NDA/BLA Multi-Disciplinary Review and Evaluation

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Division/Office	Division of Hematology Products/OHOP
Review Completion Date	May 13, 2019
Established/Proper Name	Dalteparin
Trade Name	Fragmin
Pharmacologic Class	Low molecular weight heparin
Applicant	Pfizer Inc.
Dosage form	Subcutaneous injection
Dosing Regimen	Age and weight-based dosing
Applicant Proposed Indication/Population	For the extended treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients (b) (4)
Recommendation on Regulatory Action	Regular approval
Recommended Indication/Population	For the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HIT	Heparin Induced Thrombocytopenia
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IU	International Units
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
VTE	Venous thromboembolism

1 Executive Summary

1.1. Product Introduction

Established name: Dalteparin
Proprietary Name: FRAGMIN
Pharmacologic Class: Low molecular weight heparin (anticoagulant)

Fragmin (dalteparin sodium) is a low molecular weight heparin (LMWH) with antithrombotic properties by enhancing the inhibition of Factor Xa and thrombin by antithrombin. Fragmin received initial US approval in 1994.

Current approved indications:

- Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction
- Prophylaxis of deep vein thrombosis in abdominal surgery, hip replacement surgery or medical patients with severely restricted mobility during acute illness
- Extended treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in patients with cancer. In these patients, the Fragmin therapy begins with the initial VTE treatment and continues for six months.

Proposed revised indication:

(b) (6)

(b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The information submitted by the Applicant provides substantial evidence of effectiveness for dalteparin treatment to reduce the risk of recurrence of pediatric patients with symptomatic venous thromboembolism. Efficacy is based on a single arm, open-label, multicenter trial (Study FRAG-A001-201) that included 38 pediatric patients with or without cancer and symptomatic deep vein thrombosis and/or pulmonary embolism treated with dalteparin twice daily based upon age and weight. The trial included 26 patients with an active malignancy and 12 patients without cancer. Efficacy was established by the achievement of therapeutic anti-Xa level (defined as 0.5 IU/ml – 1.0 IU/ml) within 7 days of initiation of dalteparin therapy in 34/38 (89%) patients. Attainment of plasma anti-Xa levels of 0.5 – 1.0 IU/ml is considered the goal of low molecular weight heparin therapy in the treatment of symptomatic VTE in pediatrics and is included in the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (Monagle, 2012). Efficacy is further supported by the lack of VTE progression or development of recurrent VTE while on treatment. In the 34 patients with therapeutic anti-Xa, no patient experienced progression of the qualifying VTE and one patient (3%) developed a recurrent VTE while on treatment. Additional supportive efficacy data included a dalteparin subanalysis by O'Brien et al. of the Duration of Therapy for Thrombosis in Children trial (Kids-DOTT), a prospective, multicenter, randomized trial evaluating the optimal duration of anticoagulation for pediatric patients with venous thromboembolism. The dalteparin subanalysis of the Kids-DOTT trial included 18 pediatric patients without cancer with symptomatic venous thromboembolism. All 18 patients successfully achieved a therapeutic anti-Xa level between 0.5-1.0 IU/mL. Upon study completion, no patients experienced progression of the qualifying VTE or recurrence of VTE. Therefore, the achievement of therapeutic anti-Xa level with age and weight-based dosing along with meaningful reduction in VTE recurrence or progression supports establishment of efficacy of dalteparin treatment in pediatric patients with symptomatic VTE. Moreover, dalteparin is approved for the extended treatment of symptomatic VTE to reduce the recurrence in adult patients with cancer. Despite differences in the hemostatic system between the adult and pediatric population, requiring unique dosing and treatment considerations for the pediatric population, the overall treatment goals and pathophysiology of recurrent or progressive VTE are similar in adults and pediatric patients. Therefore the efficacy of dalteparin established in the adult population with cancer can be partially extrapolated to the pediatric population, further supporting the determination that dalteparin treatment has clinically meaningful activity in pediatric patients with symptomatic venous thromboembolism.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk assessment supports regular approval of dalteparin for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients one month of age and older.

Efficacy:
Efficacy in pediatric patients is primarily based on a single arm, open-label, multicenter trial (Study FRAG-A001-201) in 38 pediatric patients with or without cancer and symptomatic deep vein thrombosis and/or pulmonary embolism treated with dalteparin twice daily based upon age and weight. In the efficacy analysis, 34 patients (89%) of 38 patients achieved a therapeutic anti-Xa level (0.5-1.0 IU/mL) within 7 days from initiation of dalteparin. Of the 34 patients, no patients experienced progression of the qualifying VTE and one patient (3%) had recurrence of VTE while on treatment. Further, supportive efficacy is provided by a dalteparin subanalysis of the Duration of Therapy for Thrombosis in Children trial (Kids-DOTT), a prospective, multicenter, randomized trial evaluating the optimal duration of anticoagulation for pediatric patients with venous thromboembolism. The dalteparin subanalysis of the Kids-DOTT trial included 18 pediatric patients without cancer with symptomatic venous thromboembolism. All 18 patients successfully achieved a therapeutic anti-Xa level between 0.5-1.0 IU/mL and no patients experienced progression of the qualifying VTE or recurrence of VTE. Furthermore, the efficacy of dalteparin treatment demonstrated in adults with cancer and symptomatic VTE can be partially extrapolated to pediatric patients, while acknowledging substantial differences between the hemostatic system within pediatric patients and compared to adults, the overall treatment goals and pathophysiology of recurrent or progressive VTE are similar in adults and pediatric patients. Dalteparin is approved for the extended treatment of symptomatic VTE to reduce the recurrence in adult patients with cancer.

Safety:
The safety profile of dalteparin in the pediatric population is tolerable and manageable. The safety of age and weight-based starting dosing of dalteparin followed by adjustments to target a plasma anti-Xa level of 0.5-1.0 IU/ml was evaluated in 50 pediatric patients in the FRAG-A001-201 and Kids-DOTT study. The median duration of exposure was 86 days (range 2 to 170 days). The most common adverse events were injection site bruising, pyrexia, and cytopenias. The majority of the adverse events reported were not considered related to study drug and

were reported in the pediatric population with cancer. The most important safety issue associated with low molecular weight heparin therapy is bleeding. Major bleeding events were rare in the safety population, occurring in only 1 (2%) patient. Minor bleeding adverse events were reported in 40% of the safety population. The overall low (12%) rate of treatment discontinuation in a complex pediatric patient population further supports safety. There was an insufficient number of neonates (N=1), defined as from birth to 28 days, included in the safety population. Neonates have altered coagulation pathophysiology compared to older pediatric populations and may be more susceptible to major bleeding as well as the clinical sequelae of major bleeding. Therefore, the safety of dalteparin in neonates has not been established.

Benefit-Risk:
The benefit-risk determination considered the totality of efficacy and safety data for dalteparin treatment in pediatric patients and partial extrapolation from adults. The FRAG-A001-201 and Kids-DOTT study provided sufficient data to establish dosing in pediatric patients based upon age and weight. Efficacy data from the two prospective pediatric trials and adult efficacy data provide evidence of effectiveness in pediatric patients with and without cancer. Pediatric patients with an active malignancy receiving dalteparin treatment for symptomatic VTE have potential for increased toxicity. Because the FRAG-A001-201 study evaluated 26 patients with an active malignancy and the toxicity profile is tolerable and manageable, the review team felt the risk associated with dalteparin treatment in pediatric patients without cancer warrants broadening the indication to a general pediatric population. Although, due to insufficient safety data in the neonatal population (birth to 28 days) and potential for increased risk of bleeding and sequalae of bleeding, the risk in neonates warrants restriction of the indication to pediatric patients greater than 1 month of age. Therefore, the benefit-risk assessment of dalteparin treatment is deemed favorable for the treatment of symptomatic venous thromboembolism to reduce the recurrence in pediatric patients 1 month of age and older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Venous thromboembolism (VTE) in pediatric patients is a rare condition reported in 0.07-0.14 per 10,000 children • The incidence of VTE is increased in hospitalized children and those with underlying morbidities • Symptomatic venous thromboembolism (VTE) in pediatric patients with and without cancer requires treatment, and if untreated can result in morbidity and mortality • Much of the current VTE treatment in pediatric patients is	Symptomatic VTE in pediatric patients is a serious and life threatening condition that requires treatment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	extrapolated from adults • Pediatric patients with cancer are at risk for VTE due to underlying illness, treatment and indwelling catheter placement	
Current Treatment Options	• Current guidelines recommend treatment of symptomatic VTE in pediatric patients. • Treatment options include unfractionated heparin, low molecular weight heparin, vitamin K antagonists • There are no approved anticoagulant therapies in pediatric patients • Low molecular weight heparin is widely used in treatment of pediatric VTE due to ease of administration compared to unfractionated heparin and vitamin K antagonists • Therapeutic anti-Xa levels of 0.5 IU/ml – 1.0 IU/ml are targeted in the treatment of pediatric VTE with low molecular weight heparin • Younger patients require higher doses of low molecular weight heparin to achieve therapeutic anti-Xa levels	Pharmacokinetic and pharmacodynamic informed dosing recommendations are needed to inform safe dosing of low molecular weight heparin in the pediatric population
Benefit	• Therapeutic anti-Xa levels were achieved within 7 days of initiation in 34/38 patients in study FRAG-A001-201 • No patient experienced progression of the qualifying VTE. Of the 34 patients, 62% experienced resolution, 21% regression, and 6% no change of symptomatic VTE • One patient (3%) developed recurrent VTE while on treatment	The Applicant's data supports the Applicant's proposed age and weight based starting dose of dalteparin
Risk and Risk Management	• The most common adverse reactions in greater than 10% of patients include injection site bruising, pyrexia, anemia, and thrombocytopenia • Minor bleeding events occurred in 40% of the safety population • A major bleeding event occurred in 1 (2%) patient	The overall safety profile of dalteparin is acceptable for pediatric patients over the age of one month with or without cancer and symptomatic VTE. There is insufficient data in the neonatal population to adequately assess

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Major bleeding events were reported at a lower rate than in the adult cancer population • Safety data in the neonatal population is insufficient (N = 1) to inform safety in this population • The protocol included dose modifications or interruptions which were sufficient to mitigate the majority of treatment related toxicities • The proposed labeling includes warnings for bleeding risk, dose modifications for thrombocytopenia, and instructions for dose adjustments based on anti-Xa level.	safety in this population. The risk of bleeding can be mitigated by dose modifications based on anti-Xa levels and thrombocytopenia

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
X	**Patient experience data was not submitted as part of this application.**			

X	X	X
Margret Merino, MD Primary Clinical Reviewer	Nicholas Richardson, DO, MPH Primary Clinical Reviewer	R. Angelo de Claro, MD Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Venous thromboembolism (VTE) in pediatric patients is rare and reported to occur in 0.07 to 0.14 per 10,000 children. The rate of VTE in hospitalized children is increased by 100 to 1000 times, and has been reported to have increased by up to 70% from 2001 to 2007 across all pediatric age groups, highlighting the association of pediatric VTE with comorbid conditions and indwelling catheters.[1,2] Pediatric malignancy is one of the most strongly associated risk factors for VTE and is thought be related to the common use of indwelling catheters, use of chemotherapeutic agents that may increase the risk of VTE and the increased recognition and diagnosis of VTE in this population. In an analysis of over 7,000 pediatric patients with cancer in Canada, the 5 year cumulative incidence of thromboembolism requiring medical intervention was 3.8%.[3]

There are recognized differences in the etiology and pathophysiology of venous thromboembolism between the adult and pediatric population. In pediatrics, VTE are more likely to be related to underlying illness or indwelling catheter vs. spontaneous VTE which are more common in the adult population and can be related to hormonal or environmental factors. Within the pediatric cancer population, specific chemotherapeutic agents (i.e asparaginase and corticosteroids) can redispose to thrombosis as well as concurrent inflammation, immobility and mechanical devices related to the primary malignancy or therapy. Similar factors may impact other pediatric patients with complex medical conditions other than cancer. Neonates are predisposed to thrombosis due to a variety of factors, including an altered levels and potential imbalance of coagulation and anti-coagulation factors and represent a unique subpopulation of pediatric patients who develop VTE.

Similar to adults, in the pediatric population, VTE can result in the significant morbidity and mortality. Complications of VTE in the pediatric population in include VTE progression resulting in pain and edema in the affected region, pulmonary embolism, post-thrombotic syndrome, thrombophlebitis, infection, and loss of catheter function in the case of catheter related VTE.

Although the etiology and sequelae of VTE differ between the pediatric population and the adult population, pathophysiology, once a patient has developed a symptomatic VTE, similar to adults, treatment with anticoagulant therapy in pediatric patients is recommended to prevent recurrence or progression.[4,5]

The increasing incidence of VTE and the overall improvements in the care of tertiary care pediatric patients with complex medical conditions with expected long-term survival of these patients, emphasize the need for effective and safe treatment of VTE in the pediatrics population. The long term sequalae of the complications related to VTE and the treatment of

VTE must be considered when weight the benefit and risk of treatment.

2.2. Analysis of Current Treatment Options

There are no FDA approved anticoagulants approved for first line treatment or prevention of recurrent venous thromboembolism in pediatric patients. The treatment of pediatric thromboembolism has historically been based upon adult experience. Pediatric patients with symptomatic VTE are typically treated in tertiary care centers with pediatric hematology involvement. Unique considerations with regards to the treatment of pediatric VTE include the dynamics of the coagulation system in the developing child, PK and PD differences in younger pediatric patients requiring higher doses of unfractionated and low molecular weight heparin in younger patients.

Indwelling catheters are associated with a significant number of thrombosis in pediatric patients who develop VTE. Contrary to the approach in the adult population, in pediatric patients for VTE associated with indwelling catheter use that are not immediately life threatening, removal of the indwelling catheter may not be initiated immediately, and anti-coagulation is initiated with the intent to prevent thrombosis propagation, maintain patency of the catheter, prevent symptoms associated with impaired blood flow and edema.

The three main classes of anticoagulants commonly used to prevent recurrence of VTE are unfractionated heparin, low molecular weight heparin, and vitamin K antagonists. There are ongoing studies evaluating direct oral anticoagulants, however these have not been incorporated into formal pediatric guideline recommendations to date. Of the current available treatments, low molecular weight heparin has an advantage of the ease of administration, availability of therapeutic monitoring, lack of the drug-drug or food interaction concerns associated with vitamin K antagonists, the ability to temporarily discontinue anticoagulation therapy for invasive procedures and the overall low risk of bleeding.

In contrast to adults, pediatric patients treated with low molecular weight heparin are treated with initial age and weight based dosing followed by dose adjustments based on anti-Xa levels to achieve and maintain a target plasma anti-Xa level of 0.5 IU/ml to 1 IU/ml. Higher doses of LMWH are required in neonates and children compared to adults to achieve therapeutic anti-Xa levels. This is thought to be at least partially due to increased clearance and decrease antithrombin levels in infants and young children.In addition to optimizing anti-Xa levels for therapeutic effect, period anti-Xa monitoring also provides an added safety measure to assure that patients do not reach supratherapeutic anti-Xa levels which may be associated with an increased risk for bleeding.

Randomized clinical trials or large single arm trials to inform dosing for anticoagulants in children are lacking, and dosing recommendations are based on smaller, single arm study reports. Suggestions included in the American College of Chest Physicians Evidence-Based on

Clinical Practice Guidelines for neonates and children receiving bid therapeutic low-molecular weight heparin include drug monitoring and titration to a target range of 0.5 to 1.0 until/mL in a sample taken 4 to 6 hours after subcutaneous injection.[4] The Chest guidelines are also referenced in the American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism.[5] Therapy is recommend for at least three months in patients with cancer or associated pro-thrombotic risk and for at least 5 weeks for patients without other co-morbidities predisposing to thrombosis.

