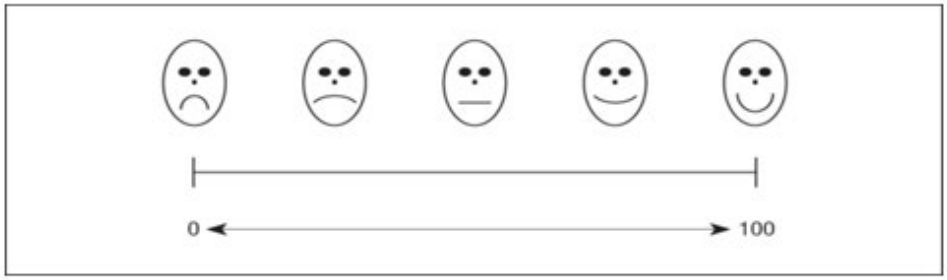
Sweetness



Overall Taste



Aroma



Comments regarding treatment: _____

_____

_____

To be filled out by site staff: - Staff Initials _ _ _

Palatability _ _ _ mm Bitterness _ _ _ mm

Sweetness _ _ _ mm Overall Taste _ _ _ mm Aroma _ _ _ mm

17.7. Schedule of Events

Table 17.1: Schedule of Events (All Cohorts)

Study Day →	**Days -21 to -2**	**Day -1/1 predose**			**Day 1[1]**	**Day 2[1]**	**Day 3[1]**	**Within 10 days after dosing**
Study Hour →	**Screening**	**Check-in[2]**	**Predose**	**Dosing**				**Follow-up[3]**
Study Event ↓								
Informed consent (parent/legal guardian)	X							
Assent form (if applicable)	X							
Eligibility assessment	X	X						
Medical/surgical history	X	X						
Demographics	X							
Physical examination	X	X	X					X
Body weight, height, and BMI	X	X	X					X
Pregnancy test based on local practice (for post-menarchal females)	X	X						
Urine drug screen for patients 12 years of age and older, for newborns, and for patients who are being breastfed	X	X						
Hematology	X[4]							X
Serum chemistry	X[4]							X[5]
Serology	X[4]							
Urinalysis	X	X						
Coagulation (PT, INR, and aPTT)[6]	X							X
Dosing[7]				X				
VAS assessment[8]				X				

Table 17.1: Schedule of Events (All Cohorts) (Continued)

Study Day →	**Days -21 to -2**	**Day -1/1 predose**			**Day 1[1]**	**Day 2[1]**	**Day 3[1]**	**Within 10 days after dosing**
Study Hour →	**Screening**	**Check-in[2]**	**Predose**	**Dosing**				**Follow-up[3]**
Study Event ↓								
AE/SAE monitoring[9]	X	X	X	X	X	X	X[9]	X
Concomitant medication[9]	X	X	X	X	X	X	X[9]	X
PK blood draw[10]					X	X	X	
PD blood draw[10]	X		X		X	X		

AE = adverse event; aPTT = activated partial thromboplastin time; BMI = body mass index; INR = international normalization ration; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; SAE = serious adverse event; SOE = schedule of events; VAS = visual analog scale.

1. The overnight stay on Day 1 or Day 2 is not mandatory. The patient may leave the clinic on Day 1 following the completion of all study procedures and return to the clinic on Day 2 for the completion of Day 2 procedures (or Day 3 for patients enrolled prior to Version 5.0 of the protocol). Any procedure occurring after hour 8 on Day 1 may be performed using a home healthcare service, depending on the availability of the service in the patient's country.
2. Check-in may occur on Day -1 or 1, depending on the site.
3. Some patients may be given the option to have a home healthcare service conduct the procedures for this visit in the patient's home, depending on the availability of the service in the patient's country.
4. Blood samples will be obtained at screening if not drawn within 2 weeks prior to screening.
5. Serum chemistry will only be obtained from patients in Cohorts 1, 2, and 3.
6. Only 1 assessment required prior to edoxaban dosing at either screening or upon check-in, as appropriate for the patient.
7. Doses will be selected based on emerging PK and safety data.
8. Patients receiving the edoxaban granule for oral suspension formulation who are developmentally capable of providing an accurate response will be asked to rate several aspects of palatability (including bitterness, sweetness, overall taste, and aroma) using 100 mm VAS. Patients who are old enough will score the VAS themselves. For younger children, the parents will provide this information, if possible. For the youngest children, there will be free text input available to provide information on whether the patient spit it out and may not have liked the flavor, etc.
9. Continuous monitoring after screening procedures are complete.
10. Refer to cohort-specific PK/PD SOE for specific timepoints.

