CLINICAL STUDY PROTOCOL

A THREE MONTH PROSPECTIVE OPEN LABEL STUDY OF THERAPY WITH FRAGMIN® (DALTEPARIN SODIUM INJECTION) IN CHILDREN WITH VENOUS THROMBOEMBOLISM WITH OR WITHOUT MALIGNANCIES

Compound:	PN180524
Compound Name :	Dalteparin Sodium Injection (Fragmin®)
United States (US) Investigational New Drug (IND) Number:	IND 79,617
European Clinical Trials Database (EudraCT) #:	2016-000394-21
Protocol Number:	FRAG-A001-201 (A6301094)
Phase:	II
Version #:	Amendment 9 – 18 October 2016

[redacted]

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Document History

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Document	Date	Summary of Changes and Rationale
Original Protocol	June 23, 2008	Legacy Eisai Inc Protocol
Protocol Amendment 1	September 04, 2008	Legacy Eisai Inc Protocol
Correction to Amendment 1	January 05, 2009	Legacy Eisai Inc Protocol
Protocol Amendment 2	February 20, 2009	Legacy Eisai Inc Protocol
Protocol Amendment 3	September 15, 2010	Legacy Eisai Inc Protocol
Protocol Amendment 4	September 01, 2011	Legacy Eisai Inc Protocol
Protocol Amendment 5	April 21, 2015	Administrative changes per transition of study to Pfizer Inc from Eisai; Updating of Safety Section per Pfizer safety reporting processes and procedures, and other relevant sections per Pfizer Inc processes and procedures.
Protocol Amendment 6	09 September 2015	This version was never finalized or submitted and was replaced by Amendment 7.
Protocol Amendment 7	18 November 2015	Includes protocol modifications endorsed by FDA in a Type C Meeting conducted on 05 November 2015, including updating age cohort groups, inclusion of all patients with VTE and removal of the central imaging reader and Adjudication Committee.
Protocol Amendment 8	24 March 2016	Includes various minor text clarification modifications per Quality Gate 1 findings and other noted discrepancies and discussion during US Investigator Meeting that took place on March 11-12, 2016 to

		add clarity regarding procedures, inclusion/exclusion, clinical supply and other sections.
Protocol Amendment 9	18 October 2016	Incorporation of administrative changes from Protocol Administrative Change Letters; Inclusion of Schwartz Method and Revised Schwartz Method for Creatinine Clearance calculations; other minor changes

PROTOCOL SYNOPSIS

Study Number:	FRAG-A001-201 (A6301094)
Study Title:	A THREE MONTH PROSPECTIVE OPEN LABEL STUDY OF THERAPY WITH FRAGMIN® (DALTEPARIN SODIUM INJECTION) IN CHILDREN WITH VENOUS THROMBOEMBOLISM WITH OR WITHOUT MALIGNANCIES
Primary Objectives:	• To determine the pharmacodynamic (PD) profiles for treatment doses of dalteparin in pediatric subjects of different ages with venous thromboembolism (VTE), and with or without cancer, using anti-Xa (Xa) levels and a population PD analysis methodology; • To determine the median dose (IU/kg) required to achieve therapeutic anti-Xa levels (0.5 to 1.0 International Units [IU]/mL) based on subject age and weight.
Secondary Objectives:	• To assess the proportion of major bleeding events during dalteparin treatment. • To assess the proportion of minor bleeding events during dalteparin treatment; • To explore the proportion of objectively documented new or progressive symptomatic VTE during dalteparin treatment; • To explore the relationships of recurrent VTE and major bleeding events with anti-Xa levels if data permits; • To explore the proportions of subjects with progression, regression, resolution or no change in the qualifying VTE during dalteparin treatment; • To describe the overall safety profile of dalteparin in pediatric subjects of different ages with or without cancer and VTE; • To assess proportion of subjects achieving an anti Xa therapeutic range of 0.5 to 1.0 IU/mL during the Dose Adjustment Phase.
Study Phase:	II
Study Design:	A prospective, multicenter, open-label cohort study in North America and Europe Divided into three phases: Dose Adjustment Phase, PD Phase and Follow- up Phase.
Number of Centers:	Approximately 40 sites in North America and Europe.
Sample Size:	Subjects will be enrolled into the following five age groups:

	• 0 to < 8 Weeks; • ≥8 Weeks to < 2 Years; • ≥2 Years to < 8 Years; • ≥8 Years to < 12 Years; • ≥12 Years to < 19 Years. The target enrollment is 50 subjects who have PD profiles after treatment doses of dalteparin.
Inclusion Criteria:	Subjects meet inclusion if all of the following are true: 1. Have been objectively diagnosed with a venous thrombotic event documented using one of the following acceptable imaging modalities within 4 days of the Screening Visit: • Compression ultrasound with Doppler [CUD]; • Computed tomography with/without venography [CT/CTV]; • Magnetic resonance imaging with/without venography [MRI/MRV]; • Conventional venography [CV]; • Ventilation-perfusion scan [V/Q] (for pulmonary artery); • Spiral CT angiography [SCTA]; • Conventional pulmonary angiogram [CPA]. 2. Are judged clinically to require anticoagulation therapy. 3. Are in the age range of ≥36 weeks gestation and <19 years at the Screening Visit. 4. Have given signed informed consent (and assent, as appropriate) to participate prior to the Screening Visit. 5. For cancer patients, a diagnosis of active malignancy (currently under treatment), other than basal cell or squamous cell carcinoma of the skin. 6. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. 7. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. 8. Female subjects of non-childbearing potential must meet at least

	1 of the following criteria: a. Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or psychiological cause; [status may be confirmed with/and have] a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state; b. Have undergone a documented hysterectomy and/or bilateral oophorectomy; c. Have medically confirmed ovarian failure. 9. All other female subjects (including female subjects with tubal ligations) are considered to be of child bearing potential.
Exclusion Criteria:	Subjects are excluded if any one of the following apply: 1. Weight ≤3.0 kg or >100 kg at the Screening Visit. 2. Platelet count ≤ 50,000/mm^3 (despite appropriate medical measures to support platelet count). 3. Received oral anticoagulant (OAC) therapy within 3 days of the Screening Visit. 4. History of administration of therapeutic doses of Low Molecular Weight Heparin (LMWH) or unfractionated heparin for a period of > 4 days (or >8 doses of LMWH) for the qualifying VTE. 5. Received unfractionated heparin within 3 hours, or LMWH within 12 hours, of the first dose of dalteparin. 6. Acute VTE intervention which includes thrombolytic therapy. 7. Subjects with major bleeding or bleeding disorders such as Platelet Dysfunction, Protein Deficiency, Disseminated Intravascular coagulation (DIC), Factor Deficiency, Hemophilia, Idiopathic Thrombocytopenic Purpura (ITP) or Von Willebrand Disease at the time of the Screening Visit or an unacceptably high risk of bleeding, at the discretion of the investigator, should not be considered candidates.. 8. Activated partial thromboplastin time (aPTT) ≥5 seconds above upper limit of normal (ULN), and that corrects to within normal limits upon 1:1 mixing with normal plasma. 9. Prothrombin time (PT) ≥2 seconds above ULN, and that corrects to within normal limits upon 1:1 mixing with normal plasma. 10. Creatinine clearance <60 mL/min/1.73m^2 in subjects >1 month of age. 11. Uncontrolled hypertension characterized by a sustained systolic pressure or diastolic pressure >99th percentile of age- and height-

	related norms. 12. History of heparin-induced thrombocytopenia (HIT). 13. Any condition in which the investigator feels the subject is unsafe or inappropriate for study participation. 14. Participation in other clinical studies involving investigational drug(s) within the past 30 days. 15. Insufficient subcutaneous tissue to facilitate subcutaneous drug administration. 16. Pregnant female subjects; breastfeeding female subjects; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of assigned treatment. 17. Unable or unwilling to comply with scheduled follow-up visits. (See Section 6.2 for complete listing of Inclusion Criteria and Exclusion criteria).
Study Drug/Dosing:	Dalteparin sodium (Fragmin®) will be provided in: • Multiple dose vials of 25,000 IU/1 mL (3.8mL for US or 4mL for ROW) containing preservative benzyl alcohol; • Preservative-free single dose vials of 2,500 IU/1 mL (4mL) [where available]; • Preservative-free 10,000 IU / 1 mL single-dose graduated syringe (can be diluted as needed per the IP Manual). Dosing administration is subcutaneous, twice daily. Study medication can only be administered to a subject by a healthcare professional (ie, study nurse) or trained parent/caregiver. Hospital nurses that may administer study medication to in-patient subjects do not require GCP training. However, they must receive study medication administration training from the site staff and the training should be documented. Subject's aged 0 to less than 8 weeks will receive an initial dose of 125 IU/kg twice daily. Subjects aged greater than or equal to 8 weeks to less than 2 years will receive an initial dose of 150 IU/kg twice daily. Subjects aged greater than or equal to 2 years to less than 8 years or greater than or equal to 8 years to less than 12 years will receive an initial dose of 125 IU/kg twice daily. Subjects aged greater than or equal to 12 years to less than 19 years will receive an initial dose of 100 IU/kg twice daily. All subjects will have dose adjustments in the Dose Adjustment Phase in 25 IU/kg increments/decrements based upon an anti-Xa therapeutic goal

	range of 0.5 to 1.0 IU/mL.
Study Procedures:	In the Dose Adjustment Phase, all eligible subjects will receive dalteparin sodium subcutaneously every 12 hours ±1 hour (no less than 8 hours between doses) for up to 7 days. However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time. The first anti-Xa level after initial study medication treatment may be taken 4 hours ±1 hour after the first, second or third dose per Investigator judgment . All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the sample is drawn. Plasma samples drawn during the Dose-Adjustment phase that deviate outside the 4 ± 1 hr window cannot use the anti-Xa reference range, 0.5-1.0 IU/ml, and should be repeated the next day for both central lab and local lab. The actual dosing time prior to the repeat plasma sample draw and the actual time of the repeat sample draw must be recorded. Subsequent anti-Xa levels will be measured to determine if the anti-Xa level is within the target therapeutic range of 0.5 to 1.0 IU/mL. If the therapeutic range is not achieved, the dalteparin dose must be adjusted per protocol. After any dose adjustment, anti-Xa should be re-drawn after the first, second or third dose per Investigator judgment. If the target range is not achieved within the 7 day period, the subject's study participation will be terminated. In the PD Phase, subjects completing the Dose Adjustment Phase will receive their maintenance therapeutic dose of dalteparin sodium (last dose from Dose Adjustment Phase) subcutaneously every 12 hours ±1 hour (no less than 8 hours between doses). However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time. Subjects from each age group will be randomized to two different plasma sampling windows (1 to 3 h and 5 to 8 h or 3 to 5 h and 8 to 12 h) for the anti-Xa plasma samples for the central lab, only. A total of two plasma samples will be drawn for each subject per their randomization schedule during the PD Phase. The plasma sampling times can be spread over the duration of the PD phase (up to 7 days) if necessary. All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the sample is drawn. The sample should be repeated if possible at the correct time point. In the Follow-Up Phase (Visits 5, 6, 7), subjects will continue to receive their maintenance therapeutic dose of dalteparin sodium subcutaneously every 12 hours ±1 hour (no less than 8 hours between doses) through Visit 7. However, if a dose is not able to be delivered

	every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time. Anti-Xa levels and safety/efficacy assessments will be conducted at Visits 5, 6 and 7. Anti-Xa plasma samples will be collected at 4 hours ± 1 hour post-dose at each Follow-Up Visit to check if anti-Xa levels remain within the target therapeutic range. All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the sample is drawn. Plasma samples drawn during the Follow-Up Phase that deviate outside the 4 ± 1 hr window cannot use the anti-Xa reference range, 0.5-1.0 IU/ml, and should be repeated the next day. The actual dosing time prior to the repeat plasma sample draw and the actual time of the repeat sample draw must be recorded. The Principal Investigator or designee will follow up weekly with a telephone interview to all subjects or parents/guardians after discharge from hospital to assess study compliance and general well-being. At the end of the study or on the presentation of a recurrent or progressive VTE, evaluation of thrombus regression or resolution will be performed using the same imaging technique as for VTE diagnosis at study entry. If an image has been captured prior to the end of study (EOS) and it demonstrates complete resolution of the qualifying VTE, then a repeat image does not need to be done at EOS. For purposes of the study, the complete resolution image will be considered as part of the EOS evaluation.
Study Duration:	Study duration is 90 days of open-label treatment with dalteparin sodium (Fragmin®) for cancer patients and treatment of non-cancer patients should be aligned with the 2012 American College of Chest Physicians (ACCP) Guidelines[15] which suggest a total duration of anticoagulation treatment of between 6 weeks and 3 months rather than shorter or longer durations (Grade 2C), following completion of the PD Phase. Non-cancer patients will be required to remain in the study, however for the full 3 months to complete all remaining study visits, regardless of dalteparin treatment duration. For non-cancer patients who stop dalteparin treatment prior to 3 months, Anti-Xa and Anti-IIa plasma sampling will not be required after study medication discontinuation
Pharmacodynamic Endpoints	**Pharmacodynamic Evaluation:** Primary Endpoints: • Determine the median dose of dalteparin (IU/kg) associated with the achievement of the therapeutic anti-Xa level (0.5-1.0 IU/mL) among subjects that achieved their therapeutic anti-Xa level during the dose adjustment phase, for each age cohort group; • Anti-Xa activity versus time profile following dalteparin treatment will be explored using a population PD analysis methodology. Population PD parameters such as clearance, volume of

	distribution, absorption rate constant will be estimated based on anti-Xa levels collected during dose adjustment phase, PD phase and follow-up phase. Age and other relevant covariates will be explored in the population PD analysis.
Efficacy Endpoints (all are secondary):	• Proportion of subjects achieving an anti Xa therapeutic range of 0.5 to 1.0 IU/mL during the Dose Adjustment Phase; • Proportion of subjects with objectively documented new or progressive symptomatic VTE during dalteparin treatment; • Proportions of subjects with progression, regression, resolution, or no change in the qualifying VTE during dalteparin treatment; • Time to first episode of recurrent VTE during dalteparin treatment.
Safety Endpoints (all are secondary):	• Proportion of subjects with major bleeding during dalteparin treatment; • Proportion of subjects with minor bleeding during dalteparin treatment; • Relationship between major bleeding event and the Anti-Xa level during dalteparin treatment if data permits; • Description of subjects' adverse events (AE) throughout the study period; • Summary of chemistry, hematology, vital signs and physical examinations; • Time to first major bleeding events during dalteparin treatment.
Statistical Methods:	**Sample Size:** A sample size of 50 subjects is sufficient to estimate anti-Xa total body clearance of the drug (CL) and volume of distribution (V_d) of dalteparin. Enrollment will continue until 50 subjects have provided viable PD Phase anti-Xa data. Sample size determination. Based on historical data and a population pharmacokinetic (PK)/PD model, evaluated the effect of sample scheme and sample size per age stratum on the bias and precision of key PK/PD parameters. • Evaluated total N of 10, 20, 30, 40 and 50 (2, 4, 6, 8, and 10 per age stratum, as available); • Evaluated single and 2-point sample densities and impact of randomization across stratum. • 100 trial simulations per design examined. Sampling Density.