Table 1: Summary of Treatments available for the treatment of VTE in Pediatric Patients with Cancer

Product (s) Name	Dosing/ Administration (initial treatment dose)	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Enoxaparin	< 2 months 1.5mg/kg/dose q 12 hours > 2 months 1.0mg/kg/dose Q 12 hours	Target anti-Xa level of 0.5 – 1 IU/ml	Major bleeding risk reported of approximately 3 % in adults Partial reversal possible with protamine	
Dalteparin	129 +/- 43 Unit/kg/dose q 24 h	Target anti-Xa level of 0.5 – 1 IU/ml		
Tinzaparin	0-2 months 275 u/kg/dose 2-12 months 250 u/kg/dose 1-5 years 240 u/kg/dose 5-10 years 200 u/kg/dose 10-16 years 175 u/kg/dose			
Heparin (unfractionated heparin)	Loading Dose 75 units/kg IV over 10 minutes Maintenance dose: 28 units/kg per hour for infants < 1 year 20 units/kg per hour for children > 1 year	Target aPTT of 60-85s	Major bleeding risk reported of 2-25% Major bleeding often reported due to accidental overdose Full reversal possible with protamine	Requires continuous IV administration, typically in ICU setting Requires titration to target aPTT
Warfarin	0.2 mg/kg PO loading dose, titrated to achieve INR 2-3		Major bleeding rate of 12% Reversal with vitamin K	Not commonly used in infants or pediatric patient with cancer due difficulty in optimal titration,

				monitoring requirements, concomitant meds and DDI concerns, and risk of bleeding

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fragmin received initial US approval in 1994 and currently has regular approval for the following indications:

- Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (NDA 020287/S-10, 05/1999)
- Prophylaxis of deep vein thrombosis in abdominal surgery, hip replacement surgery or medical patients with severely restricted mobility during acute illness (NDA 020287, 12/1994; NDA 020287/S-8, 03/1999; NDA 020287/S-32, 12/2003, respectively)
- Extended treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in patients with cancer. In these patients, the Fragmin therapy begins with the initial VTE treatment and continues for six months (NDA 020287/S35, 05/2007)

3.2. Summary of Presubmission/Submission Regulatory Activity

Following the approval of Fragmin in 2007, for extended treatment of symptomatic VTE to reduce the recurrence in patients with cancer, the Sponsor was required to conduct a study to evaluate efficacy and safety of dalteparin in pediatric patients with cancer under the Pediatric Research Equity Act (PREA). In response, the former Sponsor (Eisai) of dalteparin initiated the FRAG-A001-201 trial titled: A Three Month Prospective Open Label Study of Therapy with Dalteparin in Children with Malignancies and Venous Thromboembolism.

Following repatriation of dalteparin sodium from Eisai to Pfizer on 01 April 2015, a Type C meeting was held on 05 November 2015 to expand the study outside the US and include pediatric patients with VTE with or without cancer in an effort to accrue 50 primary efficacy evaluable patients. Further, the Agency agreed with submission of the clinical study report for FRAG-A001-201 by 31 December 2018 and that additional clinical data from other trials could be used to support the evaluation of efficacy and safety of dalteparin in pediatric patients.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The FDA Office of Scientific Investigations was not consulted for this submission.

4.2. Product Quality

There are no product quality issues with this supplement.

4.3. Clinical Microbiology

There were no clinical microbiology issues identified.

4.4. Devices and Companion Diagnostic Issues

Factor-Xa levels were assessed locally and centrally. There were no issues identified during the course of the review related to plasma anti-Xa assessments that impacted the clinical conclusions of the study.

5 Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology data for dalteparin supporting approval and labeling of Fragmin was reviewed under previous submission of NDA 020287. The current application contains no new pharmacology/toxicology data.

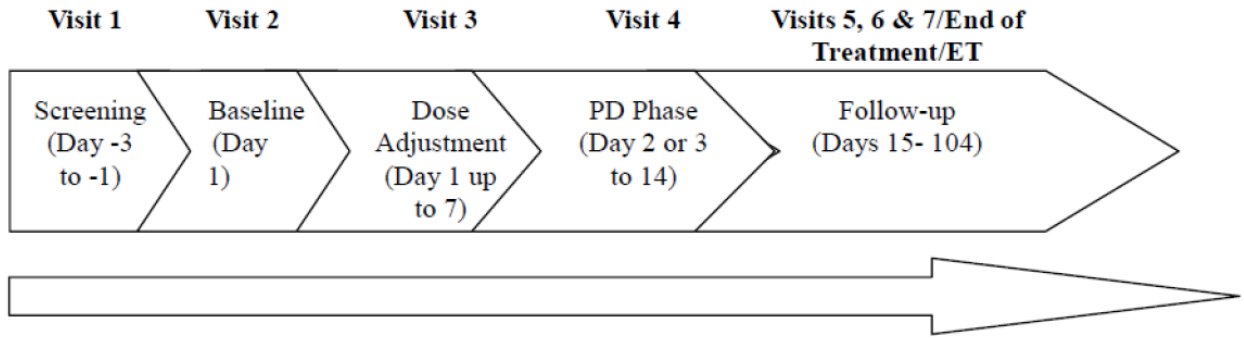
6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking approval of Fragmin (dalteparin sodium) for the extended treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients (b) (4)

The clinical dosing and efficacy of Fragmin in pediatric subjects is supported by the FRAG-A001-201 (A6301094) study. The study was a 3-month, multicenter, open-label, pharmacodynamic (PD) study with no control group. The primary PD endpoints of the study were to determine the PD profiles for treatment doses of dalteparin in pediatric subjects of different ages with or without cancer and VTE, using anti-Factor Xa (anti-Xa) levels and a population PD analysis methodology, and to determine the median dose (IU/kg) required to achieve therapeutic anti-Xa levels (0.5 to 1.0 IU/mL) based on subject age and weight.

Figure 1: Study Schematic



[Source: CSR FRAG-A001-201, Adapted from (9.1) Figure 1]

Briefly, the design of the study was as shown in Figure 1. The study was divided into 3 phases: 1) Dose Adjustment phase of up to 7 days; 2) PD phase; and 3) Follow-Up phase, to allow completion of up to 90 days of treatment. Subjects were enrolled into one of the following five age groups (cohorts): newborn (0 - <8 weeks), infants (≥8 weeks - <2 years), preschool (≥2

years - <8 years), school (≥8 years - <12 years), and adolescents (≥12 years - <19 years). The target enrollment was a total of 50 subjects who completed the PD Phase.

In 2007, under the Pediatric Research Equity Act (PREA), the Agency required that the former Applicant of the NDA, Eisai, conduct FRAG-A001-201 study in children with malignancies and VTE to fulfill a post marketing requirement (PMR) in conjunction with the approval of Fragmin for extended treatment of symptomatic VTE in adult patients with cancer. Following NDA transfer to Pfizer on 01 April 2015, the PREA commitment is now between Pfizer, Inc. and the Agency. Following a Type C Meeting with Pfizer on 05 November 2015, it was agreed that because of enrollment challenges this study could also include acute VTE pediatric subjects without cancer in an effort to accrue 50 primary efficacy evaluable patients. Further, the Agency agreed with submission of the clinical study report for FRAG-A001-201 by 31 December 2018 and that additional clinical data from other trials could be used to support the evaluation of efficacy and safety of dalteparin in pediatric patients.

The results of the FRAG-A001-201 study indicated that younger subjects required a higher dose of dalteparin to achieve a therapeutic anti-Xa level (subjects in the ≥8 weeks to <2 years cohort required a median dose of dalteparin of 207.5 IU/kg (every 12 hours ± 1 hour), versus 128, 125, 116.7 IU/kg (every 12 hours ± 1 hour) for the ≥2 to <8 years, ≥8 to <12 years, ≥12 years to <19 years cohorts respectively. In addition, subjects in the younger age cohorts required more time to achieve therapeutic anti-Xa levels with more dose adjustments relative to the older age cohorts. The PD data from FRAG-A001-201 study have been combined with data from two third-party published literature studies [the Kids-DOTT Dalteparin Sub-Study[1] (referred to as "Kids-DOTT study"), and the Mayo Clinic Study[2]] for a pooled population PD analysis to optimize the starting dose for all the age groups. Based on the simulation results, the following starting doses of dalteparin administered q12h subcutaneously (SC) are proposed:

(b) (4)

The purpose of this review is to evaluate and confirm the Applicant's proposed dosing regimen for Fragmin in pediatric patients.

[1] O'Brien SH, Kulkarni R, Wallace A, et al. Multicenter dose-finding and efficacy and safety outcomes in neonates and children treated with dalteparin for acute venous thromboembolism. J Thromb Haemost 2014;12(11):1822-5.

[2] Warad D, Rao AN, Mullikin T, et al. A retrospective analysis of outcomes of dalteparin use in pediatric patients: A single institution experience. Thromb Res 2015;136(2):229-33.

6.1.1. Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology information submitted to this NDA supplement and is in agreement with the Applicant's proposed dosing regimen for Fragmin in pediatric patients. However, dosing recommendations are not provided in the USPI for neonates (birth to <4 weeks) due to lack of sufficient safety information in this age group.

6.1.2. Post-Marketing Requirements and Commitments

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology	
Mechanism of Action	Dalteparin is a low molecular weight heparin with antithrombotic properties. It acts by enhancing the inhibition of Factor Xa and thrombin by antithrombin. In humans, dalteparin potentiates preferentially the inhibition of coagulation Factor Xa, while only slightly affecting the activated partial thromboplastin time (APTT).
General Information	
Bioanalysis	Plasma samples were assayed for anti-Xa plasma levels using a validated method by (b) (4) The samples were analyzed using a chromogenic assay with the lower limit of quantification of 0.1 IU/mL for anti-Xa activity.
Dose proportionality	Increasing the dose from 2,500 to 10,000 IU resulted in an overall increase in anti-Xa AUC that was greater than proportional by about one-third. Peak anti-Xa activity increased more or less linearly with dose over the same dose range.
Accumulation	No appreciable accumulation of anti-Xa activity was observed with twice-daily dosing of 100 IU/kg SC for up to 7 days.
Absorption	
Bioavailability	The absolute bioavailability in healthy volunteers, measured as the

	anti-Xa activity, was 87 ± 6%.
T_{max}	Mean peak levels of plasma anti-Xa activity were attained in about 4 hours in most subjects.
Distribution	
Volume of distribution	The volume of distribution for dalteparin anti-Xa activity was 40 to 60 mL/kg in adults. The apparent volume of distribution ranges from 160-181 mL/kg in pediatric patients aged from 3 weeks to <20 years of age.
Elimination	
Half-life	Following intravenous doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hours, respectively. Longer apparent terminal half-lives (3 to 5 hours) are observed following SC dosing, possibly due to delayed absorption. The mean elimination half-life ranged from 2.3 to 6.3 hours in pediatric patients aged from 3 weeks to <20 years of age following SC dosing.
Excretion	
Primary excretion pathways	Dalteparin is primarily excreted by the kidneys; however, the biological activity of the renally eliminated fragments was not well characterized.
Intrinsic Factors	
Hemodialysis	In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Xa activity following a single intravenous dose of 5,000 IU Fragmin was 5.7 ± 2.0 hours, i.e., considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended starting doses of Fragmin for the treatment of VTE in pediatric subjects from 4 weeks to 17 years of age:

Table 2: Recommended starting dose of Fragmin in pediatric subjects across age groups

Age Cohort	Starting Dose
4 Weeks to less than 2 Years	150 IU/kg twice daily
2 Years to less than 8 Years	125 IU/kg twice daily

8 Years to less than 17 Years	100 IU/kg twice daily

The maintenance dose of Fragmin should be individualized based on the dose that achieves a target anti-Xa level between 0.5 and 1.0 IU/mL.

Therapeutic Individualization

Starting doses are proposed based on age group of pediatric patients as listed above in section 2.2.1. After initiation of Fragmin, anti-Xa level should be measured prior to the 4th dose. Samples for anti-Xa level should be drawn 4 hours after administration of Fragmin to coincide with time to achieve peak anti-Xa levels. Dose adjustments are made in increments of 25 IU/kg to achieve target anti-Xa level between 0.5 and 1 IU/mL. The maintenance dose of Fragmin is individualized based on the dose that achieves target anti-Xa level collected 4 hours after administration of Fragmin. Anti-Xa level should be monitored periodically in pediatric patients to maintain anti-Xa level between 0.5 and 1 IU/mL.

Outstanding Issues

Not Applicable

6.3. Comprehensive Clinical Pharmacology Review

This review is an abbreviated assessment of efficacy and safety in pediatric patients with VTE. The clinical pharmacology information pertinent to the adult indication has already been reviewed.

6.3.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology information submitted provides supportive evidence of effectiveness in that when dalteparin is dosed as per the regimen described below, 89% of pediatric patients achieved anti-Xa levels within the therapeutic range of 0.5 to 1.0 IU/mL. The design and the topline PD results are further described below.

Study FRAG-A001-201 (A6301094) was a 3-month prospective, single arm, multicenter, open-label cohort study trial in 38 pediatric patients with or without cancer and symptomatic deep vein thrombosis and/or pulmonary embolism. The study was divided into 3 phases: 1) Dose Adjustment Phase of up to 7 days; 2) PD Phase; and 3) Follow-Up Phase, to allow completion of up to 90 days. In this study, the PD effect (anti-Xa level) was used as a surrogate (PK of dalteparin) for the time course of drug exposure due to the analytical difficulty in measuring the dalteparin levels in plasma and the instantaneous drug effect quantitated by anti-Xa level. The objective of the study was to bring the anti-Xa levels in pediatric patients across various

age groups within the target range of 0.5 to 1.0 IU/mL during the Dose Adjustment phase and maintain anti-Xa levels within the therapeutic range during the remainder of the study.

Starting Doses:
The starting doses for the 5 age groups were as follows:

- 0 to <8 weeks (newborn) – 125 IU/kg twice daily;
- ≥8 weeks to <2 years (infant) – 150 IU/kg twice daily;
- ≥2 years to <8 years (preschool) – 125 IU/kg twice daily;
- ≥8 years to <12 years (school) – 125 IU/kg twice daily;
- ≥12 years to <19 years (adolescents) – 100 IU/kg twice daily.

Dosing in the study was based on prior clinical experience for Fragmin in pediatric patients as reported in the literature. Nohe et al[3] (129 IU/kg once daily) and Kids-DOTT studies (150 IU/kg twice daily in <12 months, 125 IU/kg twice daily in 1 to <13 years, 100 IU/kg twice daily in 13 to <19 years) have shown that the anti-Xa levels in pediatric subjects fell within the target range of anti-Xa levels (0.5 to 1.0 IU/mL) using a similar dosing algorithm.

Dose Adjustment Phase:
The dose adjustment phase began following the first dose of Fragmin and continued for up to 7 days. During this phase, doses were adjusted in increments or decrements of 25 IU/kg in order to achieve target anti-Xa levels (0.5 to 1.0 IU/mL). If the target range was not achieved within the 7-day period, the subject's study participation was terminated.

PD Phase:
Upon achieving the target anti-Xa level in the dose adjustment phase, subjects entered into the PD phase. Fragmin was administered SC every 12 hours at the maintenance therapeutic dose from the dose adjustment phase. The PD phase lasted for 1 to 7 days, during which subjects from each age group were randomized to two different plasma sampling windows (1 to 3 hours and 5 to 8 hours or 3 to 5 hours and 8 to 12 hours) for the collection of 2 PD samples.

Follow-Up Phase:
After subjects successfully completed the PD phase, they entered the Follow-Up phase. During this phase, subjects continued twice a day dosing with the final Fragmin dose from the dose adjustment phase until end of study and came to follow-up visits 5, 6, and 7 on days 30, 60, 90 respectively. One anti-Xa plasma sample was collected at 4 hours (±1 hour) post-dose at each

[3] Nohe N, Flemmer A, Rümler R, et al. The low molecular weight heparin dalteparin for prophylaxis and therapy of thrombosis in childhood: A report on 48 cases. Eur J Pediatr 1999;158:S134-9.

visit to check if the anti-Xa level remained within the target therapeutic range. If not, a dose adjustment may have been required, per investigator judgment.

Study Results:
Most subjects (34 [89.5%]) subjects achieved therapeutic anti-Xa levels in response to dalteparin treatment. The median dose of dalteparin required to achieve a therapeutic anti-Xa level was higher in the younger cohorts of subjects (≥8 weeks to <2 years cohort required a 207.5 IU/kg versus 128, 125, 116.7 IU/kg (every 12 hours ± 1 hour) for the ≥2 to <8 years, ≥8 to <12 years, ≥12 years to <19 years cohorts respectively) as shown in the **Table 3** below. Subjects in the younger age cohorts required more time to achieve therapeutic anti-Xa levels with more dose adjustments relative to the older age cohorts.