Table 17.2: Pharmacokinetic and Pharmacodynamic Blood Sampling Schedule for Cohort 1

Study Day →	**Days -21 to -2**	**Day -1/1 predose**		**Day 1[1]**					**Day 2[1]**	**Day 3[1]**	**Within 10 days after dosing**
Study Hour →	**Screening**	**Check-in[2]**	**Predose**	**0.25-1 hour postdose**	**1.5-3 hours postdose**	**3.5-6 hours postdose**	**6.5-8 hours postdose**	**8.5-14 hours postdose**	**24-36 hours postdose[3]**	**48-54 hours postdose**	**Follow-up[3]**
Blood sampling for PK[4]				X	X	X	X	X	X	X	
Blood sampling for PD[5]			X	X	X	X	X		X		
Vital signs	X	X	X	X	X			X		X	X

PD = pharmacodynamic; PK = pharmacokinetic.

1. The overnight stay on Day 1 or Day 2 is not mandatory. The patient may leave the clinic on Day 1 following the completion of all study procedures and return to the clinic on Day 2 for the completion of Day 2 procedures (or Day 3 for patients enrolled prior to Version 5.0 of the protocol). Any procedure occurring after hour 8 on Day 1 may be performed using a home healthcare service, depending on the availability of the service in the patient's country.
2. Check-in may occur on Day -1 or 1, depending on the site.
3. Some patients may be given the option to have a home healthcare service conduct the procedures for this visit in the patient's home, depending on the availability of the service in the patient's country.
4. Sampling scheme may be adjusted for various age cohorts based on emerging PK and safety data. The patient will check-out after the last PK sample has been collected on Day 3.
5. To be concurrent with PK sampling, after PK sampling based on age cohort.

Table 17.3: Pharmacokinetic and Pharmacodynamic Blood Sampling Schedule for Cohorts 2 and 3

Study Day →	**Days -21 to -2**	**Day -1/1 predose**		**Day 1[1]**				**Day 2[1]**	**Within 10 days after dosing**
Study Hour →	**Screening**	**Check-in[2]**	**Predose**	**0.25-1 hour postdose**	**1.5-3 hours postdose**	**4-8 hours postdose**	**9-14 hours postdose**	**24-36 hours postdose[3]**	**Follow-up[3]**
Blood sampling for PK[4]				X	X	X	X	X	
Blood sampling for PD[5]			X	X	X	X	X	X	
Vital signs	X	X	X	X	X		X		X

PD = pharmacodynamic; PK = pharmacokinetic.

1. The overnight stay on Day 1 or Day 2 is not mandatory. The patient may leave the clinic on Day 1 following the completion of all study procedures and return to the clinic on Day 2 for the completion of Day 2 procedures. Any procedure occurring after hour 8 on Day 1 may be performed using a home healthcare service, depending on the availability of the service in the patient's country.
2. Check-in may occur on Day -1 or 1, depending on the site.
3. Some patients may be given the option to have a home healthcare service conduct the procedures for this visit in the patient's home, depending on the availability of the service in the patient's country.
4. Sampling scheme may be adjusted for various age cohorts based on emerging PK and safety data. The patient will check-out after the last PK sample has been collected on Day 2.
5. To be concurrent with PK sampling, after PK sampling based on age cohort.

Table 17.4: Pharmacokinetic and Pharmacodynamic Blood Sampling Schedule for Cohorts 4 and 5

Study Day →	**Days -21 to -2**	**Day -1/1 predose**		**Day 1[1]**			**Day 2[1]**	**Within 10 days after dosing**
Study Hour →	**Screening**	**Check-in[2]**	**Predose**	**0.5-2 hours postdose**	**3-8 hours postdose**	**9-14 hours postdose**	**24-36 hours postdose[3]**	**Follow-up[3]**
Blood sampling for PK[4]				X	X	X	X	
Blood sampling for PD[5]	X			X				
Vital signs	X	X	X	X	X	X		X

PD = pharmacodynamic; PK = pharmacokinetic.

1. The overnight stay on Day 1 or Day 2 is not mandatory. The patient may leave the clinic on Day 1 following the completion of all study procedures and return to the clinic on Day 2 for the completion of Day 2 procedures. Any procedure occurring after hour 8 on Day 1 may be performed using a home healthcare service, depending on the availability of the service in the patient's country.
2. Check-in may occur on Day -1 or 1, depending on the site.
3. Some patients may be given the option to have a home healthcare service conduct the procedures for this visit in the patient's home, depending on the availability of the service in the patient's country.
4. Sampling scheme may be adjusted for various age cohorts based on emerging PK and safety data. The patient will check-out after the last PK sample has been collected on Day 2. Note: Blood is collected at only 3 of the 4 timepoints for Cohort 5; the timepoint 0.5 to 2 hours is mandatory.
5. To be concurrent with PK sampling, after PK sampling based on age cohort.