	• Single-point sampling designs yielded unacceptable bias in CL and/or Vd; confounding of effects if blocked within strata; • Compared double sampling at 2, 6 and 4, 10 hours post-dose versus 3, 8 and 5, 12 hours post-dose. Randomized two-sample designs with sampling at 3, 8 and 5, 12 hours post-dose performs more efficiently. **Analysis Populations:** There will be two analysis populations defined in the study. The Safety Population will include subjects who receive at least one treatment of dalteparin. The safety analysis will be based on this population. The PD Population will include subjects in the Safety Population who achieve therapeutic range of anti-Xa during the Dose Adjustment Phase. This population will be the primary analysis population for the PD and efficacy analysis. **Pharmacodynamic Analysis:** • Pharmacodynamic response of dalteparin will be evaluated by using a population PD analysis methodology based on anti-Xa levels; • The median dose (IU/kg) required per age group to demonstrate an anti-Xa of 0.5 to 1.0 IU/mL at 4 hours ± 1 hour post-dose during the Dose Adjustment Phase; • Proportion of subjects who achieve the therapeutic range of 0.5 to 1.0 IU/mL at 4 hours ± 1 hour post-dose of dalteparin treatment will be summarized. **Efficacy Analysis:** Proportion of subjects with objectively documented new or progressive symptomatic VTE will be summarized overall and by age group. Proportion of subjects with any VTE by age group and proportion of subjects with progression, regression, resolution and no change to the qualifying VTE during dalteparin treatment, and relationships of new or progressive VTE with anti-Xa levels will be summarized. Time to the first recurrent VTE and time to first major bleeding events will be evaluated by Kaplan-Meier method and the Cox regression model will be used to assess the recurrent VTE with prognostic factors of age group and baseline tumor type. Exploratory analyses will include a logistic regression model to assess if subjects achieved an anti-Xa therapeutic range during the Dose Adjustment Phase using the odds ratio of prognostic factors of age, gender, chemotherapy status and dose of dalteparin. **Safety Analysis:** Proportion of subjects with any major bleeding events will be

	summarized overall and by age group during dalteparin treatment, as well as monthly. Proportion of subjects with any bleeding and fatal bleeding will also be summarized. Time to the first major bleeding events will be evaluated by the Kaplan-Meier method and the Cox regression model with prognostic factors (eg, baseline anti-Xa level, age group, baseline tumor type, and chemotherapy status in the model. All other AEs will be described. All laboratory data will be summarized as well as vital signs and physical examinations.

PROTOCOL FLOWCHART

Table 1. Protocol Flowchart

					Follow-up Phase[12]				Unscheduled[13]	
Assessments	**Screen Visit 1**	**Baseline[3] Visit 2**	**Dose Adjustment Phase[12] Visit 3**	**PD[4] Visit 4**	**Telephone Contact[6]**	**Visit 5**	**Visit 6**	**Visit 7**	**Event**	**Visit**
Day(s)- (Days may vary according to number of days required for Dose Adjustment Phase. Total treatment period is 90 days.)	**-3 to -1**	**1**	**1 to 7**	**2/3 to 14**	**out-patient period**	**Days 15-44**	**Days 45-74**	**ET Days 75-104**		
Informed Consent	x									
Medical History[1,2]	x	x								
Physical Exam[3]	x	x	x	x		x	x	x	x	x
Imaging	x	x						x[7]	x[7,8]	
Vital Signs	x	x	x	x		x	x	x	x	x
Clinical Laboratory:										
• Hematology/Coagulation	x[5]	x		x		x	x	x	x[9]	x[9]
• Antithrombin Activity	x[5]	x[5]	x	x		x	x	x	x[9]	x[9]
• Clinical Chemistries[14]	X	x		x		x	x	x	x[9]	x[9]
Pregnancy test, (serum or urine) if applicable	x	x	x	x		x	x	x	x	x
Evaluate Contraception if applicable	x	x	x	x	x	x	x	x	x	
Anti-Xa level[5]		L, C	L, C	C		L, C	L, C	L, C	L[9]	L[9]
Anti-IIa level[5]		C	C	C		C	C	C		
Dispense Study Drug[11]		x	x	x	x[10]	x	x		x	
Return Study Drug			x	x		x	x	x	x	x
Concomitant Medication	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x
Medication Compliance			x	x		x	x	x	x	x

Abbreviations: L- Local Lab, C- Central Lab

1. Any change in medical history after the first dose of study medication is administered will be considered an AE.

2. All subjects at high risk for bleeding or who have bleeding disorders such as Platelet Dysfunction, Protein Deficiency, DIC, Factor Deficiency, Hemophilia, ITP or Von Willebrand disease should not be considered candidates.

3. Physical Exam including weight and height will be assessed at the end of the Dose Adjustment Phase (ie, Screening, Baseline, end of Dose Adjustment Phase, The PD Phase, and during the Follow-Up Phase at Visits 5, 6 and 7 per protocol) to determine any change resulting in an AE. Medical History, Physical Exam (including weight and height), Pregnancy test, Imaging and Clinical Labs (Chemistry, Antithrombin, and Hematology) are only required once (at Screening or Baseline visit if Screening is within 48 hours of the Baseline visit). Repeated evaluations at Baseline are at the investigator's discretion. Antithrombin activity is evaluated only once during the Dose Adjustment and PD Phases.

4. The PD phase will last for up to 7 days in order to complete two PD samples (anti-Xa). Subjects will be randomized through a randomization scheme as assigned by the electronic system, IMPALA, into two different sampling windows: 1 to 3 h and 5 to 8 h or 3 to 5 h and 8 to 12 h until at least 50 subjects provide viable PD Phase anti-Xa values. The plasma sampling times can be spread over the duration of the PD Phase if necessary to avoid blood volume shifts. Lab samples for anti-Xa and anti-IIa levels will be sent to Central (C) lab only. All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the sample is drawn and repeat it when appropriate at the correct time, if possible. Plasma samples drawn during the dose-adjustment phase and follow up phase that deviate outside the 4 ± 1 hr window cannot use the anti-Xa reference range, 0.5-1.0 IU/mL, and should be repeated the next day for both central and local labs. The actual dosing time prior to the repeat plasma sample draw and the actual time of the repeat sample draw must be recorded. NOTES: 1) Plasma samples drawn for anti-Xa and anti-IIa must not be hemolyzed. All precautions must be made to ensure that the plasma samples are not hemolyzed. 2) For non-cancer patients, if study medication is stopped prior to 3 months of treatment per the ACCP Guidelines, no further anti-Xa or anti-IIa sampling is required while study medication is not taken.

5. For subjects whose platelet counts unexpectedly fall below 50,000/mm^3, HIT antibody will be assessed. If the HIT antibody is positive, the subject must be discontinued. Antithrombin levels are to be performed once within 1 week post-diagnosis of VTE and at each study visit when anti-Xa samples are drawn. Anti-Xa levels will be measured at 4 hours post-dose (±1 hour) daily for up to 7 days (Days 1-7) during Dose Adjustment Phase. The first anti-Xa level may be drawn after the first, second or third doseper Investigator judgment during Dose Adjustment Phase. After any dose adjustment, anti Xa should be re drawn after the first, second or third dose or per institutional standard. If the target range is not achieved within the 7 day period, the subject's study participation will be terminated. These assessments are mandatory at Visits 5, 6 and 7 during follow-up Phase. The Anti-Xa samples will also be collected at 4 hours post-dose (±1 hour) at each visit during follow-up Phase. All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the sample is drawn). . Indications for monthly anti-Xa checks include but are not limited to a new compromising event change in renal function, significant weight change and suspected lack of treatment adherence. Lab samples collected for anti-Xa level during Dose Adjustment Phase and Follow-up Phase will be sent to both Local (L) and Central (C) labs. In addition, central lab samples for anti-Xa levels will also be used for anti-IIa measurement. See item 4 above for anti-Xa samples to be drawn in the PD Phase.

6. Telephone contacts are weekly following discharge from the hospital through the end of the study except weeks with clinical visits, ie, Visits 5, 6 and 7 per protocol).

7. The same imaging modality should be performed from the Screening/Baseline visit as the EOS Visit or at an Unscheduled Event visit for recurrent or new VTEs. Note: The EOS visit (per protocol) imaging is not required if a previous visit imaging has demonstrated resolution of a clot.

8. Imaging must be performed at an unscheduled visit if there is suspicion of a recurrent or new VTE; otherwise images are not required but can be performed at the discretion of the investigator as per standard of care.

9. Clinical laboratory testing should be performed per the investigator's discretion.

10. Study drug exposure to be assessed during telephone contacts.

11. Study drug will be dispensed to subjects according to their dosing requirements. Cancer patients will be dispensed study drug for the entire 3 months, whereas non-cancer patients will be dispensed study drug for the appropriate treatment period for them according the ACCP Guidelines of 6 weeks to 3 months. Non-cancer patients will, however, be required to complete all remaining study visits, but no anti-Xa or anti-IIa plasma samples will be required once the non-cancer patients stop study drug.

12. During the Dose Adjustment Phase and Follow-Up Phase, if a plasma sample for anti-Xa is drawn outside the 4 hour (+/- 1 hour) window, the plasma sample for anti-Xa must be re-drawn the next day within the correct window and sent to the Local Lab and Central Lab. If this occurs, an Unscheduled Visit must be conducted to redraw the anti-Xa plasma samples. The actual dosing time prior to the repeat plasma sample draw and the actual time of the repeat sample draw must be recorded in the CRF.

13. Unscheduled Events are bleeding or VTE events that require an Unscheduled Event visit. Unscheduled visits are conducted for any other reason.

14. Urine collection for creatinine to be conducted if applicable, per institutional standards

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1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACCP	American College of Chest Physicians
AE	Adverse Event
Anti-Xa	Anti-Factor Xa
Anti-IIa	Anti-Factor IIa
aPTT	Activated Partial Thromboplastin Time
C	Celsius
CAT	Cancer-Associated Thrombosis
CCG	CRF Completion Guideline
CFR	Code of Federal Regulations
CL	Total body clearance of the drug
CPA	Conventional Pulmonary Angiogram
CRF	Case Report Form
CSA	Clinical Study Agreement
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Computed Tomography Venography
CU	Compression Ultrasound
CUD	Compression Ultrasound with Doppler
CV	Conventional Venography
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
EC	Ethics Committee
EDP	Exposure During Pregnancy
EOS	End of Study
ET	Early Termination
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GAG	Glycosaminoglycan
GCP	Good Clinical Practice
HIT	Heparin-Induced Thrombocytopenia
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IIP	Investigator Initiation Package
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITP	Idiopathic Thrombocytopenic Purpura
IU	International Units
IUD	Intra-Uterine Device
IV	Intravenous
LFT	Liver Function Test
LMWH	Low Molecular Weight Heparin
IWRS	Interactive Web Response System
MRV	Magnetic Resonance Venography

MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OAC	Oral Anticoagulant
PD	Pharmacodynamic(s)
PE	Pulmonary Embolism
PI	Principal Investigator
PK	Pharmacokinetic
PT	Prothrombin Time
SAE	Serious Adverse Event
SC	Subcutaneous
SCTA	Spiral Computed Tomography Angiography
SOP	Standard Operating Procedure
SRSD	Single Reference Safety Document
TB	Tuberculin
V_d	Volume of Distribution
VTE	Venous Thromboembolism
V/Q	Ventilation-Perfusion Scan
tPA	Tissue Plasminogen Activator
US	United States
Xa	Factor Xa

2. INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified Investigators under the sponsorship of Pfizer Inc at approximately 40 investigational site(s) in North America and Europe.

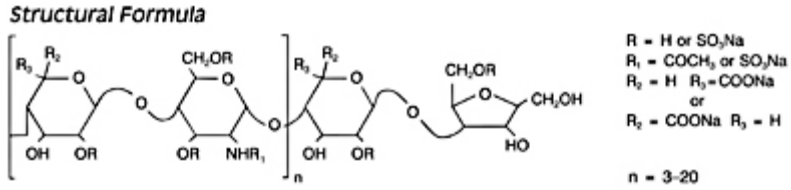
3. INTRODUCTION

3.1. Background

This protocol implements a post-approval clinical commitment originally with Eisai Inc and now between Pfizer Inc., and the Food and Drug Administration (FDA) relating to the dalteparin s NDA 20-287/S-035, "for the extended treatment of symptomatic venous thromboembolism [VTE (proximal deep vein thrombosis [DVT] and/or pulmonary embolism [PE])] to reduce recurrent VTE in subjects with cancer", hereafter referred to as the "CLOT indication".[1] The Agency indicated that a post-approval study to investigate the safety and efficacy of dalteparin in a pediatric cancer population requiring anticoagulation was warranted. Following a Type C Meeting with FDA on October 5, 2015, this study now includes both pediatric patients with and without cancer.

This phase II pharmacodynamic (PD) study is intended to provide information to guide the conditions under which dalteparin may be used for the acute treatment and secondary prophylaxis of recurrent VTE in children with or without cancer. Pharmacodynamics of dalteparin is being measured only using the Anti-Factor Xa (Xa) activity and not the drug level in the body. In this study, the PD effect (anti-Xa level) is used as a surrogate for the time course of drug exposure because 1) analytical difficulty in measuring the drug in plasma and 2) the instantaneous drug effect on anti-Xa level. Hence, the study is only characterizing the PD of dalteparin in pediatric subjects with and without cancer.