Table 3: Summary of Therapeutic (Maintenance) Dose, Time to Achieve Therapeutic Anti-Xa Levels, and Number of Dose Adjustments – PD Population

	≥8 Weeks to <2 Years (N = 2)	≥2 to <8 Years (N = 8)	≥8 to <12 Years (N = 7)	≥12 to <19 Years (N = 17)	Overall (N = 34)
Therapeutic (maintenance) dose (IU/kg)					
Median (Min, Max)	207.5 (201.5, 213.5)	128.15 (123.9, 180.3)	125.0 (124.5, 152.6)	116.7 (99.1, 159.0)	125.0 (99.1, 213.5)
Mean (SD)	207.5 (8.49)	141.9 (23.55)	132.4 (12.93)	115.1 (17.2)	130.4 (28.41)
Time to achieve anti-Xa target range from First dose (days)					
Median (Min, Max)	4.5 (4,5)	3.0 (1,7)	2.0 (1, 3)	2.0 (1, 4)	2.0 (1, 7)
Mean (SD)	4.5 (0.71)	3.8 (2.19)	1.9 (0.69)	2.1 (0.99)	2.6 (1.54)
No. of dose adjustments					
Median (Min, Max)	3.5 (3, 4)	0.5 (0, 2)	0 (0, 1)	0 (0, 2)	0 (0, 4)
Mean (SD)	3.5 (0.71)	0.8 (0.89)	0.3 (0.49)	0.5 (0.62)	0.7 (0.98)

[Source: Table 12 of CSR FRAG-A001-201 (A6301094)]

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of Fragmin (see 2.2.1) is acceptable for the treatment of VTE in pediatric patients.

Applicant's Proposal:
The population PK modeling and simulation (M&S) approach was used to provide model-informed starting dosing recommendations for dalteparin in pediatric subjects across the entire age range.

Population PK Analysis:

Objectives:

- To describe the PK of anti-Xa levels following SC injection of dalteparin sodium in pediatric patients requiring anticoagulation therapy for the treatment of VTE
- To identify covariates (e.g., age) that explain between-subject variability in the PK of anti-Xa levels and to identify the residual variability in anti-Xa levels
- To perform PK simulations to determine the starting dose of dalteparin sodium required to achieve therapeutic anti-Xa levels (0.5-1.0 IU/mL) for the following age groups in pediatric patients with or without cancer (0 to <8 weeks, ≥8 weeks to <2 years, ≥2 to <8 years, ≥8 to <12 years, and ≥12 to <19 years) and to compare these doses with the observed median dose obtained in the FRAG-A001-201 (A6301094) study

Population PK Model:

- The population PK model was built using the data from the current study and two external studies: Kids-DOTT and Mayo Clinic.
- Dalteparin PK was adequately characterized by a 1-compartment model with first-order absorption and first-order elimination (**Table 4**).
- Body weight, age, gender, and cancer status were added as covariates on apparent clearance (CL/F). Body weight was the only covariate on apparent volume of distribution (V_d/F). Both CL/F and V_d/F increased with body weight. CL/F decreased slightly with age. Gender and cancer status had little influence on CL/F.
- A reduced model was achieved by dropping all insignificant covariates in the full model, that is, gender and cancer status. The resulting model then had 2 covariates, with body weight and age on CL/F and body weight on apparent volume of distribution V_d/F.

Table 4: PK Parameters of Dalteparin in the Pediatric Population

Parameter	Birth to <8 Weeks (Neonates)	≥8 Weeks to <2 Years (Infants)	≥2 to <8 Years (Children)	≥8 to <12 Years (Children)	≥12 to <19 Years (Adolescents)
Number (N)	6	13	14	11	45
Median (range) age in years	0.06 (0.04-0.14)	0.5 (0.2-1.91)	4.47 (2.01-7.6)	9.62 (8.01-10.5)	15.9 (12.0-19.5)
Derived mean (SD) CL/F (mL/h/kg)	55.8 (3.91)	40.4 (8.49)	26.7 (4.75)	22.4 (3.41)	18.8 (3.02)
Derived mean (SD) V_d/F (mL/kg)	181 (15.3)	175 (55.3)	160 (25.6)	165 (27.3)	171 (38.8)
Derived mean (SD) $t_{½\beta}$ (hours)	2.25 (0.173)	3.02 (0.688)	4.27 (1.05)	5.11 (0.509)	6.28 (0.937)

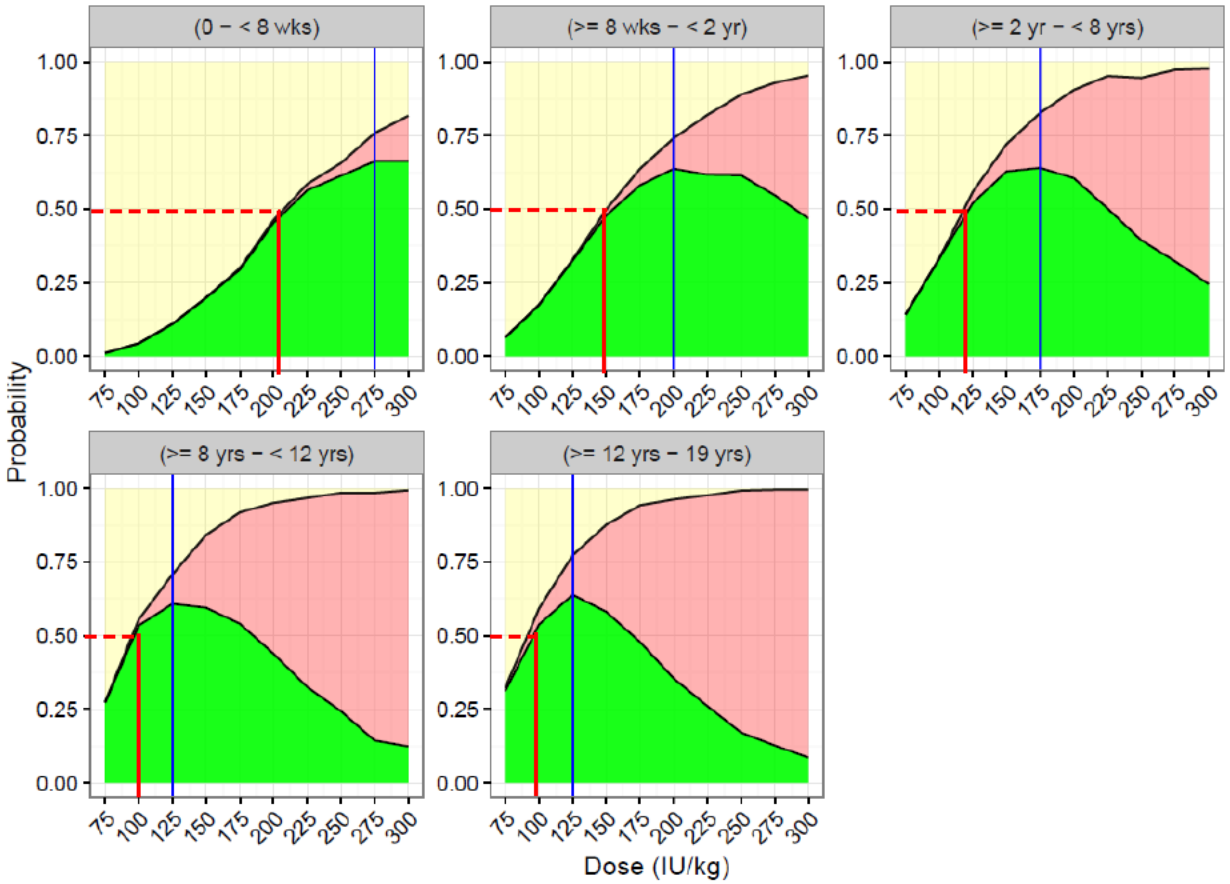
[Source: Table 2 and Table 5 of PMAR-EQDD-A630c-DP4-560]

Simulation Results:

The reduced population PK model was used to simulate anti-Xa plasma concentration-time profiles at various doses for dalteparin in pediatric patients. Simulations were performed on each of the five age groups, and given doses ranged from 75 to 300 IU/kg (with steps of 25 IU/kg) twice daily.

- For each dose and age group, the probability of target attainment (PTA) was defined as the proportion of one thousand simulated subjects who had their anti-Xa steady-state concentration at 4 hours post dose (C4hss) reaching the therapeutic target of 0.5 to 1.0 IU/mL. For each age group, the minimal dose that was required to obtain the maximal PTA (MPTA), was identified.

Figure 2: The PTA (Green), probability of over attainment (Red) and probability of under attainment (Yellow) by Dose and Age Group



The vertical solid blue line that passes the maximal height of the green area intersecting the x-axis is the dose associated with MPTA. The solid red line intersecting the x-axis is the dalteparin dose representing 50% PTA.

- Similarly, for each dose and age group, the probability of under-attainment (C4hss <0.5 IU/mL) and probability of over-attainment (C4hss >1.0 IU/mL) were also calculated.

- The relationship between the dalteparin dose and the 3 probabilities (PTA, probability of under -attainment, and probability of over-attainment) by pediatric age groups are presented graphically in Figure 2. At each dose level, the sum of the 3 probabilities is equal to 1.
- As shown in Figure 2, dalteparin dose versus PTA showed bell-shaped relationship (green region). Initially, an increase in the dalteparin dose results in an increase in PTA, but then the PTA declines after it peaks.
- MPTA across each age group ranged between 61 % and 66% and ~ 10 to 20% of pediatric subjects had anti-Xa plasma levels > 1.0 IU/mL, which is associated with risk of bleeding.
- The Applicant proposes starting doses based on 50% PTA because they ascertain that it achieves a balance between minimizing bleeding risk and to get subjects in target therapeutic range. By reducing PTA across various age groups from 61- 66% to 50%, the over-attainment of anti-Xa levels was markedly reduced from a range of 10 to 19% to 1 to 5%.
- (b) (4)
- (b) (4)

Table 5: MPTA, 50% PTA, Proposed Doses of Fragmin in the Pediatric Population across age groups

	(b) (4)	≥8 Weeks to <2 Years (Infants)	≥2 to <8 Years (Children)	≥8 to <12 Years (Children)	≥12 to <19 Years (Adolescents)
MPTA Dose (IU/kg)		200	175	125	125

50% PTA Dose (IU/kg)	(b) (4)	150	125	100	100
Proposed Dose (IU/kg)		150	125	100	100

[Source: 2.7.2 Summary of Clinical Pharmacology Studies]

Review Team's Proposal:

The Applicant's approach of using linear function for age to describe renal maturation in the population PK model may not be appropriate. The Review Team performed sensitivity analysis on Applicant' model by incorporating renal maturation function[4]. The revised model had parameters of renal maturation function fixed from literature, which were shown to better describe renal maturation in infants and neonates. Effect of body weight on clearance was included through allometric scaling.

The final model developed by the Review Team (Table 6) was then used for Monte Carlo simulations to determine the starting doses of dalteparin, targeting concentrations of anti-Xa to fall within 0.5 and 1 IU/mL. The starting dose was determined at 50% PTA. Table 7 and Figure 3 summarizes the MPTA for each age group and related doses at MPTA and 50% PTA.

Table 6: Parameter estimates for the Applicant and Review Team's final models

	Applicant's model estimate (%RSE)	Review Team's model estimate (%RSE)
CL/F (mL/hr)[a]	906 (7.0)	1070 (8.0)
V/F (mL)	7180 (14)	6820 (13)
Ka (hr^{-1})	0.972 (58)	0.808 (36)
WT exponent in CL/F	0.75 (Fixed)	0.75 (Fixed)
WT exponent in V/F	1 (Fixed)	1 (Fixed)
AGE exponent in CL/F	-0.0546 (48)	n/a
PMA50 (weeks)	n/a	48 (Fixed)
HILL	n/a	3.38 (Fixed)
IIV_CL/F (%)	20.2 (32)	36.5 (23)
IIV_V/F	34.8 (41)	40.7 (28)
Additive error (IU/mL)	0.0162 (41)	0.0172 (33)
Proportional error (%)	5.02 (39)	5.25 (36)

[4] Holford, N. (2017). Pharmacokinetic variability due to environmental differences. Transl Clin Pharmacol. 25(2), 59-62.

CL/F – clearance, V/F- volume of distribution in plasma, Ka – first order absorption rate constant, WT-body weight included in the model through allometric scaling, PMA50 - time to 50% renal maturation, HILL-factor regulating the shape of the curve, IIV -interindividual variability.
[a]The applicant tested age on clearance as $(AGE/12)^{exponent}$. The Review Team used renal maturation function parameterized as PMA/(PMA50+PMA) where PMA is post-menopausal age.

Table 7: Summary of MPTA for each age group and related doses at MPTA and 50% PTA

Age Group	% MPTA	Dose at MPTA (IU/kg)	Dose at 50% PTA (IU/kg)
0 - <8wks	56	150	100
8wks - < 2yrs	55	175	150
2 - <8yrs	60	175	125
8 - <12yrs	55	125	110
12 -19yrs	57	125	100

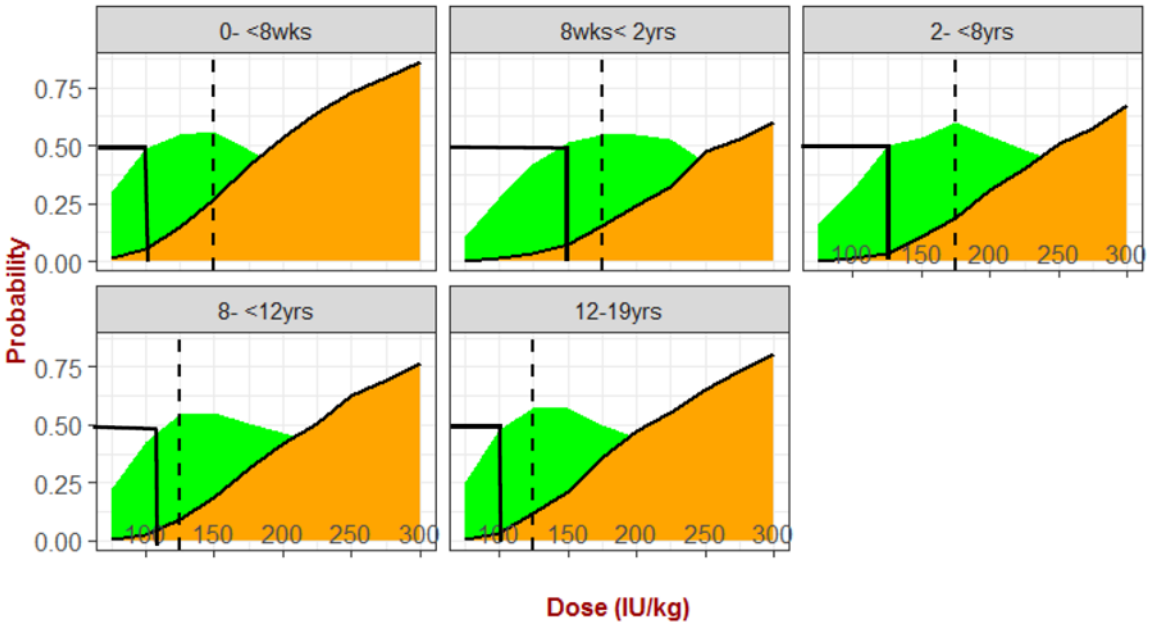


Figure 3: Plot of MPTA for each age group and related doses at MPTA and 50% PTA

[Source: Reviewer's Analysis]

The shaded green area represents the probability Anti-Xa levels of falling within the target while the orange shaded area is the probability of falling above 1.0 IU/mL of anti-Xa. The dashed vertical lines show dalteparin dose associated with MPTA. The solid lines show Dalteparin doses associated with 50% PTA.

The model revised by the Review Team after incorporating the renal maturation function suggested that the Applicant proposed dose is acceptable, based on 50% PTA and MPTA for all age groups. However, dosing recommendations for neonates (birth to 4 weeks) are not being provided due to lack of sufficient safety data in this age group. Overall, our revised model yields similar starting doses, across all age groups >8 weeks, (b) (4).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant submitted data from 2 prospective clinical trials of dalteparin treatment in pediatric patients with symptomatic venous thromboembolism. For supportive evidence, the Applicant submitted published literature. Table 8 lists the efficacy safety studies analyzed in this review.