Figure 1. Chemical Structure of Dalteparin Sodium



3.2. Rationale

Dalteparin sodium (Fragmin®) is a low molecular weight heparin (LMWH), produced by degradation of heparin, a member of the glycosaminoglycan (GAG) family of biological entities found in the intestinal mucosa. Dalteparin was first approved in the US in December 1994 for primary prophylaxis of DVT in subjects undergoing abdominal surgery. This was followed by approvals for primary prophylaxis of DVT in subjects undergoing hip surgery and in medical subjects with severely restricted mobility during acute illness. Dalteparin sodium is also indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy.

Daltaperin was approved in 2006 for the extended treatment of VTE in adult patients (age ≥18 years) with cancer. For these indications, dalteparin has an acceptable safety profile. Further information regarding dosage, safety profile, etc., can be found in the current US Package Insert or local Summary of Product Characteristics, which will serve as the Investigators' Brochure for this study.

Multiple retrospective studies have shown that cancer-associated thrombosis (CAT) is a significant entity previously under recognized and under treated.[2-9] When compared to subjects without cancer, cancer subjects are far more prone to develop VTE; in fact, VTE may represent the initial presenting finding for an otherwise occult cancer.[10] When compared to cancer-free subjects with symptomatic VTE, cancer subjects with VTE are more prone to recurrence and to treatment-related bleeding complications.

The CLOT study ["Randomized ***C***omparison of ***L***ow Molecular Weight Heparin (Dalteparin, Fragmin®) versus ***O***ral Anticoagulant ***T***herapy for Long Term Anticoagulation in Cancer Subjects with Venous Thromboembolism"] was the first multinational prospective randomized clinical trial in a general cancer population to show the superiority of LMWH therapy for secondary prophylaxis compared to standard of care therapy using vitamin K antagonists (oral anticoagulants [OAC]) in cancer subjects with confirmed symptomatic lower extremity DVT, PE, or both.[1] However, the CLOT study did not include pediatric subjects and there is limited information in the literature regarding the proper dosing of dalteparin for treatment of VTE in pediatric subjects with cancer.

The use of LMWHs has been evaluated in several published pediatric studies. In a 1996 report, Massicote et al.,[11] described their evaluation of enoxaparin in 25 pediatric subjects in Canada either with VTE or at risk of VTE, and deemed by their physicians to be at risk of bleeding with unfractionated heparin. It was observed that an inverse relationship existed between the subject's age (correlated with body weight) and dosing required to achieve effective anti-Xa inhibition, with "newborns" requiring a greater than 50% increased dose per kg (perhaps due to a larger volume of distribution [V_d]).

Likewise, in a 1999 report by Nohe et al.,[12] doses of dalteparin in 48 children were shown to be effective (129±43 anti-Xa International Units (IU)/kg, q24h for treatment; 92±52 anti-Xa IU/kg, q24h for prophylaxis as recommended in the 7th ACCP Guidelines[15]), with higher dosing required for younger children to achieve the same target anti-Xa level. Risk factors for thrombosis in this cohort included the presence of carcinoma in some of the children.

Dosing with enoxaparin in 173 pediatric thrombosis subjects was also evaluated by Dix et al. and reported in 2000.[13] The authors concluded again, as above, that the use of LMWH in children was "…a safe and effective form of anticoagulation".

The combination of the published data and recognition that for more than 10 years children worldwide have been treated with LMWH for VTE, outside of the approved indication, supports the safety of the recommended doses of LMWH in children.

4. STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is to:

- To determine the PD profiles for treatment doses of dalteparin in pediatric subjects of different ages with or without cancer and VTE, using Anti-Xa levels and a population PD analysis methodology;
- To determine the median dose (IU/kg) required to achieve therapeutic Anti-Xa levels (0.5-1.0 IU/mL) based on subject age and weight.

Secondary objectives will be:

- To assess the proportion of major bleeding events during dalteparin treatment;
- To assess the proportion of minor bleeding events during dalteparin treatment;
- To explore the proportion of objectively documented new or progressive symptomatic VTE during dalteparin treatment;
- To explore the relationships of recurrent VTE and major bleeding events with anti-Xa levels, if data permits;
- To explore the proportions of subjects with progression, regression, resolution or no change in the qualifying VTE during dalteparin treatment;
- To describe the overall safety profile of dalteparin in pediatric subjects of different ages with or without cancer and VTE.
- To assess the proportion of subjects achieving an anti-Xa therapeutic range of 0.5 to 1.0 IU/mL during the Dose Adjustment Phase.

Primary Endpoints:

- Determine the median dose of dalteparin (IU/kg) associated with the achievement of the therapeutic Anti-Xa level (0.5-1.0 IU/mL) among subjects that achieved their therapeutic Anti-Xa level during the dose adjustment phase, for each age cohort group;
- Anti-Xa activity versus time profile following dalteparin treatment will be explored using a population PD analysis methodology. Population PD parameters such as clearance, volume of distribution, absorption rate constant will be estimated based on Anti-Xa levels collected during dose adjustment phase, PD phase and follow-up phase. Age and other relevant covariates will be explored in the population PD analysis.

Secondary Endpoints:

- Proportion of subjects achieving an Anti-Xa therapeutic range of 0.5 to 1.0 IU/mL during the Dose Adjustment Phase (up to 7 days);
- Proportion of subjects with objectively documented, new or progressive symptomatic VTE during dalteparin treatment utilizing the same objective technique performed at Baseline;
- Time to first episode of symptomatic recurrent VTE during dalteparin treatment;

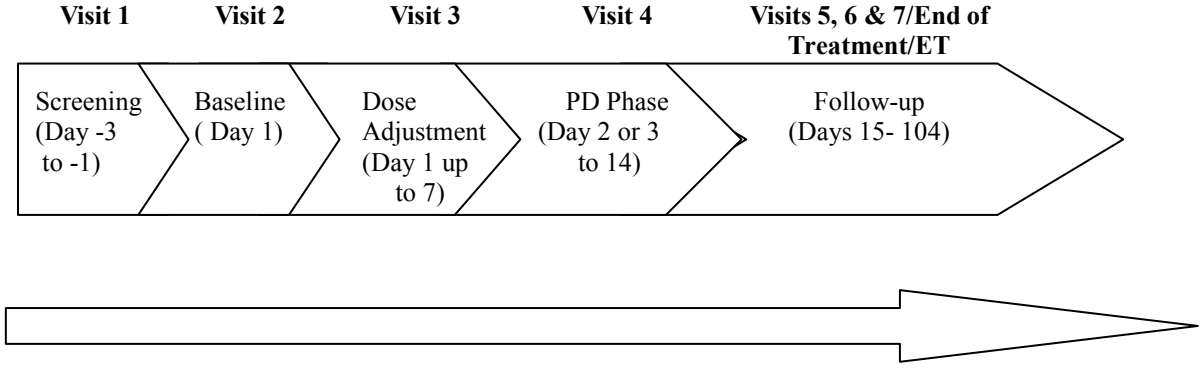
- Proportions of subjects with progression, regression, resolution and no change (in comparison to qualifying VTE) during dalteparin treatment;
- Proportion of subjects with major bleeding during dalteparin treatment;
- Proportion of subjects with minor bleeding during dalteparin treatment;
- Relationship between major bleeding event and the Anti Xa level during dalteparin treatment if data permits;Description of subjects' adverse events (AEs) throughout the study period;
- Summary of chemistry, hematology, vital signs and physical examinations.
- Time to first major bleeding events during dalteparin treatment.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan – Description

The study is a 3-month prospective, multicenter, open-label cohort study in North America and Europe to determine twice daily dosing recommendations of dalteparin as a function of age in order to achieve Anti-Xa levels of 0.5 to 1.0 IU/mL at 4 hour (± 1 hour) post-dose in children with or without various cancers and requiring anticoagulation for the treatment and secondary prophylaxis of VTE. The study is divided into 3 phases: 1) Dose Adjustment Phase of up to 7 days; 2) PD Phase; and 3) Follow-Up Phase, to complete up to 90 days of treatment for cancer patients and treatment of non-cancer patients should be aligned with the 2012 ACCP Guidelines[15] which suggest a total duration of anticoagulation treatment of between 6 weeks and 3 months rather than shorter or longer durations (Grade 2C), following completion of the PD Phase. Non-cancer patients will be required to remain in the study, however, for the full 3 months to complete all remaining study visits, regardless of dalteparin treatment duration. For non-cancer patients who stop dalteparin treatment prior to 3 months, Anti-Xa and Anti-IIa plasma sampling will not be required after study medication discontinuation.

Figure 2. Schematic Trial Design



5.2. Discussion of Study Design, Including the Choice of Subjects

This is a multi-center open-label study with no control group. This Phase II PD study is intended to provide information to guide the conditions under which dalteparin may be used for the treatment of acute and secondary prophylaxis of VTE in children with or without cancer. Subjects will be enrolled into the following five age groups:

- 0 to < 8 Weeks;
- ≥8 Weeks to < 2 Years;
- ≥2 Years to < 8 Years;
- ≥8 Years to < 12 Years;
- ≥12 Years to < 19 Years.

The target enrollment is a total of 50 subjects who have viable PD profiles after treatment doses of dalteparin.

Dose Adjustment Phase:

The Dose Adjustment Phase will begin following the first dose and continue for up to 7 days. During the Dose Adjustment Phase, doses are adjusted according to Anti-Xa levels. The starting doses for the five age groups are as follows:

- 0 to <8 weeks – 125 IU/kg;
- ≥8 weeks to < 2 years– 150 IU/kg;
- ≥2 years to <8 years – 125 IU/kg;
- ≥8 years to <12 years – 125 IU/kg and
- ≥12 years to <19 years – 100 IU/kg.

The first Anti-Xa plasma sample drawn after the initial dose of study drug treatment should be conducted 4 hours ±1 hour after the first, second or third dose of study medication per Investigator judgment. Subsequent Anti-Xa plasma samples conducted following dose adjustments will also be drawn at 4 hours ±1 hour post-dose, after the first, second or third dose of study medication per Investigator judgment. Doses will be adjusted in increments or decrements of 25 IU/kg in order to achieve target anti-Xa levels (0.5-1.0 IU/mL). All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the sample is drawn. Plasma samples drawn during the Dose-Adjustment Phase and Follow-Up Phase that deviate outside the 4 ± 1 hr window cannot use the anti-Xa reference range, 0.5-1.0 IU/mL, and should be repeated the next day for both central and local labs. The actual dosing time prior to the repeat plasma sample draw and the actual time of the repeat sample draw must be recorded.

PD Phase:

Subjects completing the Dose Adjustment Phase will enter into the PD Phase. Dalteparin sodium will be administered subcutaneously every 12 hours ±1 hour (no less than 8 hours between doses) with the maintenance therapeutic dose from the Dose Adjustment Phase.

However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time. The PD Phase will last for 1 to 7 days in order to complete two PD samples for each subject (for the central lab, only). Subjects from each age group will be randomized according to a randomization scheme provided by the electronic system, IMPALA, into two different plasma sampling windows: 1 to 3 h and 5 to 8 h or 3 to 5 h and 8 to 12 h until at least 50 subjects provide viable PD Phase Anti-Xa values. All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the plasma sample is drawn in the Case Report Form (CRF) and repeat it when appropriate at the correct time, if possible.

The plasma sampling times can be spread over the duration of the PD Phase (up to 7 days) to avoid blood volume shifts if necessary. The assignment of the time points to the subjects within each age group will be centrally randomized.

Follow-up Phase:

After subjects successfully complete the PD Phase, they will enter the Follow-up Phase. During this phase, dalteparin sodium will be administered subcutaneously every 12 hours ±1 hour (no less than 8 hours between doses) with the maintenance therapeutic dose at Visits 5, 6 and 7. However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing. One Anti-Xa plasma sample will be collected at 4 hours ±1 hour post-dose at each visit to check if the Anti-Xa level remains within the target therapeutic range. If not, a dose adjustment may be required, per Investigator judgment. All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the sample is drawn. Plasma samples drawn during the follow up phase that deviate outside the 4 ± 1 hr window cannot use the Anti-Xa reference range, 0.5-1.0, and should be repeated the next day for both central and local labs. The actual dosing time prior to the repeat plasma sample draw and the actual time of the repeat sample draw must be recorded.

For non-cancer patients who stop dalteparin treatment prior to 3 months according to the ACCP Guidelines, Anti-Xa and Anti-IIa plasma sampling will not be required after study medication discontinuation.

Throughout the 3 month study period, the actual times of dosing and anti-Xa blood draw times will be captured on the patient Case Report Form (CRF).

The use of intravenous or intra-arterial cannulas for blood sample collection is not permitted.

5.3. Definition of End of Study and Early Discontinuation

End of study (EOS) is defined as Day 90 (± 14 days) after study Baseline. Early Discontinuation from Study Drug: Early discontinuation from study drug treatment will be defined as less than 90 days of study treatment for cancer patients. For non-cancer patients, between 6 weeks and 3 months, rather than shorter or longer durations (Grade 2C), following completion of the PD Phase (2012 ACCP Guidelines[15]) due to: 1) new or recurrent VTE; 2) bleeding necessitating permanent discontinuation of anticoagulant therapy; 3) unexpected permanent discontinuation of anticoagulant therapy; 4) AEs necessitating discontinuation of study drug; 5) withdrawal of consent to participate in the

trial, or 6) inability to achieve therapeutic range during Dose Adjustment Phase. Non-cancer patients will be required to remain in the study, however, for the full 3 months, regardless of dalteparin treatment duration.

5.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact center phone number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

6. SELECTION OF STUDY POPULATION

6.1. Number of Subjects

Subjects, from approximately 40 centers in North America and Europe, will be enrolled into the following five age groups:

- 0 to < 8 Weeks;
- ≥ 8 Weeks to < 2 Years;
- ≥ 2 Years to < 8 Years;
- ≥ 8 Years to < 12 Years;
- ≥ 12 Years to < 19 Years.

The target enrollment is 50 subjects. Enrollment will continue until 50 subjects have viable PD profiles after treatment doses of dalteparin.

6.2. Inclusion Criteria

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for entry into the study.

Subjects meet inclusion if all of the following are true:

1. Have been objectively diagnosed with a venous thrombotic event documented using one of the following acceptable imaging modalities within 4 days of the Screening Visit:

   - Compression ultrasound with Doppler [CUD];
   - Computed tomography with/without venography [CT/CTV];
   - Magnetic resonance imaging with/without venography [MRI/MRV];
   - Conventional venography [CV]);
   - Ventilation-perfusion scan [V/Q] (for pulmonary artery);
   - Spiral CT angiography [SCTA];
   - Conventional pulmonary angiogram [CPA].

2. Are judged clinically to require anticoagulation therapy.

3. Are in the age range of ≥36 weeks gestation and <19 years at the Screening Visit.

4. Have given signed informed consent (and assent, as appropriate) to participate prior to the Screening Visit.

5. For cancer patients only, a diagnosis of active malignancy (currently under treatment), other than basal cell or squamous cell carcinoma of the skin.

6. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

7. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

8. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

   a. Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or psychiological cause; (status may be confirmed with/and have) (select one as appropriate) a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

6.3. Exclusion Criteria

Subjects are excluded if any one of the following apply:

1. Weight ≤3.0 kg or >100 kg at the Screening Visit.

2. Platelet count ≤50,000/mm^3 (despite appropriate medical measures to support platelet count).

3. Received OAC therapy within 3 days of the Screening Visit .

4. History of administration of therapeutic doses of LMWH or unfractionated heparin for a period of > 4 days (or >8 doses of LMWH) for the qualifying VTE.

5. Received unfractionated heparin within 3 hours, or LMWH within 12 hours, of the first dose of dalteparin.

6. Acute VTE intervention which includes thrombolytic therapy.

7. Subjects with Mmajor bleeding or bleeding disorders such as Platelet Dysfunction, Protein Deficiency, Disseminated Intravascular coagulation (DIC), Factor Deficiency, Hemophilia, Idiopathic Thrombocytopenic Purpura (ITP) or Von Willebrand Disease at the time of the Screening Visit or an unacceptably high risk of bleeding, at the discretion of the investigator, should not be considered candidates.

8. Major bleeding at the time of the Screening Visit or an unacceptably high risk of bleeding at the discretion of the investigator.

9. Activated partial thromboplastin time (aPTT) ≥5 seconds above upper limit of normal (ULN), which does not correct to within normal limits upon 1:1 mixing with normal plasma.

10. Prothrombin time (PT) ≥2 seconds above ULN, and that corrects to within normal limits upon 1:1 mixing with normal plasma.

11. Creatinine clearance <60 mL/min/1.73m^2 in subjects >1 month of age.

12. Uncontrolled hypertension characterized by a sustained systolic pressure or diastolic pressure >99th percentile of age- and height-related norms.

13. History of heparin-induced thrombocytopenia (HIT).

14. Any condition in which the investigator feels the subject is unsafe or inappropriate for study participation.

15. Participation in other clinical studies involving investigational drug(s) within the past 30 days.

16. Insufficient subcutaneous tissue to facilitate subcutaneous drug administration.

17. Pregnant female subjects; breastfeeding female subjects; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of assigned treatment.

18. Unable or unwilling to comply with scheduled follow-up visits.

6.3.1. Unscheduled Termination from the Study

Withdrawal of consent: Subjects or parents/guardians who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject or parents/guardians specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject or parents/guardians to provide this information. Subjects or parents/guardians should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible.

The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up: All reasonable efforts must be made to locate subjects to determine and report their ongoing status.

This includes follow-up with persons authorized by the subject or parents/guardians as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject or parents/guardians to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject or parents/guardians and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.3.1.1. Subject Removal from the Study

When subjects are removed from the study the following information will be obtained:

a. The date of the last administration and dose of study medication and all observations collected up to the time of termination will be recorded on the subject's CRF along with the reason for termination.

b. An examination of the subject will be conducted, if possible. All assessments that would be conducted at Visit 7 (EOS) should be performed.

6.3.2. Subject Replacement Policy

All subjects who prematurely discontinue from the study and do not complete the PD Phase will be replaced until 50 subjects have viable PD Phase Anti-Xa data.

7. TREATMENTS

Dalteparin sodium (Fragmin®) will be provided in:

- Multiple dose vials of 25,000 IU/1 mL (3.8mL for US or 4mL for ROW) containing preservative benzyl alcohol;
- Preservative-free single dose vials of 2,500 IU/1 mL (4mL) [where available];
- Preservative-free 10,000 IU / 1 mL single-dose graduated syringe (can be diluted as needed per the IP Manual).

Dosing administration is subcutaneous, twice daily. Study medication can only be administered to patient by a healthcare professional (ie, study nurse) or trained parent/caregiver. Hospital nurses that may administer study medication to in-patient subjects do not require GCP training. However, they must receive study medication administration training from the site staff and the training should be documented.

The use of cannulas to administer study medication is not permitted.

Subjects, aged 0 to less than 8 weeks will receive twice daily dose of 125 IU/kg. Subjects, aged greater than or equal to 8 weeks to less than 2 years will receive twice daily dose of 150 IU/kg. Subjects aged greater than or equal to 2 years to less than 8 years and subjects aged greater than and equal to 8 years to less than 12 years will receive twice daily dose of 125 IU/kg. Subjects aged 12 years to less than 19 years will receive twice daily dose of 100 IU/kg.

All subjects will have dose adjustments in 25 IU/kg increments or decrements based upon Anti-Xa therapeutic goal range of 0.5 to 1.0 IU/mL. Dalteparin sodium will be administered subcutaneously every 12 hours ±1 hour (no less than 8 hours between doses). However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time.

- Dose Adjustment Phase (Baseline/Day 1 up to Day 7):

Anti-Xa levels will be measured at 4 hours post-dose (±1 hour) daily for up to 7 days to determine if the anti-Xa level is within the target therapeutic range of 0.5 to1.0 IU/mL.

However, the first Anti-Xa level may be taken after the first, second or third dose per Investigator judgment. The next dalteparin dose will be adjusted if the target therapeutic range is not achieved. If the therapeutic range is not achieved, the dalteparin dose must be adjusted per protocol. All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the sample is drawn). Plasma samples drawn during the Dose-Adjustment Phase and Follow-Up Phase that deviate outside the 4 ± 1 hr window cannot use the anti-Xa reference range, 0.5-1.0 IU/mL, and should be repeated the next day for both central and local labs. The actual dosing time prior to the repeat plasma sample draw and the actual time of the repeat sample draw must be recorded.

After dose adjustment, Anti-Xa levels should be re-measured after the first, second or third dose per Investigator judgment. Dosage can be adjusted a maximum of up to 6 times (up to Day 7) to achieve Anti-Xa therapeutic range. If the target range is not achieved within the 7 day period, the subject is withdrawn from the study.

The dose at which a therapeutic Anti-Xa level is achieved is then maintained as the therapeutic dose in subsequent phases of the study unless dose adjustment is necessary.

- Pharmacodynamic Phase (Following completion of Dose Adjustment Phase) Day 2 or 3 up to Day 14 [up to 7 days]): Subjects completing the Dose Adjustment Phase will enter into the PD Phase and continue daily dosing every 12 hours ±1 hour of dalteparin sodium with the final maintenance therapeutic dose from the Dose Adjustment Phase (no less than 8 hours between doses). However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time. The plasma sample should be re-drawn, if possible, at the correct time point.

- Follow-up Phase (Visits 5, 6 and 7, following completion of Pharmacodynamic Phase): Dalteparin sodium will be administered subcutaneously every 12 hours ±1 hour (no less than 8 hours between doses) during Visits 5, 6 and 7. However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time.

- No other systemic anticoagulants are allowed during the study with the exception of allowance of hospital specific Intra Venous (IV) (including central venous catheter line patency protocols which could include tissue Plasminogen Activator (tPA) and 3 IU/kg stat dose of unfractionated heparin, if the subject is unable to be treated with study drug due to an unanticipated hospital admission or a clinical event.

For non-cancer patients who stop dalteparin treatment prior to 3 months according to the ACCP Guidelines, Anti-Xa and Anti-IIa plasma sampling will not be required after study medication discontinuation. Treatment will be continued until any of the following occurs:

- New or progressive VTE (whether symptomatic or asymptomatic);
- Bleeding necessitating permanent discontinuation of anticoagulant therapy;
- Unexpected thrombocytopenia;
- Other AE necessitating discontinuation of study drug, withdrawal of consent or, scheduled study termination completion;
- Unexpected permanent discontinuation of anticoagulation therapy.

7.1. Dose Modification

In the event of medical procedures that may be required during the study, study medication can be held according to the institutional standard of care.

7.1.1. Thrombocytopenia

Platelet count will be evaluated at Screening, Baseline, the last day of the dose adjustment and PD Phases, as well as the clinical visits during the Follow-up Phase. **For subjects whose platelet counts unexpectedly fall below 50,000/mm^3, HIT antibody testing will be performed. If the HIT antibody is positive, the subject must be discontinued.** If, during the study, the platelet count falls to below 50,000/mm^3 in a manner that is deemed to be expected by the treating oncologist (ie, consistent with chemotherapeutic effect on hematopoiesis), the administration of dalteparin should be temporarily stopped. After medical measures have been taken to increase the platelet count to a level ≥50,000/mm^3, administration of dalteparin can be restarted. If the platelet count does not increase to a level of ≥50,000/mm^3 within 2 days in spite of medical measures, discontinuation of dalteparin should be considered.

Withdrawal of the subject from the study should be considered if platelet count does not increase to a level of ≥50,000/mm^3 after 5 days following discontinuation of dalteparin.

7.1.2. Renal Dysfunction

For subjects who may experience impaired renal function during the course of the study, whose CrCl declines to <30 mL/min/1.73m^2, dalteparin sodium may need to be adjusted and Anti-Xa levels should be monitored to maintain appropriate levels (ie, trough Anti-Xa levels of <0.4 IU/mL) and the medical monitor should be notified. Subjects with major bleeding or bleeding disorders such as Platelet Dysfunction, Protein Deficiency, Disseminated Intravascular coagulation (DIC), Factor Deficiency, Hemophilia, Idiopathic Thrombocytopenic Purpura (ITP) or Von Willebrand Disease at the time of the Screening Visit or an unacceptably high risk of bleeding, at the discretion of the investigator, should not be considered candidates.

- To assess for bioaccumulation of dalteparin sodium, trough Anti-Xa levels should be checked prior to the next dose. The trough Anti-Xa levels should be <0.4 IU/mL;
- If the Anti-Xa level is above 0.4 IU/mL, the dose of dalteparin sodium should be reduced by either holding one dose or reducing by 25 IU/kg, or by doing both;
- The Anti-Xa measurement should be repeated after the next dose. The actual dosing time prior to the repeat plasma sample draw and the actual time of the repeat sample draw must be recorded.

7.2. Use of Other Anticoagulants

No other systemic anticoagulants are allowed during the study with the exception of allowance of hospital specific IV line patency protocols which could include tPA and 3 IU/kg dose of unfractionated heparin or transient use of another LMWH or un-fractionated heparin for no longer than 48 hours, if the subject is unable to be treated with study drug due to an unanticipated hospital admission or a clinical event.

Subjects are excluded if they received unfractionated heparin within 3 hours, or LMWH within 12 hours, of the first dose of dalteparin.

7.3. Identity of Investigational Product(s)

The medication used in this study will be dalteparin sodium (Fragmin®), supplied in open-label format as the following:

- Multiple dose vials of 25,000 IU/1 mL (3.8mL for US or 4mL for ROW) containing preservative benzyl alcohol;
- Preservative-free single dose vials of 2,500 IU/1 mL (4mL) [where available];
- Preservative-free 10,000 IU /1 mL single-dose graduated syringe (can be diluted as needed per the IP Manual).

The multidose vials utilized in this study include a preservative. The single-dose pre-filled syringe and single-dose vial are preservative-free.

Only study subjects that are hospital in-patients can receive the 10,000 IU/1mL dosage form, diluted to 2,500 IU/mL. If a study subject is an out-patient and will be administered study drug at home by a caregiver, they must use either the 2,500 IU / 1 mL preservative-free 4 mL vial to prepare the prescribed dose or the 10,000 IU / 1 mL preservative-free syringe undiluted to prepare the prescribed dose. The 10,000 IU / 1 mL preservative-free syringe must not be further diluted when prepared at the study subject's home.

Each of the above three study medication presentations can be dispensed to subjects when they are out-patients, however, not if they require dilution.

7.4. Labeling and Packaging of Treatments

The study medication, dalteparin sodium (Fragmin®), will be manufactured by Pfizer Inc. and packaged and distributed by a designated vendor in accordance with instructions provided by Pfizer Inc. Pfizer Inc will also provide the 0.5 mL and 1.0 mL Tuberculin (TB) latex-free, micro-dosing syringes as well as sterile empty vials for evacuation.

Each carton will contain a clinical label including text to meet the country regulatory requirements and include but not limited to the following information: sponsor name, protocol number, storage conditions, contents and directions for use.

Cartons with multidose and single-dose vials will contain 1 vial per carton. Cartons with pre-filled syringes will contain 36 syringes per carton.

Refer to the tables in Appendix 2 for guidance on subjects dosing requirements.

Dosing of the 10,000 IU/1 mL pre-filled syringe formulation should not be administered directly via the original pre-filled syringe unless the intended patient dose is exactly 10,000 IU/1 mL. All other doses using the 10,000 IU/1 mL pre-filled syringe presentation should be evacuated into a sterile vial and administered via a separate syringe to ensure accurate patient dosing. For full preparation and administration information on all three investigational product presentations refer to the Investigational Product Manual.

7.4.1. Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products (including any comparator and/or marketed products) are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

See the Investigational Product (IP) manual or package insert for storage conditions of the product once diluted.

Any storage conditions stated in the single reference safety document (SRSD) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

7.4.2. Drug Supplies

For full Investigational product details, please refer to the Investigational Product Manual.

Drug supply will be provided to sites after the site's Investigator Initiation Package (IIP) documents are received and approved All drug supplies for this study must be stored according to labeled storage conditions. If any excursion from the recommended storage (per study drug label) occurs, the study monitor or other sponsor study team member must be consulted before using the study drug.