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Table 8: Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Studies to Support Efficacy and Safety						
FRAG-A001-201 A6301094	NCT00952380	Phase 2, Single Arm, prospective, open-label, PD study	0 – 8 wk: 125 IU/kg ≥ 8 wk to < 2yr: 150 IU/kg ≥ 2 yr to < 12 yr: 125 IU/kg ≥ 12 yr to < 19 yr:100 IU/kg Twice daily subcutaneously	<u>Efficacy</u> ▪ Proportion of patients achieving anti-Xa therapeutic range during dose adjustment (DA) phase (0.5-1.0 IU/ml) ▪ Proportion of patients with objectively documented new or progressive symptomatic VTE during treatment ▪ Proportion of subjects with progression, regression or resolution, or no change in the qualifying VTE during dalteparin treatment <u>Safety</u>	Dose adjustment: 7 days PD phase: up to 7 days Follow up phase: up to 90 days Three months of therapy followed by 30 days of follow up	38	Birth to < 21 years with VTE diagnosed within 30 days of enrollment	15 centers 5 Countries - Norway - Spain - United States - Russian Federation - Slovenia

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				▪ Proportion of patients with major bleeding during dalteparin treatment ▪ Proportion of patients with minor bleeding during dalteparin treatment ▪ Relationship between major bleeding and anti-Xa levels during treatment <u>PD</u> ▪ Median dose of dalteparin (IU/kg) associated with the achievement of therapeutic anti-Xa levels (0.5-1.0 IU/mL) among subjects who achieved therapeutic anti-Xa levels during the dose adjustment phase for each age cohort				

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				▪ Population PD parameters				
KidsDOTT (Fragmin Subpopulation)	NCT00687882	Prospective, Open label, Multicenter Single arm	< 1 yr: 150 IU/kg 1-12 yr: 125 IU/kg 12-18 yr: 100 IU/kg Dose adjusted by 10-20% to achieve therapeutic anti-Xa level	▪ establish dose of dalteparin to achieve therapeutic anti-Xa level (0.5-1 IU/mL) ▪ proportion of patients who experience thrombosis resolution /non-occlusion following 6 weeks of anticoagulation ▪ rates of clinically relevant bleeding	3-6 months of treatment Median 48 days Median follow up 10.5 months	18	6 months – 19 years with diagnosed VTE within 30 days (non-cancer)	4 centers United States
Studies to Support Safety and Dosing								
Published Literature								
Nohe, et al. 1999	N/A	Prospective single arm	129 IU/kg +/- 43 required to achieve anti Xa levels of 0.4-1 IU/ml Dose adjusted for an anti-Xa level of 0.4-1 IU/ml Age dependent	Dose required to achieve therapeutic anti-Xa level Safety Thrombosis resolution	3-6 months	48 total 23 with VTE	Ages 0 -21 years with VTE or at risk for thrombosis (non-cancer patients)	1 Germany

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			relationship between age and dalteparin dose					
Warad, et al. 2015	N/A	Retrospective chart review	100 IU/kg twice per day or 200 IU/kg once per day Dose adjusted for an anti-Xa level of 0.5-1 IU/ml	Median dose to achieved therapeutic anti-Xa level	< 1mo 49% 1-3 mo 41% > 3 mo 10% (total population)	166 total 50 with VTE	Ages 0-18 with (42%) and without (48%) cancer	1 United States

7.2. Review Strategy

The key materials used for the review of efficacy and safety included:

- NDA datasets (raw and derived), clinical study report, and responses to the review team's information requests.
- Relevant published literature
- Relevant information in the public domain

The clinical review of efficacy was primarily based on an analysis of the FRAG-A001-201 trial (A6301094).

The review of safety is primarily based on the FRAG-A001-201 trial and the dalteparin substudy population of the Kids-DOTT trial. For context, additional published studies, O'Brien et al. and Warad et al., of dalteparin use in pediatrics were considered.

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using SAS/JMP 13.0 (SAS Institute, Inc., Cary, NC) and MedDRA-Based Adverse Event Diagnostics (MAED) 1.8 (Enterprise Performance and Lifecycle System Design).

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.2. FRAG-A001-201

Title: A Three Month Prospective Open Label Study of Therapy with Fragmin (Daltepatin Sodium Injection) in Children with Venous Thromboembolism With or Without Malignancies

ClinicalTrials.gov identifier: NCT00952380
First patient enrolled: 20 August 2009
Study completed: 20 March 2018
Last patient visit for primary analysis: 20 March 2018
Clinical cut-off date for this submission:25 May 2018 (efficacy and safety)

8.2.1. Overview and Objectives

The FRAG-201 study is a multicenter, open label, single-arm trial to determine pediatric dosing and evaluate safety in pediatric patients with or without cancer with symptomatic VTE. The primary endpoint is determination of the median dose associated with achievement of a therapeutic Anti-Xa level (0.5-1.0 IU/mL) by age group.

Primary Objective

- Determine the pharmacodynamic profile for treatment doses of dalteparin in pediatric patients of different ages with or without cancer and venous thromboembolism
- Determine the median dose required to achieve therapeutic Anti-Xa level (0.5-1.0 IU/mL) based on patient age and weight

Secondary Objectives

- Assess major and minor bleeding
- Evaluate the proportion of new or progressive symptomatic VTE during treatment
- Evaluate the proportion of patients with progression, regression, resolution or no change in the qualifying VTE during treatment
- Overall safety
- Proportion of patient achieving an anti-Xa therapeutic range of 0.5 to 1.0 IU/mL during the Dose Adjustment Phase

8.2.2. Study Population

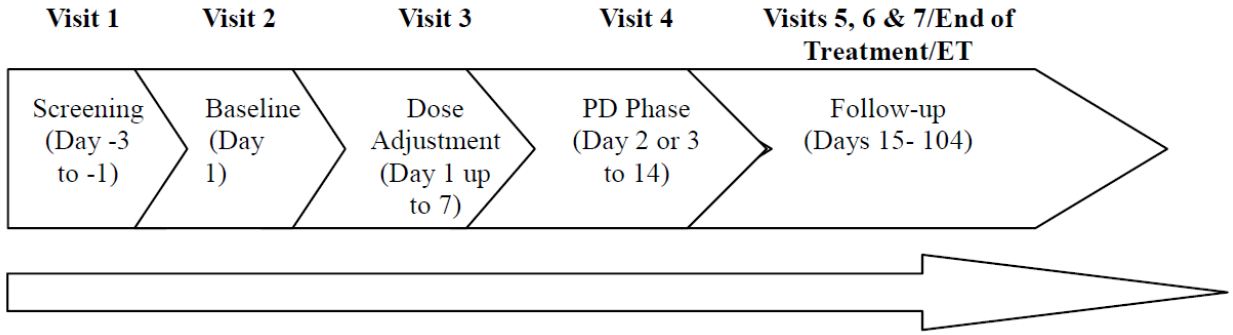
Key Eligibility Criteria

- Age ≥ 36 weeks gestation and < 19 years
- Objectively diagnosed venous thromboembolism using an accepted imaging modality
- Requires anticoagulation therapy
- For cancer patients, diagnosis of an active malignancy currently under treatment
- Excluded patients with platelets ≤ 50,000/mm3 or history of heparin-induced thrombocytopenia
- Excluded patients with acute VTE intervention, including thrombolytic therapy
- Excluded patients with major bleeding disorders, platelet dysfunction disorders, protein deficiency, disseminated intravascular coagulation, factor deficiency, hemophilia, idiopathic thrombocytopenia purpura, or von Willebrand disease.
- Excluded patients with aPTT ≥ 5 second above upper limit of normal (ULN) that does not correct upon mixing study
- Excluded patients with PT ≥ 2 seconds above ULN that corrects upon mixing study
- Excluded patients with creatinine clearance < 60 mL/min/1.73m2 or uncontrolled hypertension

8.2.3. Study Design & Treatment

The FRAG-201 study is a multicenter, open label, single-arm trial to determine pediatric dosing and evaluate safety in pediatric patients with or without cancer with symptomatic VTE.

A study schematic is show below (Figure 1).



Patients were enrolled and started on dalteparin subcutaneous every 12 hours. The starting dose was based on age and weight are:

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

The first Anti-Xa sample was drawn after the 1st, 2nd, or 3rd dose. Anti-Xa samples were to be drawn 4 hours (± 1 hour) after administration of a dalteparin dose. Doses were to be adjusted in increments of 25 IU/kg in order to achieve a target anti-Xa level of 0.5 to 1.0 IU/mL. During the Dose-Adjustment phase and Follow-up phase, Anti-Xa samples drawn outside the 4 hour (± 1 hour) window were to be repeated the following day.

Patients able to achieve a therapeutic Anti-Xa level during the Dose Adjustment phase (Up to 7 days following treatment initiation) were transitioned to the PD phase. See Section 6 for information on the PD phase.

Patients continued treatment on their maintenance therapeutic dose of dalteparin for up to 3 months, consistent with current clinical guidelines. Anti-Xa levels were monitored every 4 weeks during study treatment. For patients without cancer who discontinued dalteparin prior to 3 months, Anti-Xa levels were not required following discontinuation of dalteparin.

8.2.4. Statistical Analysis Plan

The target enrollment across all age groups was planned to be 50 subjects. Enrollment was to continue until adequate PD Phase profiles were obtained on 50 subjects. The sample size of 50 was chosen in order to estimate Anti-Xa clearance and volume of distribution of dalteparin.

Mean, standard deviation, median, minimum and maximum were to be summarized for categorical variables. Categorical variables were to be summarized by frequency and percentage. Ninety-five percent confidence intervals were specified for primary and selected

safety endpoints.

Two analysis populations were defined in the study:

- Safety Population: Subjects who receive at least one treatment of dalteparin. All safety analyses were performed on this population.
- Pharmacodynamic (PD) Population: Subjects in the Safety Population who achieve therapeutic range of anti-Xa during the Dose Adjustment Phase. This is the primary analysis population for PD and efficacy analysis.

The planned evaluation of efficacy in the PD Population was based on the following:

- Proportion of subjects with documented new or progressive symptomatic VTE. The proportions were to be summarized overall and by age groups during treatment, along with exact 95% confidence intervals.
- Proportion of subjects with progression, regression, resolution or no change in the qualifying VTE. The proportions were to be summarized overall and by age groups, along with exact 95% confidence intervals.

Reviewer Comment: Other analyses were described in the protocol; however, analysis of time-to-event endpoints or other comparative analyses are not appropriate due to the single arm design of this study.

8.2.5. Protocol Amendments

Key changes of the 9 amendments of the protocol are summarized as follows:

Amendment	Notable changes
Amendment 1 (09/2008)	• Dose adjustments were to be within 12 to 30 hours if the target therapeutic range was not achieved • Updated dose interruption and discontinuation guidelines for thrombocytopenia ≤ 50,000/mm^3
Amendment 2 (02/2009)	• Refined the age groups to the following: 0 to < 8 weeks; ≥ 8 weeks to < 1 year; ≥ 1 year to < 6 years; ≥ 6 years to < 13 years; ≥ 13 years to < 19 years (b) (4) • Excluded patients with sustained systolic or diastolic blood pressure greater than 99th percentile for age
Amendment 3 (09/2010)	• Determination of PD profile in pediatric cancer patients was updated to a primary objective • **Updated the target enrollment to 50 patients who complete the PD phase** • **Specified the PD population are patients who achieve therapeutic range of anti-Xa during Dose Adjustment Phase**
Amendment 4 (09/2011)	• Allowed the first anti-Xa blood draw to be after the first, second, or third study drug dose
Amendment 5 (04/2015)	• **This amendment implemented changes following the transition of the study to Pfizer, Inc. from Eisai, Inc. that included safety reporting processes and other administrative changes**
Amendment 6-7 (09-11/2015)	• **Instituted changes following a Type C meeting on 05 November 2015 that included 1) enrolling patients with VTE without cancer, 2) refined the age groups and dosing guidelines to 0 to < 8 weeks; ≥ 8 weeks to < 2 years; ≥ 2 years to < 8 years; ≥ 8 years to < 12 years; ≥ 12 years to < 19 years to facilitate enrollment in the lower age groups, 3) expanded study sites to include Canada and Europe, and 4) removed central adjudication review of VTE events and bleeding events**
Amendment 8 (03/2016)	• Clarified eligibility criteria for patients with and without cancer and treatment guidelines
Amendment 9 (10/2016)	• Updated anti-Xa monitoring and eligibility criteria for patients with major bleeding or bleeding disorders and renal function parameters

8.2.6. Study Results

Compliance with Good Clinical Practices

The protocol, protocol amendments, and patient or legal representative consent forms for the FRAG-A001-201 study were reviewed and approved by the Institutional Review Boards and Independent Ethics Committees of the participating study centers.

The FRAG-A001-201 study was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the US Code of Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representative voluntarily consented prior to trial enrollment. Assent was also obtained from age-appropriate patients able to provide signature or able to provide verbal assent.

Financial Disclosure

A summary of financial disclosures for Study FRAG-A001-201 is provided in the appendix (Section 13.2). The applicant submitted financial disclosure information from 100 investigators and statement of due diligence from one investigator from site (b) (4). The investigator was one of 28 sub investigators for that site which was the (b) (6) site, enrolling (b) (4) patients. Once investigator had a financial disclosure for multiple speaking honorariums totaling $27,250.00. This investigator is listed as sub investigator for site (b) (4), which enrolled (b) (6) (b) (6) Based on the primary endpoint of the study, median dose of dalteparin to achieve a therapeutic anti-Xa level, it does not appear that enrollment of patients by these investigators biased the outcome of the study.

Data Quality and Integrity

The data quality is acceptable. In general, the reviewers were able to perform independent review and confirm the Applicant's analysis results using the submitted datasets.

8.2.7. Patient Disposition

A total of 40 pediatric patients were screened, of which 38 patients were enrolled and treated. During the study, 26 patients (68%) completed treatment and 12 patients (32%) discontinued from the study (Table 9). Four patients (11%) discontinued due to adverse events, 4 patients (11%) discontinued due to investigator discretion, 3 patients (8%) discontinued due to patient withdrawal, and 1 patient (3%) discontinued due to noncompliance.

Table 9: FRAG-A001-201 Patient Disposition

Patient Disposition	N = 38 n (%)
Treated	38 (100)
Reason for end of treatment	
Treatment completed	26 (68)
Adverse event	4 (11)
Investigator discretion	4 (11)
Patient withdrawal	3 (8)

Patient Disposition	N = 38 n (%)
Noncompliance	1 (3)
Source: FDA analysis of ADDS dataset	

Protocol Violations/Deviations

Of the 38 patients enrolled, there were 26 patients (68%) with a protocol violation. The majority of protocol violations were due to missed laboratory measures, not including anti-Xa levels, pharmacodynamic sample issues, and anti-Xa sample timing. Upon review of all protocol violations, the violations do not appear to be a significant cause of bias influencing the study results.

8.2.8. Demographics and Baseline Characteristics

In the 38 patients treated with dalteparin, the median age was 12 years (range 3 weeks to 18 years), 63% were male, 76% were White, and 71% were from US sites. Twenty-six patients (68%) had an active malignancy, 28 patients (74%) had a central line and the qualifying VTE included DVT (82%), CSVT (10%), PE (5%) and 1 patient with DVT and PE (Table 10).

Table 10: FRAG-A001-201 Demographics and Disease Characteristics

Characteristic	N = 38
Age, median	12 years
Range	3 weeks, 18 years
Age category, n (%)	
0 to < 8 weeks	1 (3)
≥ 8 weeks to < 2 years	2 (5)
≥ 2 years to < 8 years	8 (21)
≥ 8 years to < 12 years	7 (18)
≥ 12 years to < 19 years	20 (53)
Male, n (%)	24 (63)
Race, n (%)	
White	29 (76)
Black	7 (18)
Asian	1 (3)
Other	1 (3)
Region, n (%)	
US	27 (71)
Russia	8 (21)
Europe	3 (8)
Weight (kg)	
Median (range)	48.0 (3.9, 96.4)
Cancer, n (%)	26 (68)
Hematologic cancer	21 (55)
Solid tumor	5 (13)
Central line, n (%)	28 (74)
Qualifying VTE	
DVT	31 (82)
CSVT	4 (10)
PE	2 (5)
DVT & PE	1 (3)

Source: FDA analysis of ADSL dataset

Table 11 summarizes the disease and treatment characteristics in individual patients treated on the FRAG-A001-201 trial.

Table 11: FRAG-A001-201 Disease and Treatment Characteristics

Age	Cancer	CVC	Site of VTE	Dalteparin starting dose (IU/kg)	Therapeutic dalteparin dose[1] (IU/kg)	Duration (days)
3 wks	No	Yes	UE-R	62.5[2]	150	100
10 wks	No	Yes	UE-R	75[2]	200	98
1 yr	Yes	Yes	UE-R	125	210	7
2 yrs	No	No	CSVT	500[3]	125	85
3 yrs	No	No	CSVT	125	150	100
4 yrs	Yes	Yes	LE-R	125	175	5
4 yrs	No	No	LE-R	62.5[2]	175	103
6 yrs	Yes	Yes	LE-R	125	150	96
6 yrs	No	Yes	CSVT	125	125	90
6 yrs	Yes	Yes	UE-R	125	150	7
7 yrs	Yes	Yes	UE-L	125	125	90
8 yrs	Yes	Yes	PE	125	150	85
9 yrs	Yes	Yes	PE	125	175	90
9 yrs	Yes	Yes	UE	125	125	48
10 yrs	Yes	Yes	UE-L	125	150	63
10 yrs	Yes	Yes	LE-L	125	125	108
10 yrs	Yes	Yes	LE-R	125	125	95
11 yrs	Yes	Yes	UE-R	125	150	11
12 yrs	Yes	Yes	UE-R	125	125	86
12 yrs	Yes	Yes	LE-R/L	125	175	32
13 yrs	Yes	Yes	UE-L	100	150	90
13 yrs	Yes	Yes	IC	100	*	2
13 yrs	Yes	Yes	LE-R	100	150	88
13 yrs	Yes	Yes	UE-R	100	100	36
15 yrs	Yes	Yes	SVC	100	100	47
15 yrs	No	No	UE-R	100	125	95
15 yrs	Yes	Yes	UE-L	100	125	95
15 yrs	No	Yes	IVC	100	125	91
15 yrs	Yes	Yes	CSVT	100	125	86
15 yrs	No	Yes	PE	100	125	101
15 yrs	Yes	Yes	UE-L	100	125	19
16 yrs	Yes	No	UE-L	100	125	89
16 yrs	No	No	UE-L	100	125	94
16 yrs	No	No	UE-R	100	150	92
17 yrs	No	No	PE/UE-R	100	100	99

Age	Cancer	CVC	Site of VTE	Dalteparin starting dose (IU/kg)	Therapeutic dalteparin dose[1] (IU/kg)	Duration (days)
18 yrs	Yes	Yes	UE	100	*	2
18 yrs	Yes	Yes	UE-L	100	100	115
18 yrs	Yes	Yes	UE-L	100	175	99

Abbreviations: CSVT: Cerebral sinus venous thrombosis, IC: Intracardiac, IVC: Inferior vena cava, PE: Pulmonary embolus, L: Left, LE: Lower extremity, R: Right, SVC: Superior vena cava, UE: Upper extremity
[1] Based on local laboratory assessment of anti-Xa
[2] Patient started at half the recommended dose in error
[3] Patient given 4 times the recommended dose in error
Source: FDA analysis of ADSL and ADMH dataset

Exposure

In 38 patients, the median exposure to dalteparin was 90 days (range 2 to 115 days). Table 12 displays the exposure per age group as defined in the FRAG-A001-201 study.

Table 12: FRAG-A001-201 Exposure

	0 to < 8 weeks n = 1	≥ 8 weeks to < 2 years n = 2	≥ 2 to < 8 years n = 8	≥ 8 to < 12 years n = 7	≥ 12 to < 19 years n = 20	Overall N = 38
Exposure (days)						
Median	100	53	90	85	90	90
Range	100, 100	7, 98	7, 103	12, 107	2, 115	2, 115

Source: FDA analysis of ADSL dataset

Patient Characteristics in the Evaluable Population

The evaluable population includes 34 pediatric patients able to achieve a therapeutic anti-Xa level (0.5 to 1.0 IU/mL) in the 7-day dose adjustment period. Of the 34 patients in the evaluable population, there were 2 patients in the age category ≥ 8 weeks to 2 years category, 8 patients in the age category ≥ 2 years to < 8 years, 7 patients in the age category ≥ 8 years to < 12 years, and 17 patients in the age category ≥ 12 years to < 19 years. In this population, the median age was 12.2 years (range 0.2 to 18.7 years), 21 (62%) were male, and 25 (73%) were White. Table 13 summarizes the demographic information in the evaluable population by age category.

Table 13: FRAG-A001-201 Demographics in the Evaluable Population

Characteristic	≥ 8 weeks to < 2 years n = 2	≥ 2 years to < 8 years n = 8	≥ 8 years to < 12 years n = 7	≥ 12 years to < 19 years n = 17	All ages N = 34
Median Age (range) in years	1.1 (0.2 – 1 .9)	5.4 (2.3 – 7.4)	10.0 (8.4 – 11.9)	15.6 (12.5 – 18.7)	12.2 (0.2 – 18.7)
Median Weight (range) in Kg	8.8 (3.9 – 13.7)	18.9 (12.4 – 34.7)	39.3 (25.4 – 66)	63 (19.2 – 95.1)	45 (3.9 – 95.1)
Sex Male Female	 1 1	 6 2	 2 5	 12 5	 21 (62%) 13 (38%)
Race White Black Other	 2 0 0	 7 0 1	 4 3 0	 12 4 1	 25 (73%) 7 (21%) 2 (6%)
Ethnicity Not Hispanic Hispanic	 2 0	 6 2	 5 2	 13 4	 26 (76%) 8 (24%)
Country US Ex-US	 1 1	 4 4	 7 0	 12 5	 24 (71%) 10 (29%)

8.2.9. Efficacy Results – Primary Endpoint

The median dose of Fragmin needed to achieve a therapeutic anti-Xa level (0.5 to 1.0 IU/mL) in the 7-day dose adjustment period was determined in the evaluable population (N=34). Table 14 summarizes the dose data in the evaluable population by age category.

Table 14: FRAG-A001-201 Dose of Fragmin to Achieve Therapeutic Anti-Xa Level (Evaluable Population)

Characteristic	≥ 8 weeks to < 2 years n = 2	≥ 2 years to < 8 years n = 8	≥ 8 years to < 12 years n = 7	≥ 12 years to < 19 years n = 17	All ages N = 34
Median Dose (range) in IU/kg	208 (202 – 214)	128 (124 – 180)	125 (125 – 153)	117 (99 – 159)	125 (99 – 214)

Reviewer Comment: Additionally, the time for patients to reach a therapeutic Anti-Xa level was calculated as the time from first dose + 1. The mean time to therapeutic Anti-Xa level was 2.6 days, with a range of 1 to 7 days.

8.2.10. Efficacy Results – Secondary Endpoints

At study completion, 21 patients (62%) had achieved resolution of the qualifying VTE, 7 patients (21%) showed regression, 2 patients (6%) showed no change, and no patients showed progression. One patient (3%) experienced two new VTEs during the study while on treatment (patient (b) (6). Four patients (12%) did not have post-treatment VTE assessments available. Table 15 summarizes the clinical response data by age category.

Table 15: FRAG-A001-201 Clinical Response in the Qualifying VTE at End of Study (Evaluable Population)

Clinical Response	≥ 8 weeks to < 2 years n = 2	≥ 2 years to < 8 years n = 8	≥ 8 years to < 12 years n = 7	≥ 12 years to < 19 years n = 17	All ages N = 34
Progression	0	0	0	0	0
No Change	0	0	1	1	2 (6%)
Regression	0	1	1	5	7 (21%)
Resolution	2	5	4	10	21 (62%)

Due to the small sample sizes, estimates of the proportion of patients achieving each clinical response type are not provided by age category. The 95% confidence interval for the overall

proportion of patients achieving regression is (9%, 38%), and the 95% confidence interval for the overall proportion of patients achieving resolution is (44%, 78%).

Reviewer Comment: Patient (b) (6) *an 11 year old female experienced two new DVTs (right wrist on study day 6 and left upper-extremity on day 11) while on study treatment. The patients risk factors for VTE included malignancy, central-line, and active infection.*

8.3. Kids-DOTT Study

O'Brien et al. conducted a subanalysis of the Duration of Therapy for Thrombosis in Children trial (Kids-DOTT), which is a prospective, multicenter, randomized trial evaluating the optimal duration of anticoagulation for pediatric patients with venous thromboembolism (O'brien et al, 2014). The primary objective of the dalteparin subanalysis was to evaluate dosing in pediatric patients with VTE treated with dalteparin. Secondary objectives included efficacy and safety outcomes. Eligible patients included age ≤ 21 years with objectively diagnosed, provoked venous thromboembolism. Patients were excluded for known pulmonary embolism, use of thrombolytic therapy, prior episode of VTE, history of cancer, systemic lupus erythematosus, pregnancy, or sever anticoagulant deficiency as defined by any of the following: protein C < 20 IU/dL, antithrombin < 30 IU/dL, or protein S < 20 IU/dL.

Patients received dalteparin administered subcutaneously twice daily. The initial weight-based dosing is shown in the table below.

Age	Starting Dose
< 12 months	150 IU/kg
1 – 12 years	125 IU/kg
13 – 21 years	100 IU/kg

Routine monitoring with Anti-Xa, drawn 4-6 hours following a dalteparin dose, was performed locally per standard of care. Dalteparin doses were adjusted by 10-20% to achieve a goal Anti-Xa level of 0.5-1.0 IU/mL.

The efficacy outcome was symptomatic recurrent VTE and safety outcomes of interest included anaphylaxis related to anticoagulant administration and major bleeding, defined as intracranial or retroperitoneal bleeding, bleeding requiring major surgical intervention under anesthesia, or clinical overt bleeding from any site associated with a decline in hemoglobin level of ≥ 2 g/dL in a 24 hours period.

Results
A total of 18 patients were included in the dalteparin subanalysis. The median age was 8 years (range 6 months to 19 years), 50% were ≥ 12 years, 67% male, 33% with lower-extremity VTE, 22% with upper-extremity VTE, 22% with cerebral sinus venous thrombosis, and 17% with

jugular VTE. The median exposure to dalteparin was 48 days (range 2 to 169 days). The median follow-up was 10.5 months (range 2 to 35 months)

All 18 patients successfully achieved a therapeutic anti-Xa level between 0.5-1.0 IU/mL. The median therapeutic dose by age group is shown in the table below.

	< 12 months n = 3	1 to 12 years n = 7	13 to 21 years n = 8
Dose (IU/kg)			
Median	180	125	100
Range	146, 181	101, 175	91, 163

For efficacy, patients were followed for 3 months plus 10 days. During that time, none of the 18 patients experienced a symptomatic recurrent VTE. Thirteen patients (72%) had complete thrombus resolution and 5 patients (28%) had an improved or stable thrombus.

For safety, please refer to Section 8.6 since safety data from the dalteparin subanalysis of the Kids-DOTT study submitted with the application is included in the dalteparin safety population.

8.4. Integrated Assessment of Effectiveness

In pediatric patients with or without cancer with symptomatic venous thromboembolism, the FRAG-A001-201 study, a multicenter, open-label, single-arm trial demonstrated that age and weight-based dosing of dalteparin could be established for pediatric patients and treatment with dalteparin resulted in clinically meaningful outcomes.

The trial enrolled 38 pediatric patients, 26 with an active malignancy, with symptomatic venous thromboembolism requiring anticoagulant therapy. The median age was 12 years (range 3 weeks to 18 years) with 1 patient < 8 weeks, 2 patients ≥ 8 weeks to 2 years, 8 patients ≥ 2 years to < 8 years, 7 patients ≥ 8 years to < 12 years, and 20 patients ≥ 12 years to < 19 years. The median exposure to dalteparin was 90 days (range 2 to 115 days). A total of 34 patients (89%) achieved a therapeutic Anti-Xa level (0.5-1.0 IU/kg) during the 7-day dose adjustment period.

See Section 6.1 and 6.3 for establishment of pediatric dosing for dalteparin.

The primary efficacy outcome was new or progressive symptomatic VTE during treatment. Upon study completion for the 34 patients able to achieve a therapeutic Anti-Xa, 1 patient (3%) experienced development of a new VTE during treatment. No patients experienced progression of the qualifying VTE while on treatment. Twenty-one patients (62%) achieved resolution, 7 patients (21%) showed regression, and 2 patients (6%) showed stable thrombus.

Similar efficacy outcomes were demonstrated in the dalteparin subanalysis of the Kids-DOTT study, a multicenter, open-label, single-arm trial in 18 pediatric patients with symptomatic venous thromboembolism. The Kids-DOTT study excluded patients with pulmonary embolism, use of thrombolytic therapy, prior episode of VTE, history of cancer, systemic lupus erythematosus, pregnancy, or sever anticoagulant deficiency .

The median age was 8 years (range 6 months to 19 years) with 3 patients < 12 months, 7 patients 1 to 12 years, and 8 patients 13 to 19 years. The median exposure to dalteparin was 48 days (range 2 to 169 days) and all 18 patients achieved a therapeutic Anti-Xa level.

Upon study completion, none of the 18 patients experienced a symptomatic recurrent VTE. Thirteen patients (72%) had complete thrombus resolution and 5 patients (28%) had an improved or stable thrombus.

In pediatric patients with or without cancer with symptomatic venous thromboembolism, treatment with dalteparin effectively reduced progression of a VTE and development of new VTE, which can be clinically meaningful.

The Applicant proposed an indication for the extended treatment of symptomatic venous thromboembolism to reduce the recurrence in pediatric patients (b) (4). The combination of the FRAG-A001-201 study and the dalteparin subanalysis of the Kids-DOTT study enrolled pediatric patients with and without cancer. Given the meaningful clinical activity of dalteparin in pediatric patients with and without cancer and the unmet medical need in pediatric patients with symptomatic venous thromboembolism requiring anticoagulant treatment, the clinical review team recommends a broad indication for all pediatric patients with symptomatic VTE.

8.5. Review of Safety

8.5.1. Safety Review Approach

Review emphasis was placed on safety data for patients less than 18 years of age with symptomatic VTE from the FRAG-A001-201 and Kids-DOTT study who received a starting age-based dose of dalteparin with the dose adjusted to target an anti-Xa level of 0.5 IU/ml – 1 IU/ml. Patients were followed for one month after discontinuation of therapy. Based on the mechanism of action and half-life of dalteparin, safety review focused on AEs experienced within 30 days of receipt of dalteparin. Particular emphasis was focused on the known AEs associated with dalteparin of bleeding, injection site reactions, and thrombocytopenia. Since the safety population included patients with and without malignancy, analysis were performed for the total population as well as separately for the cancer and non-cancer population.

Supportive safety information from two publications (Warad et al., and Nohe et al.) describing the dosing and safety of dalteparin in pediatric patients was included in the application and in

the Applicant's Integrated Summary of Safety (ISS). Since patient-level data was not provided for these patients, this information only considered supportive of safety.

Safety analysis was conducted on the dataset provide by the Applicant which included AEs for patients on study FRAG-A001-201 and the Kids-DOTT study. For the Kids-DOTTs study only the 11/18 patients were reported to have any AE reported.

The key materials used for this review of safety included:

- CSR from FRAG-A001-201
- SCS and ISS
- AE Data sets from the FRAG-A001-201 and Kids-DOTT study
- Review of Published literature
- USPI for Fragmin
- Narratives of deaths, SAEs, AEs leading to treatment discontinuation

The primary focus of the safety review were the patients in the FRAG-A001-201 study who were under the age of 18. Patients 18 years of age and older represent a young adult population and the focus of this review was to evaluate the safety of dalteparin in a pediatric population defined as less than 18 years of age. The safety profile for dalteparin in the adult population has already been established.

8.5.2. Review of the Safety Database

Overall Exposure

Patients were treated with dalteparin subcutaneously twice daily for up to three months. Starting dose was determined by age and adjusted based on anti-Xa level four hours after a dalteparin dose. For the FRAG-A001-201 study the starting dose for infants 0 to < 8 weeks of age was 125 IU/kg, patients ≥ 8 weeks but less than 2 years received 150 IU/kg/dose, for ≥ 2 years to < 12 years the starting was 125 IU/kg/dose and for ≥ 12 years to < 19 years the dose was 100 IU/kg/dose. For the Kids-DOTT study the starting dose was 150 IU/kg/dose for infants < 12 months, 125 IU/kg/dose for children 1-12 years, and 100 IU/kg/dose for children > 12 years old.

Table 16: Exposure by Age Group for Safety Population: FRAG-201 and Kids-DOTT study

Total Safety Population N = 50	< 30 days (neonate) N = 1	≥ 30 days to < 1yr N = 4	≥ 1 yr to < 6 yr N = 8	≥ 6 yr to < 12 yr N = 14	≥ 12 yr to < 18 yr N = 23
Mean (days)	100	50	70	75	67
Median (days)	100	39	78	88	88
Range (days)	(100, 100)	(24, 98)	(7,103)	(7,170)	(2,101)

For the safety population from the FRAG-A001-201 study, the median duration of treatment was 90 days (range 2-107 days). The duration of exposure for the various age groups is displayed in the table below.

Table 17: Exposure by Age Groups: FRAG-A001-201 Study < 18 years old

FRAG-201 Safety Population N = 35	< 28 days (neonate) N = 1	≥ 30 days to < 1yr N = 1	≥ 1 yr to < 6 yr N = 5	≥ 6 yr to < 12 yr N = 11	≥ 12y to ≤ 18 yr N = 17
Mean	100	98	74	71	73
Median	100	98	85	90	89
Range	(100,100)	(98,98)	(7,103)	(7,107)	(2,101)

Source: Reviewer generated from ADEX dataset

For the Kids-DOTT study, fifteen patients were under the age of 18 years and were included in the safety analysis. The median duration of treatment was 49 days (range 3-170) days. Duration of exposure by age group is displayed in the table below.

Table 18: Exposure by Age Groups of Safety Population: Kids-DOTT Study < 18 years old

Kids-DOTT Safety Population N = 15	< 30 days (neonate) N = 0	≥ 30 days to < 1yr N = 3	≥ 1 yr to < 6 yr N = 3	≥ 6 yr to < 12 yr N = 3	≥ 12 yr to < 18 yr N = 6
Mean (days)	0	34	63	89.3	51.2
Median (days)	0	26	61	49	46.5
Range (days)	0	(24, 52)	(46,82)	(49,170)	(3 ,101)

Source: Applicant ISS

Median exposure was similar in the cancer and non-cancer populations, displayed in the table below.

Table 19: Exposure in Cancer and Non-Cancer Population

	Cancer Diagnosis N = 23	No Cancer Diagnosis N = 27

	Cancer Diagnosis N = 23	No Cancer Diagnosis N = 27
Mean (days)	63	75
Median (days)	85	90
Range (days)	(2, 107)	(3, 170)

Reviewer comment: The FRAGMIN exposure in both the FRAG-A001-201 study and the Kids-DOTT study provide adequate exposure across the age groups older than one month to adequate assess safety. In the neonatal population, only one patient was treated. Although the treatment of this patient for 100 days supports safety, one patient does not adequately inform safety for the neonatal population. There is adequate exposure to dalteparin in both the cancer and non-cancer population to inform safety in both populations.

Relevant Characteristics of the Safety Population:

Safety data were available for the 38 patients treated on the FRAG-A001-201 study and for 18 patients treated on the Kids-DOTT sub-study. The breakdown of the study populations by age groups is displayed in the table below. The combined study population included 6 patients over the age of 18 years. The patients over the age of 18 years represent an adult population and were not included in the safety analysis for this pediatric indication. Fifty patients in the combined study populations were under the age of 18 and therefore are considered pediatric patients for safety review.

Table 20: Age Group Breakdown of Safety Population

Age Group	FRAG-A001-201 N = 38	Kids-DOTT N = 18	Total N = 56
Neonate (<1 month)	1	0	1
One month to < 1year	1	3	4
1y to < 6y	5	3	8
6y to < 12y	11	3	14
12y to < 18y	17	6	23
Less than 18 years	**35**	**15**	**50**
≥ 18 years	3	3	6

Source: Reviewer generated table from Applicant datasets

Reviewer comment: The safety population included 50 total patients who were under the age of 18 and are considered in the analysis of the safety of Dalteparin in the pediatric population. The

six patients who are over the age of 18 represent an adult population and therefore safety data from these patients only considered supportive in the pediatric safety analysis.

The safety population contained patients with and without a diagnosis of cancer at the time of the symptomatic VTE diagnosis. The safety population included 23/50 (46%) with a cancer diagnosis and 27/50 (54%) without a cancer diagnosis. The breakdown of the patients by age and cancer diagnosis is detailed in the table below.

Table 21: Safety Population Characteristics

Age Group	Cancer Diagnosis	No Cancer Diagnosis	Total N = 56
Neonate (<1 month)	0	1	1
1 month to < 1year	0	4	4
1y to < 6y	2	6	8
6y to < 12y	10	4	14
12y to < 18y	11	12	23
Total	**23**	**27**	**50**

Reviewer comment: There was adequate representation of all the pediatric age groups greater than one month of age. The age groups represented are adequate to inform safety in both the cancer and non-cancer populations. Patients with cancer were fewer in the youngest age groups (< 1 year and 1 year to < 6 years). It is reasonable to extrapolate safety from the non-cancer to the cancer population since the cancer population has more co-morbidities, concomitant medications and underlying illness. Extrapolation of safety from the older cancer pediatric population to the younger cancer population is reasonable since AEs would be expected to be similar, cancer treatments and AEs due to cancer treatment are similar.

Adequacy of the safety database:

The safety data base included a total of 50 pediatric patients (age <18 years). Five patients were less than one year old, 8 patients were between one and less than six years old and twelve were between six and 12 years. These numbers provided an adequate representation of the pediatric age groups with the exception of the neonatal population, for which there was only one patient, to draw conclusions regarding the safety of dalteparin in pediatric patients. The adequate representation of both cancer and non-cancer patients allows for adequate assessment of safety in both populations over one month of age.

8.5.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the safety data submitted was adequate to allow substantial primary review. The applicant provided analysis-ready datasets for subjects on the FRAG-A001-201 study and for patients in the Kids-DOTT study.

One IR was sent to the Applicant regarding the AEs of hemarthrosis and joint bleed reported in patient (b) (6) After confirmation with the investigator, theApplicant confirmed that the AE was actually superficial bruising on the knee and not hemarthrosis and was miscoded in the dataset. This clarification was considered in the review of safety.

Narratives were provided for patients on FRAG-A001-201 who experienced:

- Deaths
- serious adverse events (SAEs)
- nonserious AEs leading to discontinuation from treatment
- AEs leading to dose reduction or temporary discontinuation of study treatment

CSR forms and detailed narratives were not available for review for the Kids-DOTT study and details regarding specific adverse events were not provided. The review of safety was supplemented by annual reports from the investigator IND which included the Kids-DOTT study.

Categorization of Adverse Events

Adverse events were reported down to the investigator's verbatim term, graded by the investigator using the NCI-CTCAE for adverse events Version 4.03, and coded by the Applicant using MedDRA version 20.1. The Applicant provided an summary and explanation of discrepancies from CSRs and AE reports noted with transfer of study sponsorship.

Treatment emergent adverse excluded events that started prior the start of study or that started 28 days after the last dose of study drug. Treatment emergent adverse events were summarized by maximum grade per patient.

The Agency compared verbatim adverse event tern with the coded MedDRA preferred terms for all adverse events reported on study FRAG-A001-201. The FDA grouped some related preferred terms for analysis, a listing of these grouped terms can be found in Appendix 19.6.

Routine Clinical Tests

A physical exam was performed at screening and baseline, at the end of the dose adjustment phase, the PD phase and during the follow up phase at visits 5, 6 and 7. Vital signs were collected at each visit. A complete blood count (CBC), PT, aPTT, INR and serum chemistry studies were obtained at baseline, at the end of the PD phase, during the following up phase visits at weeks 5, 6 and 7 and at the end of treatment. Clinical laboratory analysis was also obtained as needed based on clinical need.

8.5.4. Safety Results

Deaths

There were two deaths reported in patients in the safety population, one occurred in a patient in the FRAG-A001-201 study and other in the Kids-DOTT study. Both events occurred after treatment discontinuation and neither death was considered treatment related.

Subject (b) (6) was a 15 year old African American female enrolled on the FRAG-A001-201 study. She had a history of sickle cell disease and a port-a-cath with a diagnosis of pulmonary embolism at the time of study enrollment. She began dalteparin at a dose of 5700 IU per dose on study day one which was adjusted to 7125 IU on study day 2. She continued on this dose until study day 101. The patient received treatment on study days 15 ,37, and 72, and 96 for pain crisis and fever for which she received IV narcotics and antibiotics. The patient completed study treatment on SD 101. On study day 253, 152 days from the last dose of dalteparin, the patient experienced multiorgan failure (MOF) in the setting of pain crisis and sepsis attributed to sickle cell disease. The patient died of MOF on (b) (6) (study day 254). Death was attributed to complications related to sickle cell disease and not considered related to study therapy.

Subject (b) (6) was a 5-month old at the time of enrollment on the Kids-DOTT study with an underlying chromosomal disorder (1p36 deletion syndrome) who received dalteparin for 26 days on study. The patient had documented complete thrombus resolution of cerebral sagittal venous thrombosis after dalteparin therapy . The patient died in follow up due to underlying seizure disorder on SD 636, the death was assessed as not related to study therapy.

Reviewer comment: Both deaths occurring in patients in the FRAG-A001-201 and Kids-DOTT study occurred after the patients had completed therapy and were likely due to the patients significant underlying illness. This reviewer agrees with the Applicant's assessment that the deaths were unlikely to be related to dalteparin. There were no fatal bleeding events associated with Dalteparin therapy in the safety population.

Serious Adverse Events

Serious Adverse Events (SAE) occurred in 48% of patients in the safety pool. The TE SAE rate was higher in the FRAG-A001-201 study 20/35 (54%), vs 4/15 (27%) in the Kids-DOTT study population. Of the reported SAEs, 4/50 (8%) were considered by the investigator as possibly related the dalteparin. These events included intestinal bleed, hypertension, seizure like phenomenon and thrombophlebitis. A breakdown of the treatment emergent SAEs occurring in more than one patient is detailed in the table below.

Table 22: Treatment Emergent SAEs occurring in more than one patient in the safety population

AE by SOC and PT	FRAG-A001-201 < 18y N = 35 n (%)	KidsDOTT < 18y N = 15 n (%)	Safety Population N = 50 n (%)
Any SAE	20 (57)	4 (27)	24 (48)
Infections and Infestations	7 (20)	1 (7)	8 (16)
Sepsis	2 (6)	0 (0)	2 (4)
Pneumonia	3 (9)	0 (0)	2 (4)
Blood and Lymphatic Disorders	8 (23)	0 (0)	8 (16)
Febrile Neutropenia	4 (11)	0 (0)	4 (8)
Thrombocytopenia	2 (6)	0 (0)	2 (4)
General Disorders and administration site conditions			
Fever	5 (14)	1 (7)	6 (12)
Mucositis	2 (6)	0 (0)	2 (4)
Metabolism and Nutrition			
Dehydration	5 (14)	1 (7)	6 (12)
Gastrointestinal Disorders			
Nausea	1 (3)	1 (7)	2 (4)
Respiratory, Thoracic and mediastinal disorders			
Hypoxia	2 (6)	0 (0)	2 (4)
Nervous System Disorders			
Seizure	1 (3)	1 (7)	2 (4)
Immune System Disorder			
Anaphylactic reaction to drug*	2 (6)	0 (0)	2 (4)

Source : Reviewer generated from Applicant datasets
* anaphylaxis to asparaginase (N=1) and vitamin K (N=1)

Reviewer comment: The majority of SAEs reported in patients in the safety population occurred in patients with cancer and could be attributed to their underlying disease or complications of underlying therapy. There were no new SAEs identified with dalteparin use in the pediatric population compared to SAEs reported in the adult population. Upon review of the 4 SAEs reported possibly related to dalteparin use, it is this reviewer's opinion that only 1 (intestinal bleed) was likely related to dalteparin. Upon review of the narratives, the other three events were likely related to underlying disease or therapy.

8.5.5. Dropouts and/or Discontinuations Due to Adverse Effects

The table below provides a summary of discontinuation, dose reductions, and dose interruptions due to treatment emergent adverse events in the safety population.

Discontinuations due to AEs were reported in 6/50 (12%) of patients in the safety population and all occurred in patients with cancer. There were no reported discontinuation of dalteparin due to adverse events in the non cancer population. Reasons for discontinuation were bleeding- related for 4 patients: intestinal hematoma (1), hematuria and thrombocytopenia (1), thrombocytopenia (1) and skin bruising (1). Non-bleeding related AEs leading to discontinuation were reported in 2 patients due to new thrombosis, skin nodule and generalized itching (1), and hypertension (1).

Table 23: Summary of Discontinuation, Dose Reductions and Dose Interruptions due to Treatment Emergent Adverse Events

	Cancer Population N = 23 n (%)	Non-Cancer Population N = 27 n (%)	Total Safety Population N = 50 n (%)
Discontinuation due to AE	6 (26)	0 (0)	6 (12)
Intestinal hematoma	1 (4)		1 (2)
Thrombocytopenia	2 (9)		2 (4)
Skin bruising	1 (4)		1 (2)
New thrombosis	1 (4)		1 (2)
Hypertension	1 (4)		1 (2)
Dose reduction due to AE	3 (13)	0 (0)	3 (6)
Dos interruption due to AE	2 (9)	3 (11)	5 (10)
AEs requiring interruption or dose reduction	5 (22)	3 (11)	8 (16)
Acute kidney injury	1 (4)		1 (2)
Seizure like activity	1 (4)		1 (2)
Injection site bleeding	1 (4)		1 (2)
Mucosal bleeding	1 (4)		1 (2)
Worsening of thrombocytopenia	1 (4)		1 (2)
Paronychia		1 (4)	1 (2)
Suicidal ideation		1 (4)	1 (2)
Neck pain		1 (4)	1 (2)

Source: FDA analysis of ADAE dataset and review of narratives

Treatment interruption occurred due to an AE in 5 (10%) of patients. In one case this was due to a bleeding related AE (bleeding at the injection site). In the remaining 4 cases, treatment

was held while evaluation of the AE (seizure-like activity, toe infection, suicidal ideation, and right neck pain) were evaluated. In all cases the AE was reported to have resolved and were not thought to be related to dalteparin therapy.

Reviewer comment: The majority of patients remained on treated for the duration of therapy. The main reason for treatment discontinuations were due to bleeding-related complications occurring in the cancer population. The low rates of treatment discontinuation support the tolerability of dalteparin in the both the cancer and non-cancer pediatric population. Low rates of discontinuation due to AEs support that dose reduction and interruption strategies are reasonable for managing possible AEs related to dalteparin.

8.5.6. Significant Adverse Events

Bleeding

The Applicant provided an analysis of major and minor bleeding events. A further analysis was performed by the Agency for the cancer and non-cancer populations.

For the FRAG-A001-201 study, major bleeding was defined as:

- Clinically overt bleeding associated with a decrease in hemoglobin of at least 2g/dL in 24 hours
- Overt bleeding deemed by the attending physician to be unrelated to the subject's underlying condition and accompanied by blood product administration
- Overt bleeding which was reported as retroperitoneal, intracranial, intraspinal, intraocular, or intra-articular
- Overt bleeding deemed by the attending physician to necessitate permanent discontinuation of study medication

Minor bleeding was defined as any bleeding that did not meet criteria for major bleeding.

For the Kids-DOTT study, major bleeding was defined as:

- Intracranial or retroperitoneal bleeding
- Bleeding requiring major surgical intervention under anesthesia
- Clinically overt bleeding from any site associated with a decline in hemoglobin level of ≥ g/dL in a 24 hour period

A listing of AE terms that were grouped for the analysis of bleeding are included in appendix 19.6.

A summary of minor and major bleeding events is detailed in the table below.

Table 24: Summary of Bleeding Events with Dalteparin Use

	Cancer Population N = 23 n (%)	Non-Cancer Population N = 27 n (%)	Total Safety Population N = 50 n (%)
All Bleeding AEs	17 (74)	4 (15)	21 (42)
Minor Bleeding Events*	16 (70)	4 (15)	20 (40)
Bruising			
Injection Site Bruising	13 (57)	3 (11)	16 (32)
Other Bruising	6 (26)	1 (4)	7 (14)
Bleeding	8 (35)	2 (7)	12 (24)
Epistaxis	4 (17)	2 (7)	6 (12)
Hematemesis	2 (9)	0 (0)	2 (4)
Lip Bleeding	1 (4)	1 (4)	2 (4)
Injection Site Bleeding	1 (4)	0 (0)	1 (2)
Hematuria	1 (4)	0 (0)	1 (2)
Hematochezia	1 (4)	0 (0)	1 (2)
Mucosal Bleeding	1 (4)	0 (0)	1 (2)
Major Bleeding			
Intestinal Hematoma	1 (4)	0 (0)	1 (2)

Source: FDA generated from ADAE data set
*percentage of patients who were reported to have the event, some patients had more than one event

The majority of the bleeding events were ≤ grade 2. There were two grade three bleeding events, both occurring in the cancer population. One event of grade 3 hematuria occurring the setting of thrombocytopenia led to treatment discontinuation was not considered related to study therapy but to the patients underlying malignancy and concomitant therapy. One major bleeding event occurred. The event was a duodenal hematoma occurring in a 23 month old receiving treatment for acute myelogenous leukemia, on SD 7. The event resulted in study drug discontinuation. There were no fatal bleeding events.

Reviewer comment: Although bleeding events were common in the overall safety population, all were low grade except for two, intestinal hematoma and hematuria. Analysis of bleeding is confounded in the pediatric cancer population by the underlying bleeding risk from thrombocytopenia or coagulopathy related to underlying disease or concomitant therapy. The low incidence of major bleeding events supports the tolerability of dalteparin in this population. Both minor and major bleeding events were less common in the non-cancer population than in patients with cancer. No serious bleeding events occurred in the setting of supratherapeutic levels of anti-Xa supporting the safety of the recommended dosing regimen.

Treatment Emergent Adverse Events and Adverse Reactions
Treatment emergent adverse events were common and reported in 94% of the safety

population. The most common TEAS occurring in greater than 10% of the population are displayed in the table below.

Table 25: Treatment Emergent Adverse Events in ≥ 10% of patients in the safety population

System Organ Class Preferred Term	FRAG-A001-201 < 18y N = 35 n (%)		KidsDOTT < 18y N = 15 n (%)		Safety Population N = 50 n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any TEAE	36 (97)	18 (51)	11 (73)	1 (7)	47 (94)	19 (38)
Infections and Infestations	13 (37)	6 (17)	6 (40)	0 (0)	25 (50)	6 (12)
Pneumonia	3 (9)	1 (3)	1 (7)	0 (0)	5 (10)	1 (2)
Blood and Lymphatic Disorders	20 (57)	12 (34)	0	0	20 (40)	12 (24)
Anemia*	9 (26)	6 (17)	0	0	9 18)	6 (12)
Febrile Neutropenia	5 (14)	2 (6)	0	0	5 (10)	2 (4)
Neutropenia***	6 (17)	6 (2)	0	0	8 (16)	7 (14)
Thrombocytopenia**	8 (23)	7 (20)	0	0	8 (16)	7 (14)
General Disorders and administration site conditions	21 (60)	2 (6)	2 (13)	0	23 (59)	2 (4)
Injection Site Bruising	15 (43)	0 (0)	0 (0)	0	15 (30)	0 (0)
Pyrexia	15 (43)	2 (6)	2 (13)	0	17 (34)	2 (4)
Respiratory, Thoracic and Mediastinal Disorders	17 (49)	1 (3)	3 (20)	1 (7)	20 (40)	1 (2)
Epistaxis	5 (14)	0 (0)	1 (7)	0 (0)	6 (12)	0 (0)

* includes anemia and hemoglobin decreased
**includes thrombocytopenia, pancytopenia, platelet count decreased
***includes neutropenia and neutrophil count decreased

8.5.7. Laboratory Findings

Hematologic Laboratory Abnormalities

The Applicant included an analysis of laboratory parameters for patients enrolled in the FRAG-A001-201 study. Laboratory data was not provided for the patients on the Kids-DOTT study. The Applicant's laboratory analysis included reports of the incidence of Hgb < 0.8 times the LLN (657%), platelets less than 0.5 times the LLN (32%) and ANC less than 0.8 times the LLN (47%).

The Agency was able to independently reproduce the analysis and the results were consistent with those of the Applicant.

In addition to the laboratory analysis provided by the Applicant, the Agency also provided an analysis of cytopenias by CTCAE criteria in the pediatric patients (< 18 years old). Additional analysis was performed in the cancer and non-cancer patients to identify the contribution of underlying cancer diagnosis and treatment to cytopenias. The table below displays the Agency analysis of hematologic laboratory abnormalities in pediatric patients on the FRAG-A001-201 study.

Table 26: Summary of Hematologic Laboratory Abnormalities

	FRAG-A001-201 < 18 years N = 35		FRAG-A001-201 < 18 years No cancer diagnosis N = 12	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Platelets Decreased	16 (45)	8 (18)	0 (0)	0 (0)
Neutrophils Decreased	18 (51)	16 (46)	2 (17)	0 (0)
Hemoglobin Decreased	28 (80)	8 (23)	6 (50)	0 (0)

Source: FDA generated from ADLB dataset

Both the FRAG-A001-201 and the Kids-DOTT study included criteria and recommendations for the identification and evaluation of possible heparin inducted thrombocytopenia (HIT). There were no reported episodes of heparin induced thrombocytopenia (HIT) in either the FRAG-A001-201.

Reviewer Comment: In general, cytopenias were under-reported as AEs compared to analysis of laboratory datasets. Cytopenias were common and were primarily driven by the cancer population, reflecting underlying treatment or malignancy. There were no new safety signals identified compared to the adult population. The most important abnormality, thrombocytopenia, which would be expected to be associated with bleeding was not associated with any major bleeding was likely not related to dalteparin, but due to underlying disease. This is further supported by no reports of thrombocytopenia reported in the non-cancer population and no reports of heparin induced thrombocytopenia. Upon review of narratives for the patients who developed thrombocytopenia, this AE was managed either by discontinuation or hold of dalteparin.

Chemistry Laboratory Abnormalities

The Applicant provided an analysis of serum chemistry abnormalities reported in all patients on the FRAG-A001-201 study. The results of selected chemistry abnormalities in pediatric patients (< 18 years) are summarized in the table below.

Table 27: Chemistry Abnormalities Reported in Patients on FRAG-A001-201

Laboratory Value	FRAG-A001-201 < 18 years all patients N = 35
	All Grades n (%)
Bilirubin increased > 1.5 ULN	1 (3)
AST increased > 1.5 ULN	5 (14)
ALT increased > 1.5 ULN	7 (20)
Creatinine increased > 1.3 X ULN	1 (3)

Source: From Applicant CSR Table 14.3.4.1.1, Agency reviewer verified

In addition to the Applicant provided chemistry analysis, the Agency conducted an analysis of AST and ALT increase based on CTCAEv4.03 criteria.

In the FRAG-A001 study increases in transaminase levels, AST and ALT, greater than three times the upper limit of normal of the laboratory reference range were reported in 20% and 14% of patients, respectively. The frequencies of Grades 3 and 4 increases in AST and ALT, as classified by were 9% and 3%, respectively.

One patient (b) (6) was reported to have a creatinine level increased >1.3 x ULN. This patient also had the reported AE of acute kidney injury (AKI) and dehydration. The patient was a 12 year old male with nasopharyngeal carcinoma and internal jugular thrombosis who was admitted on SD 21 with evidence of urinary tract infection. The patient had also received recent nephrotoxic chemotherapy. The laboratory abnormality and AE of AKI were not considered related to dalteparin therapy. A repeat creatinine at the end of therapy was normal.

Laboratory data sets were not provided for the Kids-DOTT study. There were no reported AEs of transaminase elevations or kidney injury in the Kids-DOTT study.

Reviewer comment: There were no new or unexpected laboratory findings associated with dalteparin use in the pediatric patients studied. Laboratory abnormalities noted in study patients were predominately noted in the cancer population, reflecting underlying malignancy and or treatment.

8.5.8. Vital Signs

Vitals signs were assessed at screening, baseline, during the dose adjustment phase (visit 3), PD phase (visit 4) and during follow visits 5, 6 and 7. The Applicant provided a record of vital signs and a description of changes in vital signs during treatment with dalteparin. A review of weight, heart rate, and temperature did not reveal any safety signals.

8.5.9. Electrocardiograms (ECGs)

Electrocardiograms were performed at screening or baseline and then as clinically indicated. There was no evaluation of ECG changes during or after treatment.

8.5.10. QT

There was no systematic ECG analysis for QT prolongation performed. No patients were reported to have developed prolongation of QT interval during the study.

8.5.11. Immunogenicity

No Immunogenicity data was collected during this study.

8.5.12. Analysis of Submission-Specific Safety Issues

Safety in the Cancer vs. Non-Cancer population

An analysis of safety findings in pediatric patients with cancer and without an underlying cancer diagnosis was performed. Pediatric patients with VTE and cancer and without cancer were represented across all of the pediatric age groups with the exception of the neonatal population. See sections 8.5.5. for a breakdown of treatment discontinuations, bleeding events and hematologic laboratory abnormalities analyzed separately in the cancer and non-cancer patients. In general, adverse events were reported more frequently in patients with an underlying malignancy and could generally be attributed to underlying diagnosis or therapy.

Reviewer comment: In general, dalteparin therapy was tolerated in pediatric patients with an without cancer. An adequate number of patients were analysis to assess safety in both populations and no unexpected safety findings were identified.

8.5.13. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no clinical outcome assessment data, including patient-reported outcomes, submitted with this application.

8.5.14. Safety Analyses by Demographic Subgroups

Due to the small number of patients, an analysis was conducted for the combined FRAG and Kids-DOTT safety data.

There was only one neonate (age 24 days at study initiation) in the safety population. The patient had two Grade 1 AEs reported. Both were asymptomatic laboratory findings, platelets increased, and ALT increased. Both AEs were reported to have resolved with no modifications to dosage.

Reviewer comment: The combined safety population of 50 patients provides adequate analysis of safety across all age groups over one month. There were an insufficient number of neonates studied to adequate inform safety in neonates The risk of bleeding complications and the unique pathophysiology of the coagulation system in the neonatal population, does not allow for extrapolation of safety from the older pediatric population to neonate. It is this reviewer's opinion that due the inadequate safety data in neonates, approval should be restricted to pediatric patients over the age of one month.

8.5.15. Specific Safety Studies/Clinical Trials

Due to the overall rarity of symptomatic VTE and relatively small number of pediatric patients for which there was safety data available, the Applicant provided additional published data to support the safety of dalteparin in pediatric patients, summarized below.

Warad, et al. published a retrospective review of 166 pediatric patients (1 year to 18 years) who received dalteparin for prophylaxis (N = 116) or treatment (N = 50) of VTE. Patients who received treatment for VTE received age and weight based dosing once or twice per day with the dose adjusted to target an anti-Xa level of 0.5 – 1 IU/ml). Of the 50 patients who received therapeutic dosing, 13 were less than one year of age, 20 were between 1 and 10 years of age, and 27 were between 10 and 18 years of age. Twenty-one patients had an underlying malignancy diagnosis. There were no major bleeding events identified in this review. Minor bleeding occurred in 4% (2/50). There were no reports of heparin induced thrombocytopenia or osteopenia.

Nohe et al, published their experience of 48 pediatric patients who received dalteparin for either prophylaxis (10) or treatment (38) of arterial or venous thrombosis. The age range was 31 weeks gestation to 18 years. Dalteparin dose was adjusted to target an anit-Xa level of 0.4

IU/ml to 1 IU/ml for the therapeutic group. Minor bleeding occurred in 2/48 patients (4%). There were no reports of major bleeding and no reports of heparin induced thrombocytopenia or osteopenia.

Reviewer comment: Both of the above published reports included in the application are single center, and one is retrospective, therefore limited conclusions can be drawn regarding the specific rates of SAEs or AEs associated with dalteparin dosing. This data, however can be considered supportive as it provides experience of an additional 88 patients who receive dalteparin targeting a similar anti-Xa level to what was targeted in the study patients. The lack of major bleeding and similar approach to age and weight based dosing provide support for the applicants proposed indication and dosing.

8.5.16. Additional Safety Explorations

Human Reproduction and Pregnancy

Section 8.1 of the USPI describes the risk associated with dalteparin use in pregnancy. There were no additional evaluations conducted in the studies include in this application.

Pediatrics and Assessment of Effects on Growth

There were no specific studies conducted on the effect of dalteparin on growth or bone metabolism.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was one report of overdose in a patient in the FRAG-A001-201 study. Subject (b) (6) was a 2 year old reported to have received four times the intended dose due to a pharmacy error on SD1. Pre protocol, this 12.4kg patient should have received 125 IU/kg or 1,550 IU per dose. The patient instead received two doses of 6000 IU or 483 IU/kg, the patient had a supratherapeutic anti-Xa level of 2 IU/ml. Once recognized, dalteparin was held for 24 hours and then restarted after a therapeutic anti-Xa level of 0.51 IU/ml was documented. There were no AEs that were reported to be related to the unintentional overdose.

Reviewer comment: The current USPI contains adequate description of the risk for bleeding with overdose and recommendations for management. The inadvertent overdose that occurred in the FRAG-A001-201 study highlights the risk for medication error with dose calculations and administration in pediatric patients.

8.5.17. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Osteopenia has been reported with dalteparin in the post marketing experience as well as with

unfractionated heparin and other low molecular weight heparin agents. Osteopenia has not been assessed systematically in any pediatric studies with dalteparin.

Reviewer comment: There have been no reported complications related to osteopenia reported in pediatric patients receiving dalteparin in clinical studies or in the literature. At this time there is insufficient data to assess the safety of dalteparin with regards to osteopenia with long term use, however there does not appear to be a risk of osteopenia related complications with the use of dalteparin for up to three months.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed in the clinical studies reviewed in this application and what is known from adult post marketing safety data.

8.5.18. Integrated Assessment of Safety

The safety of dalteparin was evaluated in 50 pediatric patients with symptomatic DVT. The safety population consistent of 23 (46%) patients with an underlying cancer diagnosis. Patients received aged-based dalteparin dosing subcutaneously, twice daily for up to three months. The median duration of exposure for the combined safety population was 85 days.

There were no patient deaths during study treatment and no reports of heparin induced thrombocytopenia. Major bleeding events were rare and were only reported in one patient. There were no new or unexpected safety signals identified in the pediatric population compared to the established safety profile in the adult population.

The most serious safety concern associated with dalteparin is bleeding. Bleeding complications are a specific concern in pediatric cancer patients who may have additional increased risk of bleeding due to thrombocytopenia due to malignancy or treatment of malignancy. The low incidence of major bleeding and treatment discontinuation due to AEs supports the safety of dalteparin in this population and ability to mitigate the risk of bleeding with dose modifications and interruptions for thrombocytopenia.

The most common treatment emergent adverse events in pediatric patients were pyrexia (34%), injection site bruising (30%), pneumonia (10%). Cytopenias were common (anemia (18%), neutropenia (16%) and thrombocytopenia (16%) in the cancer population but were not reported in the non-cancer population and therefore likely related to underlying malignancy and therapy and non considered related to dalteparin. Minor (grade 1, 2) bleeding events were common and consistent with the known safety profile of dalteparin and, in general, did not lead to treatment discontinuation.

An additional safety consideration includes the recommendation for periodic monitoring of anti-Xa levels in pediatric patients with dose adjustments to maintain therapeutic (0.5 IU/ml-1

IU/ml) levels. The inclusion of recommendations for ongoing, regular monitoring of anti-Xa levels provides additional safety measures to mitigate against additional bleeding risk that may be associated with supratherapeutic levels of dalteparin.

A comprehensive review of the safety demonstrates that dalteparin is tolerable and the AEs management in both the pediatric cancer and non-cancer population with symptomatic VTE.

8.6. Statistical Issues

The statistical review team did not uncover any substantive statistical issues that would materially impact the risk-benefit assessment for this supplement.

8.7. Conclusions and Recommendations

The benefit-risk assessment supports regular approval of dalteparin for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients one month of age and older.

Efficacy:
Efficacy in pediatric patients is primarily based on a single arm, open-label, multicenter trial (Study FRAG-A001-201) in 38 pediatric patients with or without cancer and symptomatic deep vein thrombosis and/or pulmonary embolism treated with dalteparin twice daily based upon age and weight. In the efficacy analysis, 34 patients (89%) of 38 patients achieved a therapeutic anti-Xa level (0.5-1.0 IU/mL) within 7 days from initiation of dalteparin. The median dose of Fragmin needed to achieve a therapeutic anti-Xa level in the 7-day dose adjustment period in the 34 patients was 208 IU/kg, 128 IU/kg, 125 IU/kg, and 117 IU/kg in the age categories ≥ 8 weeks to 2 years, ≥ 2 years to < 8 years, ≥ 8 years to < 12 years, and ≥ 12 years to < 19 years, respectively. Of the 34 patients, no patients experienced progression of the qualifying VTE and one patient (3%) had recurrence of VTE while on treatment. Further, supportive efficacy is provided by a dalteparin subanalysis of the Duration of Therapy for Thrombosis in Children trial (Kids-DOTT), a prospective, multicenter, randomized trial evaluating the optimal duration of anticoagulation for pediatric patients with venous thromboembolism. The dalteparin subanalysis of the Kids-DOTT trial included 18 pediatric patients without cancer with symptomatic venous thromboembolism. All 18 patients successfully achieved a therapeutic anti-Xa level between 0.5-1.0 IU/mL and no patients experienced progression of the qualifying VTE or recurrence of VTE. Furthermore, the efficacy of dalteparin treatment demonstrated in adults with cancer and symptomatic VTE can be partially extrapolated to pediatric patients, while acknowledging substantial differences between the hemostatic system within pediatric patients and compared to adults, the overall treatment goals and pathophysiology of recurrent or progressive VTE are similar in adults and pediatric patients. Dalteparin is approved for the extended treatment of symptomatic VTE to reduce the recurrence in adult patients with cancer.

Safety:
The safety profile of dalteparin in the pediatric population is tolerable and manageable. The safety of age and weight-based starting dosing of dalteparin followed by adjustments to target a plasma anti-Xa level of 0.5-1.0 IU/ml was evaluated in 50 pediatric patients in the FRAG-A001-201 and Kids-DOTT study. The median duration of exposure was 86 days (range 2 to 170 days). The most common adverse events were injection site bruising, pyrexia, and cytopenias. The majority of the adverse events reported were not considered related to study drug and were reported in the pediatric population with cancer. The most important safety issue associated with low molecular weight heparin therapy is bleeding. Major bleeding events were rare in the safety population, occurring in only 1 (2%) patient. Minor bleeding adverse events were reported in 40% of the safety population, most often bruising and epistaxis. The overall low (12%) rate of treatment discontinuation in a complex pediatric patient population further supports safety. There was an insufficient number of neonates (N=1) included in the safety population. Neonates have altered coagulation pathophysiology compared to older pediatric populations and may be more susceptible to major bleeding as well as the clinical sequelae of major bleeding. Therefore, the safety of dalteparin in neonates has not been established.

Benefit-Risk:
The benefit-risk determination considered the totality of efficacy and safety data for dalteparin treatment in pediatric patients and partial extrapolation from adults. The FRAG-A001-201 and Kids-DOTT study provided sufficient data to establish dosing in pediatric patients based upon age and weight. Efficacy data from the two prospective pediatric trials and adult efficacy data provide evidence of effectiveness in pediatric patients with and without cancer. Pediatric patients with an active malignancy receiving dalteparin treatment for symptomatic VTE have potential for increased toxicity due to the underlying disease and concomitant treatment. Because the FRAG-A001-201 study evaluated 26 patients with an active malignancy and the toxicity profile is tolerable and manageable, the review team felt the risk associated with dalteparin treatment in pediatric patients without cancer warrants broadening the indication to a general pediatric population. Although, due to insufficient safety data in the neonatal population and potential for increased risk of bleeding and sequalae of bleeding, the risk in neonates warrants restriction of the indication to pediatric patients greater than 1 month of age. Therefore, the benefit-risk assessment of dalteparin treatment is deemed favorable for the treatment of symptomatic venous thromboembolism to reduce the recurrence in pediatric patients 1 month of age and older.

X	X
Lisa Rodriguez, Ph.D. Primary Statistical Reviewer	Jingjing Ye, Ph.D. Statistical Team Leader

X	X	X
Margret Merino, MD Primary Clinical Reviewer	Nicholas Richardson, DO, MPH Primary Clinical Reviewer	R. Angelo de Claro, MD Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

This application was not presented to the Oncology Drug Advisory Committee or any other external consultants because the application did not raise significant efficacy or safety issues for the proposed indications.

10 Pediatrics

This submission fulfills PMR 923-1 established to fulfill the PREA requirement for supplement 35 for dalteparin NDA 020287 approved 01 May 2007.

Study FRAG-A001-201 was conducted primarily in pediatric patients (age 24 days to 19 years), with 35 of 38 patients under the age of 18. All pediatric age groups were studied (see Section 6.3.1), which allowed for adequate PD assessment across all pediatric age groups. Since the expected action of dalteparin would be the same for adult and pediatric patients the VTE and is correlated with anti-Xa levels, efficacy for dalteparin in patients who achieve a factor anti-Xa level in the therapeutic range (0.5 – 1.0 IU/ml) can be partially extrapolated from adults for the proposed indication. Additional safety data from the KidsDOTT study provided data from a total of 50 pediatric patients with safety data with adequate representation from all subgroups except neonates, providing for adequate safety assessment in non-neonatal pediatric age groups. There is an insufficient number of neonates (N=1) included in the safety population to establish safety. Therefore, the safety and efficacy of dalteparin has been demonstrated in pediatric patients 1 month and older.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

With this supplement, revisions to the Prescribing Information were proposed in the following sections:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights, Indications and Usage	(b) (6)	The Division requested that the pediatric indication be separated from the adult indication and that the pediatric indication reflect the inclusion of pediatric patients without cancer. In addition, the indication was restricted to pediatric patient 1 month and older due to insufficient data to establish safety in neonates.
1.4 Indication and Usage	(b) (4)	Added indication of symptomatic VTE in pediatrics
2.4 Dosage and Administration	Addition of starting dose age-based table in pediatrics	The Division requested additional information regarding monitoring of anti-Xa levels and dose adjustment recommendations. The Division requested that dosing recommendations for thrombocytopenia added in tabular format for adults and pediatrics .
5.2 Warnings and Precautions Thrombocytopenia	No changes were proposed by the Applicant	The Division requested that information on the pediatric experience with thrombocytopenia be included in section of 5.2.
5.4 Warnings and Precautions Laboratory Tests	No changes were proposed by the Applicant	The Division requested that a statement should be included to monitor anti-Xa levels in all pediatric patients.
6.1 Adverse Reactions	No specific pediatric Adverse reaction data was proposed to be included by the Applicant	Division requested that inclusion of adverse reaction data from the pediatric clinicals trials be added to section 6.1 under a new section “Pediatric Patients with Symptomatic VTE.”
6.2 Postmarketing Experience	No changes other than typographical edits proposed by the Applicant	Division recommended the inclusion of the risk of osteopenia, as this has been reported in preclinical studies, in postmarketing reports with dalteparin use and is a known risk with same-in-class agents.
8.4, Use in Specific Populations, Pediatrics	A brief reference to the FRAG-201 study was included with a cross reference to section 14 was added	The Division recommended revision of section 8.4 to include a detailed statement regarding the establishment of efficacy and safety in pediatrics.
12.3 Pharmacokinetics	Inclusion of Table 11	The division requested revision of the table to reflect the

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
	"Pharmacokinetic parameters of Dalteparin in Pediatric Population"	minimum age (3 weeks) in the pediatric database used to generate the PK parameters
14.6 Clinical Studies		The Division recommended a revision of the trial description to simplify language to terms that were universally understood. Trial data was expanded to more accurately describe the trial population and a description of how efficacy was determined was added. The Division requested that the reference to published literature be removed as the reference did not meet the criteria of important to prescribing information.

12 Risk Evaluation and Mitigation Strategies (REMS)

The risks of dalteparin, including bleeding, can be adequately managed in the post-marketing setting through product presentation and labeling. No additional risk management strategies are recommended.

13 Postmarketing Requirements and Commitment

The following Postmarketing Commitments (PMCs) are recommended:

1. To characterize safety of dalteparin treatment in neonates (defined as gestational age 35 weeks to 28 days of age) with symptomatic venous thromboembolism (VTE), conduct a study to describe the safety, dosing, pharmacodynamics, and efficacy using real-world evidence in at least 12 neonates receiving dalteparin. Submit the final report, case report forms, and datasets.

2. To enable safe and effective use of dalteparin in infants and children requiring treatment for symptomatic venous thromboembolism, develop a lower strength formulation of dalteparin that will require no less than a 0.1 ml dose volume.

Refer to action letter for final wording.

14 Division Director (OCP) Comments

X _____

Mehul Mehta, Ph.D.

15 Division Director (OB) Comments

X _____

Thomas Gwise, Ph.D.

16 Division Director (Clinical) Comments

For all those who take care of pediatric patients this approval is well over due. This approval is the first US FDA approval of an anticoagulant with a pediatric indication and specific dosing instructions. I agree with the partial extrapolation approach used for this supplement with pediatric data. Also, I concur with the review teams' assessments of the data and specifically concur with sections 1.2 and 1.3 of this document. As noted by the clinical team above this submission fulfills PMR 923-1 established to fulfill the PREA requirement for dalteparin NDA 020287.

X

Ann T. Farrell, M.D.

17 Appendices

17.1. References

1. Jaffray J, Mahajerin A, Young G, Goldenberg N, Ji L, Sposto R, et al. A multi-institutional registry of pediatric hospital-acquired thrombosis cases: The Children's Hospital-Acquired Thrombosis (CHAT) project. Thromb Res. 2018;161:67-72.

2. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics. 2009;124(4):1001-8.

3. Pelland-Marcotte MC, Pole JD, Kulkarni K, Athale U, Stammers D, Sabapathy C, et al. Thromboembolism Incidence and Risk Factors in Children with Cancer: A Population-Based Cohort Study. Thromb Haemost. 2018;118(9):1646-55.

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5. Monagle P, Cuello CA, Augustine C, Bonduel M, Brandao LR, Capman T, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood Adv. 2018;2(22):3292-316.

6. Hepponstall M, Chan A, Monagle P. Anticoagulation therapy in neonates, children and adolescents. Blood Cells Mol Dis. 2017;67:41-7.

7. Nohe N, Flemmer A, Rumler R, Praun M, Auberger K. The low molecular weight heparin dalteparin for prophylaxis and therapy of thrombosis in childhood: a report on 48 cases. Eur J Pediatr. 1999;158 Suppl 3:S134-9.

8. O'Brien SH, Kulkarni R, Wallace A, Hamblin F, Burr S, Goldenberg NA. Multicenter dose-finding and efficacy and safety outcomes in neonates and children treated with dalteparin for acute venous thromboembolism. J Thromb Haemost. 2014;12(11):1822-5.

9. Warad D, Rao AN, Mullikin T, Graner K, Shaughnessy WJ, Pruthi RK, et al. A retrospective analysis of outcomes of dalteparin use in pediatric patients: a single institution experience. Thromb Res. 2015;136(2):229-33.

17.2. Financial Disclosure

Covered Clinical Study: FRAG-A001-201/A6301094

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 100		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

17.3. Grouped Preferred Terms

Bleeding

AUTOLIMITED BLEEDING IN LOWER LIP
BILATERAL BACK OF ARMS BRUISING AT CHEMOTHERAPY SITE
BLEEDING FROM GUM OVERNIGHT

BLEEDING FROM STUDY DRUG INJECTION SITE (ABDOMEN)
BLEEDING FROM STUDY DRUG INJECTION SITE ON ABDOMEN
BLOOD IN STOOL
BRIGHT RED BLOOD IN STOOL
BRUISE AT INJECTION SITE
BRUISE BILATERAL SHINS
BRUISE MIDDLE LEFT THIGH
BRUISE ON LEFT LOWER ABDOMEN AT INJECTION SITE
BRUISE RIGHT POSTERIOR UPPER ARM AT INJECTION SITE
BRUISE SKULL (RIGHT SIDE OF SKULL)
BRUISES ON BACKS OF UPPER ARMS
BRUISES ON BOTH SIDES OF BACK OF ARMS AT CHEMOTHERAPY INJECTION SITE
BRUISING
BRUISING ABDOMEN AT INJECTION SITES
BRUISING AT INJECTION SITES ON ARMS AND LEGS
BRUISING AT SITE OF INJECTION
BRUISING AT THE SITE OF STUDY DRUG INJECTION
BRUISING FROM INJECTION SITE
BRUISING LEFT MEDIAL THIGH (FROM INJECTION SITE)
BRUISING ON ABDOMEN AT INJECTION SITE
BRUISING OVER MEDIPORT AREA
BRUISING OVER RIGHT THIGH INJECTION SITE
BRUISING TO ABDOMEN AT INJECTION SITE
COFFEE GROUND EMESIS
ECCHYMOSIS RLE
ECCHYMOTIC LESION ON ABDOMINAL WALL
EMESIS WITH BLOOD
EPISTAXIS
FAINT BRUISING ON TOP OF RIGHT FOOT
GENERALISED BRUISING AT INJECTION SITE-LEFT + RIGHT THIGHS, ABDOMEN, UPPER ARMS
HAEMATOMA IN LEFT HIP
HAEMATOMA IN LEFT LEG
HAEMATOMA IN WRIST
HEALING BRUISE LEFT ARM
HEMATOMA IN LEFT LEG
HEMATOMA LLQ ABDOMEN
HEMATOMA ON RIGHT ARM AT CHEMOTHERAPY INJECTION SITE
HEMATURIA
HEMOPTYSIS
INJECTION SITE BRUISING ON BILATERAL THIGHS
INTESTINAL HEMATOMA

KNEES HEMATOMA
LEFT ARM BRUISE
LEFT ARM BRUISE AT CHEMOTHERAPY INJECTION SITE
LEFT ARM BRUISE AT STUDY DRUG INJECTION SITE
LEFT LQ INJECTION SITE BRUISE
LLQ INJECTION SITE BRUISE
MID-ABDOMEN INJECTION SITE BRUISE
MINIMAL HAEMATOMA IN KNEES
MINIMAL HEMATOMA IN INJECTION AREA
MINOR BLEEDING AT INJECTION SITE
MINOR BRUISING AT INJECTION SITES (ANTERIOR THIGHS)
MUCOSAL BLEED
MULTIPLE SKIN BRUISES FROM INJECTION
MULTIPLE SKIN BRUISES FROM INJECTIONS
MULTIPLE SKIN BRUISES FROM INJECTIONS - BILATERAL THIGHS
NOSE BLEED
RIGHT ARM BRUISE AT CHEMOTHERAPY INJECTION SITE
RIGHT LQ INJECTION SITE BRUISE
RIGHT UPPER ABDOMINAL BRUISE AT INJECTION SITE
RIGHTABDOMINAL BRUISE AT INJECTION SITE
RIGHTLEG BRUISE ON CALF
RLQ INJECTION SITE BRUISE
SEVERAL BRUISES AT SITES OF FRAGMIN
SMALL AMOUNT EPISTAXIS

Thrombocytopenia

PANCYTOPENIA
THROMBOCYTOPENIA
PLATELETS DECREASED
PLATELET COUNT DECREASED
PLATELET COUNT DECREASED
PLATELETS DECREASED
PLATELETS DECREASED
PLATELETS DECREASED
PANCYTOPENIA
LOW PLATELETS
LOW PLATELETS
LOW PLATELETS
WORSENING THROMBOCYTOPENIA
THROMBOCYTOPENIA
THROMBOCYTOPENIA
THROMBOCYTOPENIA

DECREASED PLATELET
THROMBOCYTOPENIA
WORSENING OF THROMBOCYTOPENIA

Pneumonia

PNEUMONIA
LEFT LOWER LOBE PNEUMONIA

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