Two different size syringes (1 mL TB syringe and 0.5 mL TB syringe) will be available to all sites. Investigators will use their clinical judgment regarding which size syringe is most applicable for administration of each subject's individual study drug dose level.

7.4.3. IP Accountability Log

The Investigator or delegated personnel on the study site must maintain records of the receipt of study drug to the study site, the inventory at the site, the amount dispensed to each subject, and the return of the unused study medication by the subject to the Investigator.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

All used syringes will be disposed as per local biohazard requirements.

The IP Accountability Log must be available for monitoring, auditing or inspection. Details of the accountability of clinical supplies will be recorded.

8. ADMINISTRATION OF TREATMENTS

All subjects will be dosed based on age, weight, and anti-Xa levels. After the Baseline evaluations have been completed, subjects will receive their first dose of study medication by subcutaneous injection according to the following dosing administration instructions below:

- Patients should be sitting or lying down for FRAGMIN® deep subcutaneous administration injection. Based on experience in adults, dalteparin sodium (Fragmin®) should be injected in a U-shape area around the navel, the upper outer side of the thigh or the upper outer quadrangle of the buttock. However, other sites may be more suitable for pediatric patients. Using the thumb and forefinger, you must lift up a fold of skin while giving the injection. The entire length of the needle should be inserted at a 45 to 90 degree angle. The injection site should be varied daily;
- If a subject receives a partial dose due to a dosing error, a second dose should not be given to supplement the initial partial dose. This should be stressed to parents and caregivers if administering study drug to subjects who are out-patients and to hospital staff that will dose the study subjects who are in-patients;
- Clinical supply that is unused by one subject and returned to the site cannot be redispensed for another visit for the same subject or be redispensed to a different subject.

8.1. Dosing Groups:

1. Subjects ages 0 (greater than or equal to 36 weeks gestation) to less than 8 weeks will receive an initial dose of 125 IU/kg twice daily by subcutaneous injection of **preservative-free solution ONLY** supplied in single-dose prefilled graduated syringes, containing 10,000 IU/1 mL or preservative-free 4 mL single-dose vials containing 2,500 IU/1 mL if available. If the 2,500 IU/1 mL vials are not available, the 10,000 IU/1 mL dosage form can be diluted in the hospital pharmacy to 2,500 IU/1 mL by a trained pharmacist or pharmacy technician as needed, according to the suggested dilution process outlined in the IP Manual.
2. Subjects aged greater than equal to 8 weeks to less than 2 years will receive an initial dose of 150 IU/kg twice daily by subcutaneous injection of **preservative-free solution ONLY** supplied in single-dose prefilled graduated syringes, containing 10,000 IU/1 mL, or preservative-free 4 mL single-dose vials containing 2,500 IU/1 mL if available. If the 2,500 IU/mL vials are not available, the 10,000 IU/1 mL dosage form can be diluted in the hospital pharmacy to 2,500 IU/1 mL by a trained pharmacist or pharmacy technician as needed, according to the suggested dilution process outlined in the IP Manual.
3. Subjects aged greater than or equal to 2 years to less than 8 years and subjects ages greater than or equal to 8 years to less than 12 years will receive an initial dose of 125 IU/kg by subcutaneous injection of preservative-free solution supplied in prefilled syringes containing 10,000 IU/1 mL, or preservative-containing 95,000 IU/3.8 mL (US) or 100,000/4mL (Europe) (25,000 IU/1 mL) multidose vials. For smaller doses, preservative-free 4 mL single dose vials containing 2,500 IU/1 mL

may be used for dose preparation if available. If the 2,500 IU/1 mL vials are not available, the 10,000 IU/1 mL dosage form can be diluted in the hospital pharmacy to 2,500 IU/1 mL by a trained pharmacist or pharmacy technician as needed, according to the suggested dilution process outlined in the IP Manual.

4. Subjects aged greater than or equal to 12 years to less than 19 years will receive an initial dose of 100 IU/kg by subcutaneous injection of preservative-containing solution supplied in either preservative-free pre-filled syringes prefilled syringes containing 10,000 IU/1 mL or preservative containing 95,000 IU/3.8 mL (25,000 IU/1 mL) multidose vials.

- If hospitalized during the Dose Adjustment and PD Phases, all doses will be prepared daily by the trained hospital staff. After hospital discharge, study drug will be dispensed to the parents/guardians who will be trained in the handling and storage of the study drug. If a subject receives a partial dose due to a dosing error, a second dose should not be given to supplement the initial partial dose. This should be stressed to parents and caregivers if administering study drug to subjects who are out-patients and to hospital staff that will dose the study subjects who are in-patients.

While subjects are in-patients at the hospital, study drug administration will be conducted by the delegated, trained investigative site staff, or, delegated other hospital personnel who are trained by the Investigator regarding correct study drug administration. When subjects are released from the hospital, the designated parents/guardians will be trained by the Investigator regarding correct study drug dosing and administration. The trained parents/guardians will dose and administer study drug to the subjects at home.

If parents/guardians are not deemed capable or are not willing to administer study drug to the subjects when they are released from the hospital, a visiting nurse, may be trained and made available by the Principle Investigator (PI) or designee, to prepare and administer a daily dose for subjects as needed, if this service is available through the investigative site..

To calculate dosing volumes refer to the protocol dosing directions below. Subjects weighing greater than 3 kg and less than or equal to 100.1 kg are allowed in the study. For age- and weight-based dosing calculations, see Appendix 2.

- For subjects 0 (≥36 weeks gestation) to <2 year of age, weighing ≥3.0 kg: Preservative-free dosing solutions must be used in these subjects. The final dose is to be prepared by drawing up the appropriate dose of drug solution into the appropriate syringe supplied;
- For subjects ≥2 years to <12 years: Withdraw dosing volume needed (obtained from dosing charts) from the 95,000 IU/3.8 mL (25,000 IU/1 mL) multidose vial using a 1.0 mL micro-dosing syringe or per Investigator's judgment, the 2,500 IU/1mL single dose vial **or**, utilize the prefilled syringes containing 10,000 IU/1 mL labeled Fragmin® (dalteparin sodium), for the required dose. Note that if the required dose is exactly 10,000 IU/mL, the dose can be administered directly from the pre-filled syringe.
- For subjects ≥ 12 years to < 19 years of age: Withdraw dosing volume needed (obtained from dosing charts) from 95,000 IU/3.8 mL (25,000 IU/1 mL) multidose vial labeled Fragmin® (dalteparin sodium) using a 1.0 mL micro-dosing syringe, or

per the Investigator's judgment or utilize the prefilled syringes containing 10,000 IU/1 mL labeled Fragmin® (dalteparin sodium). Note that if the required dose is exactly 10,000 IU/mL, the dose can be administered directly from the pre-filled syringe.

8.2. Dosing Scheme: Three Phases

1. **Dose Adjustment Phase**:
   All subjects will receive daily dosing every 12 hours ±1 hour with dalteparin sodium with the final dose from the Dose Adjustment Phase (no less than 8 hours between doses). However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time. The first Anti-Xa plasma sample drawn after the initial dose of study drug treatment should be conducted 4 hours ±1 hour after the first, second or third dose of study medication per Investigator judgment. Subsequent Anti-Xa plasma samples conducted following dose adjustments will also be drawn at 4 hours ±1 hour post-dose, after the first, second or third dose of study medication per Investigator judgment. . If the Anti-Xa level is not within the target therapeutic range of 0.5-1.0 IU/mL, the dose must be adjusted in increments or decrements of 25 IU/kg in order to achieve target Anti-Xa levels (0.5 to 1.0 IU/mL). After dose adjustment, Anti-Xa levels should be measured also after the first, second or third dose per Investigator judgment. If the therapeutic range is not achieved after a maximum of 6 adjustments (up to Day 7), the subject will be withdrawn from the study.

2. **Pharmacodynamic Phase**:
   Subjects completing the Dose Adjustment Phase will enter into the PD Phase and will continue with daily dosing every 12 hours ±1 hour with dalteparin sodium with the final dose from the Dose Adjustment Phase (no less than 8 hours between doses). However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time. Subjects will be randomized to two different plasma sampling windows (1 to 3 h and 5 to 8 h or 3 to 5 h and 8 to 12 h) for anti-Xa plasma samples (for the central lab, only) via the Pfizer Interactive Web Response System (IWRS) system, IMPALA (see below). IMPALA will only provide the subject Screening ID number and randomized plasma sampling group assignment (and respective Randomization Number) during the study (it will not manage drug supply inventory). The plasma sampling times can take place over the duration of the PD Phase to avoid blood volume shifts if necessary. If a plasma sample is not drawn during the correct assigned time point, it should be repeated if possible, at the correct time point when appropriate.

The assignment of the plasma sampling time points to the subjects within each age group will be centrally randomized via the IMPALA system (note that only plasma sampling groups will be randomized, not study medication. This is an open-label treatment study).

The two plasma samples will be collected from each subject during the PD Phase based on the subject's assigned plasma sampling randomization group:

- Randomization Schedule A:

- One sample at 1 to 3 hours post-dose;
- One sample at 5 to 8 hours post-dose.

- Randomization Schedule B:
  - One sample at 3 to 5 hours post-dose;
  - One sample at 8 to 12 hours post-dose.

3. **Follow-up Phase**:
   In the Follow-Up Phase, subjects will continue daily dosing every 12 hours ±1 hour with dalteparin sodium with the final dose from the Dose Adjustment Phase (no less than 8 hours between doses) until EOS or ET. However, if a dose is not able to be delivered every 12 hours ±1 hour, administer the dose (no less than 8 hours between doses) and record the actual dosing time. In-clinic visits will occur on Visits 5, 6 and 7 for safety, and efficacy assessments, and Anti-Xa plasma samples. Dose adjustments can be made during these visits if necessary. The Principal Investigator or designee will follow-up weekly during a telephone interview with subjects and/or caregivers after discharge from the hospital to assess study compliance and general well-being. Subjects will have repeat imaging (using the same imaging method used at Screening) at the EOS visit or Early Termination (ET) visit to measure clot resolution.

For non-cancer patients who stop dalteparin treatment prior to 3 months according to the ACCP Guidelines, Anti-Xa and Anti-IIa plasma sampling will not be required after study medication discontinuation.

Treatment will continue until any of the following occurs:

- New or progressive VTE (whether symptomatic or asymptomatic);
- Bleeding necessitating permanent discontinuation of anticoagulant therapy;
- Unexpected thrombocytopenia;
- Other AEs necessitating discontinuation of study drug, withdrawal of consent, or scheduled study termination completion;
- Unexpected permanent discontinuation of anticoagulation therapy.

For procedures that require interruption of study treatment, it is recommended to follow the ACCP guidelines.[1] The guidelines state that it may be advisable to omit two doses of LMWH before procedures being performed and resume 12 to 24 hours after the procedures.

8.3. Method of Assigning Subjects to Treatment Groups

This is an open label study. All 50 subjects will receive dalteparin sodium (Fragmin®). During the PD Phase, subjects will be centrally randomized to one of two different plasma sampling windows (1 to 3 h and 5 to 8 h or 3 to 5 h and 8 to 12 h) via the Pfizer IWRS system, IMPALA.

8.4. Selection of Doses in Study

Dosing in the study was based upon published literature describing the dosing previously used in this subject population with (Fragmin®). Nohe et al have shown that the Anti-Xa levels in these subjects have fallen within the target range of Anti-Xa levels (0.5 to 1.0 IU/mL) using similar dosing.[12]

8.5. Blinding

This is an open-label trial.

8.6. Prior and Concomitant Therapy

No other systemic anticoagulants are allowed during the study with the exception of allowance of hospital specific IV line patency protocols which could include tPA and 3 IU/kg stat dose of unfractionated heparin, if the subject is unable to be treated with study drug due to an unanticipated hospital admission or a clinical event. Subjects are excluded from the study if they received unfractionated heparin within 3 hours, or LMWH within 12 hours, of the first dose of dalteparin. Use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is not allowed due to risks of VTE.

9. ASSESSMENTS AND ENDPOINT DEFINTIONS

9.1. Endpoint Definitions

9.1.1. VTE Endpoints

A suspected new or progressive symptomatic VTE, in the same anatomical region, should be documented with the same imaging method used at Screening/ Baseline. Suspected new or progressive VTE in a different anatomical region should be documented utilizing institutional standards. These images should be collected and be included in the primary source records. Thrombus resolution of the qualifying event will be measured by repeat imaging at the EOS visit (using the same modality as that which was used to diagnosis the thrombosis prior to enrollment). If an image has been captured prior to the EOS and it demonstrates complete resolution of the qualifying VTE, then a repeat image does not need to be done again at day 90. For purposes of the study, the complete resolution image will be the "EOS" image for the index event.

In the assessment of a new or progressive symptomatic thrombus, the following general definitions will be utilized;

Symptomatic New VTE: Symptomatic VTE confirmed by at least one radiographic test. Asymptomatic VTE within a venous segment noted to be patent on a prior imaging study. Symptomatic will be defined as: New or progressive signs and symptoms as judged by the investigator including but not limited to:

- Objective swelling;
- Pain or tenderness;
- Pitting edema;
- Erythema or cyanosis.

All New VTE: All VTE confirmed by at least one radiographic test.

Stable VTE: Follow-up study demonstrating stable clot burden utilizing the same imaging modality as the Screening Visit.

Regression of VTE: Follow-up study demonstrating regressed clot burden utilizing the same imaging modality as the Screening Visit.

Progression of VTE: Progression of clot burden on a follow-up study in terms of severity of occlusion, or involvement of new venous segments at any time after the initial diagnosis.

In the assessment of a new or recurrent PE, the following general definitions will be utilized;

New PE: Symptomatic PE confirmed by presence of an intraluminal filling defect of the pulmonary artery on CT angiography and/or a mismatched defect on a nuclear V/Q scan. All new PE's will be considered to be a symptomatic event.

Stable PE: Follow-up study demonstrating stable clot burden utilizing the same imaging modality as the Screening Visit.

Regression of PE: Follow-up study demonstrating regressed clot burden utilizing the same imaging modality as at the Screening Visit.

Progression of PE: Progression of clot burden on a follow-up study in terms of involvement of new pulmonary arterial segments within 14 days after the initial diagnosis or PE.

Determination of the above definitions will be made utilizing set criteria based on clot location and imaging modality utilized.

DVT and PE specific definitions;

To meet the criteria for new or progressive DVT one of the following criteria must be met:

1. A new intraluminal filling defect in two or more projections on venography (New VTE).
2. 5 cm or more extension or an intraluminal filling defect previously seen on ultrasound or venography (progression of VTE).
3. Presence of intraluminal thrombus.

PE Specific Definition*:*

To meet the criteria for new or progressive PE one of the following criteria must be met:

1. A new intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on a pulmonary angiogram.

2. An intraluminal filling defect on CT angiography involving the main pulmonary artery, or proximal generations of the branch pulmonary arteries that are reliably evaluated by CT.
3. High probability V/Q scans.

9.1.2. Bleeding/Safety Events

Safety assessments: (as described in the Protocol Flow Chart) will include the following: medical history, physical examination, vital signs, and study drug exposure/compliance, review of AEs and concomitant medications, and laboratory evaluations.

Bleeding events will be classified as follows:

MAJOR BLEEDING *(Composite of the following)*

a. Fatal bleeding.
b. Clinically overt bleeding associated with a decrease in Hgb of at least 2 g/dL in 24 hours.
c. Overt bleeding deemed by the attending physician to be unrelated to the subject's underlying condition and accompanied by blood product administration.
d. Overt bleeding which is retroperitoneal, intracranial, intraspinal, intraocular, or intra articular.
e. Overt bleeding deemed by the attending physician to necessitate permanent discontinuation of trial medication.

CLINICALLY RELEVANT NON MAJOR BLEEDING

- Bleeding resulting in any medical or surgical interventions but which did not meet the criteria for major bleeding.

MINOR BLEEDING

- Bleeding that does not meet the criteria for Major or clinically relevant non major bleeding.

- Screening evaluations may be used as the baseline assessments.

Antithrombin levels are to be performed once within 1 week post-diagnosis of VTE and at each study visit when Anti-Xa samples are drawn.

9.1.3. Medical History

A complete medical history will be obtained at Screening from the subject and/or guardian. All body systems, conditions and diagnoses will be reviewed noting onset and end dates. Any clinically significant changes and/or exacerbations of condition from following the first dose of study medication will be considered an AE.

9.1.4. Physical Examination

A complete physical examination will be performed at Screening and/or Baseline visit per Investigator judgment, the end of the Dose Adjustment Phase, the PD Phase, and during the Follow-Up Phase at Visits 5, 6, and 7. This exam will include evaluation of the head, eyes, ears, nose, throat, neck, circulatory system, heart, chest, lungs, abdomen, extremities, skin, neurological status and weight measurements, as well as any other physical condition of note.

9.1.5. Pregnancy Test

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 IU/mL, will be performed at screening, before investigational product administration at the Baseline visit, unless the Baseline visit is conducted within 2 days of the Screening Visit, and at all other study visits. During the Dose Adjustment Phase, if multiple study visits are conducted, the pregnancy test will only be required once in the 7-day Dose Adjustment Phase. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and repeated at follow-up visits and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Correctly placed copper -containing intrauterine device (IUD).

2. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate **(See Appendix 4 regarding countries where this method of birth control is not considered highly effective).**
3. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
4. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

The use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception are not allowed due to risks of VTE. If a subject was using a hormonal based contraceptive prior to study entry, it should be discontinued prior to study entry. There is no required wash-out period required for recently discontinued hormonal based contraception.

9.1.6. Imaging

Documentation of an objectively diagnosed venous thrombotic event will be diagnosed using the following acceptable imaging at Screening:

- Compression ultrasound with Doppler [CUD];
- Computed tomography with/without venography [CT/CTV];
- Magnetic resonance imaging with/without venography [MRI/MRV];
- Conventional venography [CV]);
- Ventilation-perfusion scan [V/Q] (for pulmonary artery);
- Spiral CT angiography [SCTA];
- Conventional pulmonary angiogram [CPA].

The investigator will make every effort to have a repeat imaging performed using the same method at the end of study (EOS) (Visit 7) at ET or due to progression of a VTE. The Visit 7 EOS visit imaging is not required if a previous visit imaging has demonstrated resolution of clot.

A copy of all images should be kept with the source documents.

9.1.7. Vital Signs

Vital signs will be measured at each visit. Evaluations will include the following measurements, a resting supine or sitting position for 2 minutes:

- Blood Pressure;

- Temperature (recorded in Celsius);
- Heart Rate;
- Respiratory Rate;
- Height and Weight.

For the weighing of infants and newborns, clothing should be removed leaving only a clean, dry diaper and be positioned in the center of the scale tray, which should be placed on a stable, flat surface. For older children, a scale with appropriate range and resolution should be used. Shoes, bulky layers of clothing and jackets must be removed prior to weight measurement so that only light clothing remains. The contents of pockets should be emptied. Subjects should remain still during the measurement of weight.

9.1.8. Clinical Laboratory Assessments

Anti-Xa assessments will be conducted at both the local and central laboratories at each visit, except during the PD Phase, when the Anti-Xa assessment will be conducted at only the central laboratory. Additionally, the Anti- IIa assessments will be conducted only at the central laboratory at each visit. Anti-Xa levels will be measured at 4 hours (±1 hour) post-dose daily for up to 7 days during the Dose Adjustment Phase. The first Anti-Xa level after initial study medication dosing may be drawn after the first, second or third dose or per Investigator judgment and sent to both the central and local laboratories until a target therapeutic range of 0.5 to 1.0 IU/mL is obtained. Plasma samples may be drawn after the morning or evening dose. After any dose adjustments, the Anti-Xa samples may also be drawn after the first, second or third dose, per Investigator judgment.

During the PD Phase, subjects will be randomized to 1 of 2 different plasma sampling windows. The Anti-Xa plasma samples (2 samples per subject) will be obtained at either 1 to 3 hours and 5 to 8 hours or 3 to 5 hours and 8 to12 hours (for central lab, only). This plasma sampling can occur over a 7-day time frame. Once in the Follow-up Phase, subjects will then have Anti-Xa plasma samples drawn at Visits 5, 6 and 7 post-dose and sent to both the local and central laboratories.

The use of cannulas for blood collection are not permitted.

NOTE: Plasma samples drawn for Anti-Xa and Anti-IIa must not be hemolyzed. All precautions must be made to ensure that the plasma samples are not hemolyzed.

Throughout the 3 month study period, the actual times of dosing and Anti-Xa blood draw times will be captured on the patient CRF.

Pharmacodynamic Measurements

Blood volumes for PD measurements (Anti Xa and Anti IIa) will be as follows for the Central Lab blood sample collection:

- Newborn and Infant Cohort Groups: One 2.0 mL Blue Topped Tube filled to the top with 1.8 mL of blood (tube provided by Central Lab) for processing the plasma samples (contains 0.2 mL of sodium citrate anticoagulant)

- Pre School, School Age and Teen Cohort Groups: One 3.0 mL Blue Topped Tube, filled to the top with 2.7 mL of blood (tube provided by Central Lab) for processing the plasma samples (contains 0.3mL of sodium citrate anticoagulant).

The 2.0 mL tubes will be provided to the site in a bulk shipment, whereas the 3.0 mL tubes will be provided in kits per visit.

Instructions for collection, processing, and shipment of samples for anti Xa and anti IIa analysis by the central lab will be provided in the Laboratory Manual. Please refer to the Laboratory Manual for all details regarding the drawing and processing of the anti Xa and anti IIa plasma samples.

Unfractionated heparin contamination is a major concern when blood samples are taken from a port when testing for low molecular weight heparin (Fragmin®). The following procedure will help eliminate the interference of unfractionated heparin in the anti Xa PD samples:

- Access the port according to the institutional protocol.

- Prior to plasma sampling, flush the port with 5 ml of heparin free normal saline. For subjects 0 1 years of age, follow the institutional protocol for flush and discard.

- For children <7 kg body weight use 3ml discard. Draw 5 ml of whole blood for discard for children > 7kg body weight. The institutional protocol takes precedent over the above procedure for saline flush and discard volumes.

Subjects will be randomized to two different plasma sampling windows (1 to 3 h and 5 to 8 h or 3 to 5 h and 8 to 12 h), so each subject will have two blood draws during the PD Phase for the central lab, only. The plasma sampling times can be spread over the duration of the PD Phase (up to 7 days) to avoid blood volume shifts if necessary. All plasma samples should be drawn within the assigned window at each visit, however, if this is not possible, record the actual time the sample is drawn. If the PD Phase sample is drawn outside the required randomization assigned time period, it should be repeated if possible.

Plasma samples drawn during the Dose Adjustment Phase and Follow Up Phase that deviate outside the 4 ± 1 hr window cannot use the Anti Xa reference range, 0.5 1.0 IU/mL, and should be repeated the next day. The actual dosing time prior to the repeat plasma sample draw and the actual time of the repeat sample draw must be.

In this study, the PD effect (Anti Xa level) is used as a surrogate (PK of dalteparin) for the time course of drug exposure because 1) analytical difficulty in measuring the dalteparin levels in plasma and 2) the instantaneous drug effect quantitated by Anti Xa level. Hence, the study is only characterizing the PD of dalteparin

The safety lab tests below will be conducted at the institutional local lab.

- Hematology/Coagulation: red blood cells (RBC), Hemoglobin, Hematocrit, Total White Blood Cell Count with differential, Platelet Count, PT, aPTT, International Normalized Ratio (INR);
- Antithrombin level at every visit that anti-Xa levels are drawn, and as per investigator's discretion at the Unscheduled Visit;
- Clinical Chemistry: Albumin, Alkaline Phosphatase, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Calcium, Phosphorus, Total Protein, Magnesium, lactate dehydrogenase (LDH), Creatinine, Glucose, Total Bilirubin, Sodium, Potassium, Chloride, Carbon Dioxide, and Blood Urea Nitrogen (BUN), Creatinine Clearance:
- Pregnancy: Serum beta Human Chorionic Gonadotropin (β hCG) assessments or urine pregnancy tests will be performed for post-menarchal females at Screening or Baseline and all other study visits;
- Contact the sponsor if a subject is <1 month old.
- For any study sites that also require urine specimen collection in addition to blood draw for Creatinine Clearance reporting, according to local standards, urine collection will be conducted as required per local standards and Creatinine Clearance results will be provided in the CRF accordingly.
- If any study site's institutional laboratory does not conduct Creatinine Clearance tests, or if the Creatinine Clearance test is deemed not feasible or reliable by the Investigator given the study participant's clinical circumstances the Investigator can calculate the estimated Creatinine Clearance value via the Schwartz Method Formula or the Revised Schwartz Method Formula below. It is preferable, for the Creatinine Clearance value to be provided by the laboratory, if possible. If the estimated Creatinine Clearance is used, the estimated Creatinine Clearance results must be noted in the subject's primary source records indicating which of the above formulas was used and the results must also be entered in the CRF accordingly.
- If the Creatinine Clearance is estimated, the same Schwartz/Revised Schwartz method formula should be used throughout the study for each subject for consistency
- Creatinine Clearance values are not to be used from any electronic creatinine clearance calculators. These are not validated methods and do not meet Pfizer standards.

- **Schwartz Method Formula**:

Child Age	k
Infant (Low Body Weight < 1 year)	0.33
Infant (Term < 1 year)	0.45
Child or Adolescent Girl	0.55
Adolescent Boy	0.70

1. Serum Creatinine = ☐ mg/dL

2. Height = ☐ ☐ cm ☐ inch

CrCl = ☐ mL/min per 1.73 m^2

- **Revised Schwartz Method Formula**:

$$GFR = \frac{0.413 * Height}{CR_{Serum}}$$

- Height is measured in cm
- Serum creatinine is measured in mg/dl

9.1.9. Telephone Follow-Up

The Principal Investigator or designee will be responsible, after hospitalization, for weekly follow-up telephone interviews to all subjects or parents/guardians. The following information will be documented, from the subject and/or caregiver/visiting nurse, (where applicable) a provided service, as needed:

- General health; changes in medications or cancer treatment(s);
- Signs and symptoms of bruising or bleeding episodes;
- Local injection site reactions;
- Medication Exposure;
- Concomitant medications;
- Adverse experiences;
- Study medication compliance.

9.1.10. VTE Assessment and VTE Definitions

For the qualifying event, the diagnostic technique used at Screening should be repeated at EOS or early termination. If an image has been captured prior to the EOS and it demonstrates resolution of the qualifying VTE, then a repeat image does not need to be done on the index event. Full images should be captured of the qualifying event at Screening/Baseline and at EOS. For new and recurrent VTEs, the institution's diagnostic standard shall be utilized.

For these events, full images should be captured of the new or recurrent event. For instructions, please refer to Section 9.1.1. A copy of all images should be kept with the source documents.

9.2. Screening Schedule

The nature and purpose of the investigation must be explained to the subjects and parents/guardians and written informed consent/assent obtained from both parties, where applicable, prior to initiating any screening activities.

Under certain circumstances, rescreening of a subject may be conducted one time, only if approved by the Study Clinician. If you wish to rescreen a subject, contact the Study Clinician prior to rescreening the subject to discuss the specifics and to receive approval. Documentation of rescreening approval must be included in the primary source records of the subject.

9.3. Treatment Period

This Baseline assessment can be conducted within 4 days of the Screening visit. If the Screening visit is conducted within 48 hours of the Baseline visit, the Medical History, Physical Exam (including weight and height), Pregnancy Test, Imaging and Clinical Labs (Chemistry, Antithrombin and Hematology) do not need to be repeated at the Baseline visit.

Baseline- Day 1 –The first study drug dose is administered. The subject could potentially have their first dose adjustment conducted on Day 1 if the Investigator deems it appropriate.

The following procedures will be conducted:

9.3.1. Screening/Baseline (Visit 1/Visit 2)

- Informed Consent/Assent where applicable;
- Medical History;
- Imaging of qualifying VTE;
- Vital Signs including height and weight;
- Physical Exam;
- Anti-Xa level (Baseline only: local and central laboratories) and Anti-IIa (central lab only);

- Antithrombin level;
- Clinical Laboratory (hematology/coagulation/clinical chemistry);
- Serum or urine pregnancy tests (on post-menarche females) (only to be conducted once during the Dose Adjustment Phase, if there are multiple site visits during this phase);;
- Prior and Concomitant Medications/Treatments;
- AEs;
- Dispense Study Drug;
- Study Drug Administration at Baseline;
- Contraception check;
- Clinical lab for urine creatinine if applicable

9.3.2. Dose Adjustment Phase (Visit 3)

If first dose adjustment is on conducted on Day 1, the first Dose Adjustment Phase Visit date would be the same as the Baseline Visit date. If first dose adjustment is conducted on Day 2, that would be the first Dose Adjustment Visit.

- (CRF pages to be completed when optimal dose is achieved)
- Physical Exam (at the end of the Dose Adjustment Phase);
- Vital Signs including weight and height (at the end of the Dose Adjustment Phase);
- Anti-Xa level (local and central laboratories) and Anti-IIa (central Lab only). Plasma samples drawn during the Dose-Adjustment Phase that deviate outside the 4 hour (± 1 hour) window cannot not use the Anti-Xa reference range of 0.5-1.0 IU/mL and should be repeated the next day for both central and local laboratories;
- Antithrombin level (once at the end of the Dose Adjustment Phase);
- Serum or urine pregnancy tests (on post-menarche females) (only to be conducted once during the Dose Adjustment Phase, if there are multiple site visits during this phase);
- Dosing and administration compliance;
- Concomitant Medications/Treatments;
- AEs;
- Dispense Study Drug;
- Return Study Drug;
- Contraception check;
- Clinical lab for urine creatinine if applicable.

9.3.3. Pharmacodynamic Phase

- (CRF pages to be completed when both of the two plasma samples have been drawn)
- Physical Exam (at the end of the PD Phase if it is >1 day);
- Vital Signs including weight and height (at the end of the PD Phase if it is >1 day);
- Clinical Laboratory (hematology/coagulation/clinical chemistry at the end of this phase);
- Serum or urine pregnancy tests (on post-menarche females);
- Anti-Xa level and Anti-IIa (central laboratory, only);
- Antithrombin level (once at the end of the PD Phase);
- Dosing and administration compliance;
- Concomitant Medications/Treatments;
- AEs;
- Dispense Study Drug
- Return Study Drug;
- Contraception check;
- Clinical lab for urine creatinine if applicable.

9.3.4. Follow-up Phase (For Out-Patients only)

NOTE: For non-cancer patients who stop dalteparin treatment prior to 3 months according to the ACCP Guidelines, Anti-Xa and Anti-IIa plasma sampling will not be required after study medication discontinuation.

- Telephone Interview (Weekly, through EOS, except weeks with clinical visits, ie, Visits 5, 6 and 7;
- Physical Exam;
- Vital Signs including weight and height;
- Dosing and administration compliance;
- Clinical Laboratory (hematology/coagulation/clinical chemistry);
- Serum or urine pregnancy tests (on post-menarche females);
- Anti-Xa level (local and central laboratories) and Anti-IIa (central Lab only). Plasma samples drawn during the Follow-Up Phase that deviate outside the 4 hour (± 1 hour) window cannot not use the anti-Xa reference range of 0.5-1.0 IU/mL and should be repeated the next day for both central and local laboratories;
- Antithrombin level;
- Concomitant Medications/Treatments;

- Adverse Events;
- Dispense Study Drug, if applicable;
- Return Study Drug
- Contraception check;
- Clinical lab for urine creatinine if applicable.

9.3.5. Final Visit/Early Termination (ET)

NOTE: For non-cancer patients who stop dalteparin treatment prior to 3 months according to the ACCP Guidelines, Anti-Xa and Anti-IIa plasma sampling will not be required after study medication discontinuation.

- In-clinic visit (Visit 7 or ET);
- Physical Exam;
- Vital Signs including weight and height;
- Clinical Laboratory (hematology/coagulation/clinical chemistry);
- Serum or urine pregnancy tests (on post-menarche females);
- Imaging (same imaging modality at Screening). Note: Visit 7/EOS visit imaging is not required if a previous visit imaging has demonstrated resolution of a clot;
- Dosing and administration compliance;
- Anti-Xa level (local and central laboratory) and Anti-IIa (central Lab only);
- Antithrombin level;
- Concomitant Medications/Treatments;
- Adverse Events;
- Return Study Drug.

9.3.6. Unscheduled Event (In-Clinic Visit, if Required)

Unscheduled Events are conducted if the subject experiences a bleeding event or VTE.
NOTE: For non-cancer patients who stop dalteparin treatment prior to 3 months according to the ACCP Guidelines, Anti-Xa and Anti-IIa plasma sampling will not be required after study medication discontinuation.

- Physical Exam;
- Vital Signs including height and weight;
- Clinical Laboratory (hematology/coagulation/clinical chemistry);
- Serum or urine pregnancy tests (on post-menarche females);
- Imaging (same imaging modality at Screening);
- Antithrombin level;

- Dosing and administration compliance;
- Anti-Xa level (local laboratory, if required);
- Concomitant Medications/Treatments;
- Adverse Events;
- Dispense Study Drug, if applicable;
- Return Study Drug.

9.3.7. Unscheduled Visit (In-Clinic visit, if required)

Unscheduled visits are conducted for any other reason, aside from bleeding events or VTE concerns, per the above Unscheduled Event (In-Clinic Visit, if Required) section.

NOTE: For non-cancer patients who stop dalteparin treatment prior to 3 months according to the ACCP Guidelines, Anti-Xa and Anti-IIa plasma sampling will not be required after study medication discontinuation.

- Physical Exam including height and weight;
- Vital Signs including height and weight;
- Clinical Laboratory (hematology/coagulation/clinical chemistry);
- Serum or urine pregnancy tests (on post-menarche females);
- Antithrombin level;
- Dosing and administration compliance;
- Anti-Xa level (local laboratory, if required;
- Concomitant Medications/Treatments;
- Adverse Events;
- Dispense Study Drug, if applicable;
- Return Study Drug.

10. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND REPORTING

10.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

10.1.1. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

10.1.2. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;

- Medication error;
- Occupational exposure.
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.2. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

10.3. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

10.4. Serious Adverse Events

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

- Results in death;

- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the section on Sponsor's Reporting Requirements to Regulatory Authorities). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

10.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

10.4.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
- For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

Concurrent with

- For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. For oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for Liver Function Test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

10.5. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

10.6. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

10.7. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

10.8. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

a. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

10.9. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

10.10. Withdrawal Due to Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

10.11. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about AEs.

10.12. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

10.12.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured

on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality.

Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

10.12.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

10.12.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

10.13. Breaking the Blind

This is an open-label study and breaking the blind is not applicable.

11. GUIDANCE TO THE INVESTIGATOR

Risk/Benefit Statement FRAGMIN (dalteparin sodium) was first approved for marketed use in 1985 and there has been extensive post-marketing and clinical trial exposure. However, the safety and effectiveness of FRAGMIN in the pediatric population has not been established. This is primarily a study of the safety and pharmacodynamics of FRAGMIN in children with or without cancer and venous thromboembolism. As with any medication, it must be emphasized that serious adverse events, previously identified or not, may occur. Subjects participating in this study cannot be guaranteed a clinical benefit from the administration of the test drug. Thus, for each subject, the possibility of a positive therapeutic effect and their contribution to the scientific understanding of the long term safety of FRAGMIN are the only possible benefits.

12. STATISTICAL METHODS

12.1. Determination of Sample Size

Subjects, with or without a diagnosis of various cancers within 6 months of the Screening Visit and requiring anticoagulation for the treatment and secondary prophylaxis of VTE, will be enrolled into the following five age groups:

- 0 to < 8 Weeks;
- ≥ 8 Weeks to < 2 Years;
- ≥ 2 Years to < 8 Years;
- ≥ 8 Years to < 12 Years;

- ≥ 12 Years to < 19 Years.

Target enrollment is 50 subjects. A sample size of 50 subjects is sufficient to estimate Anti-Xa clearance and V_d of dalteparin. Enrollment will continue until 50 subjects have viable PD profiles after treatment doses of dalteparin.

The sample size was determined based on historical data and a population pharmacokinetic (PK)/PD model, evaluation of the effect of sample scheme and sample size per age stratum on the bias and precision of key PK/PD parameters, after evaluation of total N of 10, 20, 30, 40 and 50 (2, 4, 6, 8, 10 per age stratum as available) and evaluation of single and 2-point sample densities and impact of randomization across strata with 100 trial simulations per design examined. In addition, blood sampling density was also considered after the subject sample size was determined. Single-point sampling designs yielded unacceptable bias in total body clearance of the drug (CL) and/or Vd; confounding of effects if blocked within stratum. Double sampling at 3, 8 and 5, 12 hours post-dose performs more efficiently. Therefore, randomized two-sample design per each subject was also determined.

See Appendix 3 for additional information regarding the trial simulation strategy.

12.2. PD Phase Plasma Sampling Randomization Plan

Enrolled subjects who achieve the target therapeutic Anti-Xa level in the Dose Adjustment Phase will advance to the PD Phase. Subjects will be randomized (at Baseline) to two different plasma sampling schemes (1 to 3 h and 5 to 8 h, or 3 to 5 h and 8 to 12 h) in the PD Phase with a ratio of 1:1 in each age group and the randomization will be blocked and stratified by age group via the electronic system, IMPALA. Randomization will continue until 50 subjects have viable PD Phase profiles.

12.3. Statistical Plan

12.3.1. Statistical Methodology

All statistical analyses will be performed using SAS® (Version 9.1 or higher), and will be assessed at the two-sided 0.05 level. Mean, standard deviation, median, minimum and maximum will be summarized for continuous variables. Frequency and percentage will be summarized for categorical variables. Ninety-five percent (95%) confidence intervals will be provided for primary and selected secondary safety endpoints. Paired t-tests will be performed for the changes from baseline for selected continuous variables. Time to event will be described by using the Kaplan-Meier method. In addition, the Cox Proportional Hazard Regression model will be employed to assess the hazard ratio of the event with prognostic factors.

12.3.2. Definition of Study Populations for Analysis

There will be two analysis populations defined in the study.

- Safety Population: Subjects who receive at least one treatment of dalteparin. All safety analysis will be based on this population;
- Pharmacodynamic Population: Subjects in the Safety Population who achieve therapeutic range of anti-Xa during Dose Adjustment Phase. This population will be the primary analysis population for PD and efficacy analysis.

12.3.3. Analysis of Baseline and Demographic Variables

Demographic and pretreatment characteristics for the safety population will be summarized for all subjects and by age group using descriptive statistics including number of subjects, mean, standard deviation, median and range for continuous variables; and the frequency and percent for categorical variables.

12.3.4. Analysis of Pharmacodynamic Variables

All PD variables will be analyzed within the PD population.

The primary study analysis will be a PD evaluation of dalteparin based on Anti-Xa levels using a population PD analysis methodology. Due to the sparse plasma sampling strategy, population PD analyses will be explored. The PD effect (Anti-Xa level) is used as a surrogate PK of dalteparin for the time course of drug exposure. The population PD analysis may also be named as a population PK analysis. Details of the Population PD analysis will be described in a separate population PD modeling analysis plan document and results will be presented in a separate population PD report.

The secondary PD analyses will include the proportion of children achieving an Anti-Xa therapeutic range of 0.5 to 1.0 IU/mL at 4 hours ± 1 hour post-dose during the Dose Adjustment Phase (up to 7 days) and the proportion of subjects who remain within therapeutic range over the Follow-Up Phase (Visits 5, 6 and 7). These analyses will be descriptively summarized for all subjects and by age groups.

The final dose of dalteparin given to a subject during the Dose Adjustment Phase of the study will be considered the maintenance therapeutic dose (ie, the dose achieving an Anti-Xa level of 0.5 to 1.0 IU/mL at 4 hours ± 1 hour post-dose). The time to achieve the target range is defined as the number of days from the first dose to the final dose that achieves the target Anti-Xa level. The maintenance dose, time to achieve the target range, and number of dose adjustments during the Dose Adjustment Phase will be summarized by age group using summary statistics.

Aggregate PD profiles (curves of Anti-Xa level versus hours after dosing time) and summary measures will be calculated using combined data for all subjects within a given age group.

Additionally, for each age group, the percentage of Anti-Xa levels measured 4 hours post-dose ± 1 hour post-dose that are outside the target range will be calculated during the Follow-up Phase of the study.

12.3.5. Analysis of Efficacy Variables

All efficacy variables will be analyzed within the PD population.

Efficacy variables include:

- Proportion of subjects with objectively documented new or progressive symptomatic VTE will be summarized overall and by age groups during dalteparin treatment; the proportions will be accompanied by an exact 95% confidence interval;
- Proportions of subjects with progression, regression, resolution, or no change in the qualifying VTE will be summarized overall and by age groups during dalteparin treatment; the proportions will be accompanied by an exact 95% confidence interval;
- Time to first episode of recurrent VTE will be analyzed using Cox regression model to assess recurrent VTE during dalteparin treatment, with prognostic factors (eg, age group, baseline tumor type). Kaplan Meier estimates of time will also produced.

Exploratory analyses:

- Logistic regression model assessing if subjects achieve an Anti-Xa therapeutic range during the Dose Adjustment Phase, using the Odds Ratio of prognostic factors of age, gender, chemotherapy status, and dose of dalteparin.

12.3.6. Analysis of Safety Variables

All safety variables will be summarized within the safety population.

Safety analysis will focus on bleeding, AEs, laboratory tests, physical exam, vital signs, treatment exposure, study drug compliance, and subject disposition during dalteparin treatment.

The investigators' assessments for bleeding events will be collected and used as secondary analyses.

1. The safety analysis will include the following:
    - Proportion of subjects with any major bleeding events will be summarized overall and by age group during dalteparin treatment; the proportion will be accompanied by an exact 95% confidence interval;
    - Proportion of subjects with any bleeding events (major and minor) will be summarized overall and by age group during dalteparin treatment; the proportion will be accompanied by an exact 95% confidence interval;
    - Proportion of subjects with any minor bleeding events will be summarized overall and by age group during dalteparin treatment; the proportion will be accompanied by an exact 95% confidence interval;
    - Time to first major bleeding events will be analyzed using Cox Proportional Hazard Regression model to assess the major bleeding events during dalteparin treatment with prognostic factors (eg, age group, baseline tumor type, baseline chemotherapy status) in the model. Kaplan Meier estimates of time will also be produced.
    - Relationship between major bleeding event and the Anti-Xa level during dalteparin treatment will be analyzed using logistic regression for major bleeding event assessed on prognostic factors (eg, baseline Anti-Xa level [observed at the end of dose adjustment], age).

2. AE and SAEs will be summarized for the number of subjects with treatment-emergent AEs by System Organ Class and Preferred Term (MedDRA coded) overall, by Severity (NCI CTC version 3.0), by Relationship to study drug, by Seriousness, by if leading to dose change and by if leading to subject's discontinuation of the study.
3. Subject disposition, PE, Vital Signs and Labs will be descriptively summarized. Change from baseline for continuous variable will be analyzed using paired-T test.
4. Treatment Exposure: Treatment duration, summary of daily dose, number of subjects with any dose change and number of changes per each subject, frequency of missed or interrupted study drug and the duration per each interruption or missed, and reasons for study drug interruption or missed will be descriptively summarized.
5. Study Compliance:
    - Study Compliance is defined based on the number of daily doses of study medication administered divided by the intended days of treatment;
    - ≥80% in this variable will indicate that the subject was compliant. The proportion of subjects that were compliant will be presented.

12.3.7. Some Statistical Considerations

Censoring Criteria for Time to Events:

When there is no occurrence of the event, time to event will be censored to the date of last event assessment (last visit, death, or date of ET).

13. DATA MONITORING COMMITTEE

This study will not use a data monitoring committee.

It should be emphasized that the subject, the subject's parent and/or legal representative are at liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects, their parents and/or legal representatives, who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact their subsequent care.

13.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

13.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP), International Conference on Harmonisation (ICH 6), and the Declaration of Helsinki (World Medical Association (1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3. Subject Information and Consent

Protection and safety of vulnerable subjects (including illiterate subjects) will be ensured to uphold the subjects' well-being, rights, and confidentiality and the integrity of their data will be safeguarded. This includes both consent procedures and methods to ensure the veracity of study assessments.

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent

signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

13.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

13.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

14. TREATMENT COMPLIANCE

14.1. Drug Accountability Procedures

An Investigational Product Accountability Log must be kept current and available for inspection by the clinical trial monitor, and should contain the following information:

- Initial Inventory upon receipt of study drug and clinical supplies at the clinical study site;
- The identification number of each subject to whom study drug was administered;
- The date(s), quantities, lot numbers, and the dispenser's initials for all study drug administered;
- Running and final inventory (upon completion of the clinical study).

This inventory must be available for inspection by the clinical trial monitor.

Following the closeout of the study, all unused clinical supplies are to be destroyed on site or shipped by the monitor to Pfizer Inc's designated drug destruction site.

14.2. Receipt of Study Drug

The Investigator (or Pharmacist, as appropriate) must maintain records of the delivery of the study medication to the study site, the inventory at the site, the use for each subject, and the return to a delegate of Pfizer Inc.

14.3. Handling of Study Drug

All drug supplies for this study must be stored according to labeled storage conditions. If any excursion from the recommended storage (per study drug label) occurs, the study monitor or other sponsor study team member must be consulted before using the study drug.

14.4. Records of Study Drug

Study Drug will be dispensed at Baseline, Dose Adjustment Phase, PD Phase, Follow-Up and Unscheduled Visits as appropriate, and returned at Dose Adjustment Phase, PD Phase, Follow-Up and Unscheduled Visits as appropriate and End of Study. All drug dispensation and return will be documented on the IP Accountability Log. The Drug Dispensing Log must be available for monitoring, auditing, and inspection.

15. STUDY MANAGEMENT AND ADMINISTRATION

15.1. Monitoring

Pfizer Inc, or designee, will perform all monitoring functions. Monitors will work in accordance with Pfizer monitoring Standard Operating Procedures (SOPs) or the SOPs of the contract research organization, as designated in the contract. Monitors will be responsible for establishing and maintaining regular contact between the Investigators and the Sponsor. Monitors will also control adherence to the protocol at the Investigative sites.

Monitors will evaluate the competence of each study site. Monitors will inform Pfizer Inc regarding problems relating to facilities, technical equipment, or medical staff. Monitors will arrange for the supply of study drug and ensure appropriate storage conditions are maintained. Monitors will ensure that written informed consent/assent has been correctly obtained from all subjects/responsible party prior to administration of any study procedures or drug administration and during the study will ensure that data are recorded correctly and completely in the CRF.

Monitoring visits will be made to each center approximately every 6 to 8 weeks and may need to occur more or less frequently if deemed necessary by Pfizer Inc. In addition, the Monitor will maintain regular contact with the site to follow study progress including subject disposition and occurrence of SAEs. The Monitor will make written reports to Pfizer Inc on each visit made to the Investigative site.

During monitoring visits, original source documents will be compared to entries in the CRF. For all subjects, monitoring of source data documentation will occur at 100%. The Monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigators (or his/her designee) agree to cooperate with the Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

15.2. Audit and Inspection

Investigator sites, the study database, and the study documentation may be subject to quality assurance audits during the course of the study either by Pfizer Inc, or their appointed representatives. In addition, regulatory bodies at their discretion may conduct inspections.

15.3. Quality Control and Quality Assurance

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

16. DATA HANDLING AND RECORD KEEPING

16.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the

data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

16.1.1. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

16.2. Investigator Site File

At the beginning of the study, an investigator's study file will be established at the study center. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

The following guidelines, instructions and certifications are regarded as relevant supplements and will be provided for the investigator's study file at each center:

- World Medical Association Declaration of Helsinki (See Appendix 1);
- Package Insert to serve as the Investigator's Brochure;
- Sample shipment details.

16.3. Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a time set by Pfizer Inc. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

16.4. Publication of Study Results

16.4.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

16.4.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16.5. Clinical Study Report

A final integrated clinical/statistical report will be prepared that is compliant with the ICH Harmonized Tripartite Guideline.

16.6. Subject Insurance and Indemnity

Pfizer Inc will provide the insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. The terms of insurance will be kept in the study files.

16.7. Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The ethics committee must be informed of all protocol amendments and should be asked for its opinion as to whether a full reevaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The investigator must not implement any deviation from or change to the protocol, without discussion with, and, agreement by Pfizer Inc and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor(s), change of telephone number(s)). Protocol amendments will be submitted to the appropriate authority (ies) as required by the applicable regulatory requirement(s).

16.8. Disclosure of Information and Results

In signing the final protocol, every participating investigator agrees to keep all information and results concerning the study and the investigational product confidential. The confidentiality obligation applies to all personnel involved at the investigational site.

16.9. Publication and Presentation Policy

The results of this study will be published and/or presented at scientific meetings in a timely manner. Any formal publication of study results will be a collaborative effort between Pfizer Inc and the investigator(s). All manuscripts or abstracts will be reviewed and approved in writing by Pfizer Inc prior to submission.

16.10. Archiving and Data Retention

All study documents should be retained 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 elapsed since the formal discontinuation of clinical development of the investigational product, in accordance with 21 CFR (Code of Federal Regulations) 312.62. These documents should be retained for a longer period however, if required by regulatory requirements or by 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.

The final database will be archived by Pfizer Inc, according to regulatory requirements.

16.11. Data Protection

Personal and sensitive personal data will be treated as confidential. The results of the study will be made available for review by authorized representatives of Pfizer Inc and/or submitted to one or more sponsor offices worldwide, the ethics committee and regulatory authorities.

For this purpose the data may be transferred within Europe or to countries outside the European Union, where the laws about the protection of personal/sensitive data may not be as strict as in Europe. The data collected from this study is considered as personal/sensitive data as defined under the European Union Directive 95/45/EC. The data controller of Pfizer Inc will take steps to ensure that data are protected.

Prior to the subject's Screening Visit in the study, the subject's consent is required for the data to be used for these purposes and to gain direct access to their medical records for data verification purposes.

The subject must be assured that their identity will be protected. To facilitate this, a unique identification code will be assigned by the investigator to each study subject. This will be used instead of the subject's name and cross-referenced with the subject's date of birth when reporting AEs and /or other study-related data.

17. REFERENCES

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12. Nohe N, et al. The low molecular weight heparin dalteparin for prophylaxis and therapy of thrombosis in childhood: a report on 48 cases. Eur J Pkediatr 1999; 158 Suppl 3:S134-9.
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18. APPENDICES

Appendix 1. World Medical Association Declaration Helsinki

Recommendations guiding physicians in biomedical research involving human subjects.

- Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964.
- 29th World Medical Assembly, Tokyo, Japan, October 1975.
- 35th World Medical Assembly, Venice, Italy, October 1983.
- 41st World Medical Assembly, Hong Kong, September 1989.
- 48th General Assembly, Somerset West, Republic of South Africa, October 1996.
- 52nd WMA General Assembly Edinburgh, Scotland October 2000.

Note of Clarification:

Paragraph 29 added by the WMA General Assembly, Washington 2002.

Paragraph 30 added by the WMA General Assembly, Tokyo 2004.

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a subject, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the

future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health, or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every subject including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the subject to participate in a study must never interfere with the physician-subject relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the subject.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or subjects for whom the experimental design is not related to the subject's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Appendix 2. Study Drug (dalteparin sodium) Dosing Calculation Examples (Additional dosing administration instructions can be found in the Investigational Product (IP) Manual)

Example: Subject DOSING LEVEL (IU/kg) X Pt Weight (kg) = Dose to administer (IU)

Dose to administer (IU)/Drug concentration (IU/mL) = Volume to administer (mL)

Protocol Age Group	**Example Patient Age**	**Required Starting Dose**	**Example weight (kg)**	**Dose to Administer (IU)**	**Drug Concentration* Used (IU/mL)**	**Volume to Administer (mL)**
0 to <8 Weeks	4 wks	125 IU/kg	4 kg	500 IU	**2500 IU/mL PF**	0.2 mL
≥8 Weeks to <2 Years	10 wks	150 IU/kg	7 kg	1050 IU	**2500 IU/mL PF**	0.42 mL
≥2 years to <8 Years	3 yrs	125 IU/kg	12 kg	1500 IU	**2500 IU/mL PF**	0.6 mL
≥8 Years <12 Years	8 yrs	125 IU/kg	24 kg	3000 IU	**10,000 IU/mL PF**	0.3 mL
≥12 Years <19 years	15 yrs	100 IU/kg	82 kg	8200 IU	**10,000 IU/mL PF**	0.82 mL
≥12 Years <19 years	15 yrs	100 IU/kg	82 kg	8200 IU	**25,000 IU/mL**	0.33 mL

- *Important to note the concentration of dalteparin sodium being used in order to determine the correct volume to administer to the subject

Appendix 3. Dalteparin Simulation Strategy

Background:

In support of this trial, simulations of dalteparin activity (anti-Xa activity) in response to SC administration are suggested to support the sampling scheme and sample size requirements. Simulations will be based on a nonlinear mixed effect model defined in the NONMEM algorithm and constructed for an analysis of children at increased risk for TE receiving once-daily SC dalteparin.[1] The analysis of these study results (n=43 subjects/31 evaluable), suggests that differences in the rate of uptake of dalteparin may be expected across various age strata. This effect was evaluated by the calculation of the time of maximum anti-Xa activity (Tmax) across the age group. In this situation Tmax serves as a surrogate for absorption rate (ka) as there was little data collected with the sparse sampling scheme during the absorption phase. Likewise, simulations for the this study will be consider various sampling schemes and examine the bias and precision in key PK parameters (principally CL and V_d but including ka) as well as the likely sample size required to demonstrate a statistical difference in Fragmin® anti-Xa clearance in pediatric versus adult populations.

Plan:

Two sampling designs will be considered:

1. Blocked randomization design: This design will consider the randomization of subjects into single sample collection groups within age strata (4, 7, 12 and 24 hour collections) for each age range category.
2. Two-sequence, two-sample randomization design: This design will consider randomization to two different sampling windows (1 to 3 h, 5 to 8 h or 3 to 5 h, 8 to 12 h).

Demographic data from the pediatric TE study will be used as sampling characteristics for the various age strata. The population model will be used to simulate anti-Xa activity profiles for each of the proposed sampling schemes for sample sizes of 10, 20, 30 and 40 subjects per strata. One hundred trials for each of sample size and scheme scenario will be simulated (4x2x100 = 800 simulated trials). Data will be refit to the population model and bias and precision of PK parameters will be evaluated. The impact of sample size to detect a 30% difference in CL between historical adult values will also be examined.

[1] Barrett JS, Mitchell LG, Patel D, et al. A Population based Analysis of Dalteparin Pharmacokinetics in Pediatric Patients at Risk for Thromboembolic Events. *Abstract submitted (American College of Clinical Pharmacology)*.

Appendix 4. Regional Amendment for Highly Effective Methods of Contraception

As per the European Heads of Medicines Agency's Clinical Trial Facilitation Group's recommendation (Recommendations related to contraception and pregnancy testing

in clinical trials – Final Version 2014-09-15) any European Union Member State or other country that follows these recommendations and does not recognize condoms with spermicide as a highly effective method of contraception will follow the highly effective methods of contraception as indicated below in the revised Section 9.1.5, Pregnancy Test.

9.1.5. Pregnancy Test

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 IU/mL, will be performed at screening, before investigational product administration at the Baseline visit, unless the Baseline visit is conducted within 2 days of the Screening Visit, and at all other study visits. During the Dose Adjustment Phase, if multiple study visits are conducted, the pregnancy test will only be required once in the 7-day Dose Adjustment period. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and repeated at follow up visits and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is not allowed due to risks of VTE.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

4. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

Female partner who meets the criteria for non-childbearing potential, as described below:

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;

- Have medically confirmed ovarian failure; or

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject. If this option is selected for a female subject of childbearing potential, then the subject would be required to undergo interval urine pregnancy testing (specify a schedule) and would be asked to record stop and start dates for menstruation throughout the course of the study.

The use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception are not allowed due to risks of VTE. If a subject was using a hormonal based contraceptive prior to study entry, it should be discontinued prior to study entry. There is no required wash-out period required for recently discontinued hormonal based contraception.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential. All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose.