



**Protocol A6301094**

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

**Statistical Analysis Plan  
(SAP)**

**Version:** 2  
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## 1. VERSION HISTORY

**Table 1. Summary of Major Changes in SAP Amendments**

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	Administrative Changes due to protocol amendments	<p>Transition of study to Pfizer Inc from Eisai; Updating of Safety Section per Pfizer safety reporting processes and procedures, and other relevant sections per Pfizer Inc processes and procedures</p> <p>Include protocol modifications endorsed by FDA in a Type C Meeting conducted on 05 November 2015, including updating age cohort groups, inclusion of all patients with VTE and removal of the central imaging reader and Adjudication Committee</p>

## 2. INTRODUCTION

*This protocol implements a post approval clinical commitment between Pfizer Inc., and the Food and Drug Administration (FDA) relating to the dalteparin sNDA 20-287/S-035, “for the extended treatment of symptomatic venous thromboembolism [VTE (proximal deep vein thrombosis [DVT] and/or pulmonary embolism [PE])] to reduce recurrent VTE in subjects with cancer”. This phase II pharmacodynamic (PD) study is intended to provide information to guide the conditions under which dalteparin may be used for the treatment of acute and secondary prophylaxis of VTE in children. The PD profiles for treatment doses of dalteparin using anti-Xa levels will also be assessed in a population PD analysis methodology.*

### 2.1. Study Objectives

**The primary objective of this study is to:**

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

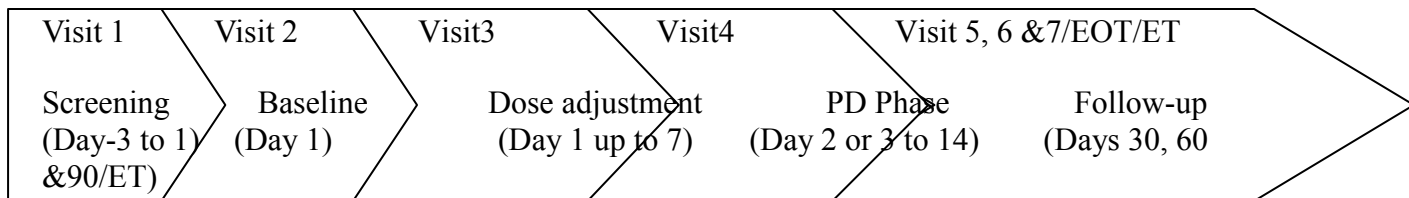
**Secondary objectives will be:**

- *To assess the proportion of subjects with major bleeding events during dalteparin treatment.*
- *To assess the proportion of subjects with minor bleeding events during dalteparin treatment.*
- *To explore the proportion of subjects with objectively documented new or progressive symptomatic VTE during dalteparin treatment.*
- *To explore the relationships of recurrent VTE and major bleeding events with anti-Xa levels if data permits.*
- *To assess proportion of subjects achieving an anti-Xa therapeutic range of 0.5 to 1.0IU/mL during the Dose Adjustment Phase.*
- *To explore the proportions of subjects with progression, regression, resolution or no change in the qualifying VTE during dalteparin treatment.*
- *To describe the overall safety profile of dalteparin in pediatric subjects of different ages with VTE.*

**2.2. Study Design**

*The study is a 3 month prospective, multicenter, open-label cohort study in North America and Europe to determine twice daily dosing recommendations of dalteparin as a function of age in order to achieve anti-Xa levels of 0.5 to 1.0 IU/mL at 4 hour postdose in children with or without various cancers and requiring anticoagulation for the treatment and secondary prophylaxis of VTE. The study is divided into 3 phases (Figure 1): 1) Dose Adjustment Phase of up to 7 days; 2) PD Phase; and 3) Follow-up Phase, to complete up to 90 days of treatment.*

**Figure 1. Schematic Trial Design**



Subjects will be enrolled into one of the following five age groups (cohorts): newborn (0-<8 weeks), infants (>=8weeks - <2 years), preschool (>=2 years - <8 years), school (>= 8 years - < 12 years), and teen (>= 12 years - < 19 years).

The target enrollment is a total of 50 subjects who have completed the PD Phase.

All age groups will receive dalteparin twice daily. The initial dose for each age group are: 125 IU/kg for 0 to <8 weeks, 150 IU/kg for  $\geq$ 8 weeks to < 2 years, 125 IU/kg for  $\geq$ 2 weeks to < 8 years and  $\geq$ 8 years to < 12 years, and 100 IU/kg for  $\geq$ 12 years to <19 years.

The Dose Adjustment Phase will begin following the first dose and continue for up to 7 days. During the Dose Adjustment Phase, doses are adjusted according to anti-Xa levels. The first anti-Xa level may be taken 4 hours  $\pm$ 1 hour after the first, second or third dose per institutional standard. Subsequent anti-Xa levels will be drawn at 4 hours  $\pm$ 1 hour postdose. Doses will be adjusted in increments or decrements of 25 IU/kg in order to achieve target anti-Xa levels (0.5-1.0 IU/mL).

Subjects completing the Dose Adjustment Phase will enter into the PD Phase and continue on the final twice daily dosing (Q12h  $\pm$ 1 hour) regimen from the Dose Adjustment Phase. The PD Phase will last for up to 7 days in order to complete two PD samples. After subjects successfully complete the PD Phase, they will enter the Follow-up Phase.

During this phase, subjects will continue receiving twice daily dalteparin q12h ( $\pm$ 1 hour) and will be followed according to the visit schedule. The maximum duration is 90 days after first dose of dalteparin.

### **3. ENDPOINTS AND BASELINE VARIABLES: DEFINATIONS AND CONVENTIONS**

#### **3.1. PD Endpoint(s)**

##### **3.1.1. Primary PD Endpoints**

- Anti-Xa activity versus time profile following dalteparin treatment in pediatric subjects of different ages with VTE.

Note: This is beyond the scope of the SAP and it will be detailed in a separated population modeling analysis plan (PMAP-EQDD-A630c-DP4-560).

- Median dose required per age group to achieve an anti-Xa level of 0.5 to 1.0 IU/mL during the dose adjustment phase.

##### **3.1.2. Secondary PD endpoints**

- Proportion of children achieving an anti-Xa therapeutic range of 0.5 to 1.0 IU/mL during the Dose Adjustment Phase.
- Proportion of subjects who remain within therapeutic range during the follow up phase (Visit 5, Visit 6 and Visit 7).
- The percentage of anti-Xa levels measured 4 hours post dose  $\pm$ 1 hour that are outside the target range will be calculated during the follow up phase of study (Visit 5, Visit 6 and Visit 7).

- The maintenance dose, time to achieve the target range, and number of dose adjustment during dose adjustment phase.

### **3.2. Efficacy Endpoint(s)**

All efficacy endpoints are secondary endpoints.

- Proportion of subjects with objectively documented new or progressive symptomatic VTE during dalteparin treatment.
- Relationship between objectively documented new or progressive symptomatic VTE and the anti-Xa level during dalteparin treatment if data permits.
- The proportions of subjects with progression, regression, resolution or no change in the qualifying VTE during dalteparin treatment.
- Time to first episode of symptomatic recurrent VTE during dalteparin treatment.

### **3.3. Baseline Variables**

#### **3.3.1. Stratification and Randomization**

Enrolled subjects who achieve the target therapeutic anti-Xa level in Dose Adjustment Phase will advance to the PD phase. These subjects will be centrally randomized (at baseline) to two different blood sampling scheme (1-3 h & 5-8 h or 3-5 h & 8-12 h) for the PD phase with a ratio of 1:1 and the randomization will be blocked and stratified by age group.

#### **3.3.2. Covariates**

As an objective of the study is to examine safety and efficacy within different age groups, subjects will be presented split into the age categories: 0-<8 weeks, >=8weeks - <2 years, >=2 years - <8 years, >= 8 years - < 12 years, and >= 12 years - < 19 years.

### **3.4. Safety Endpoints**

All safety endpoints are secondary endpoints.

- Proportion of subjects with major bleeding events during dalteparin treatment.
- Relationship between major bleeding event and the Anti-Xa level during dalteparin treatment if data permits.
- Proportion of subjects with minor bleeding events during dalteparin treatment.
- Time to first major bleeding events during dalteparin treatment.

Safety will also be assessed by adverse event reports, physical examination, laboratory test results, and vital signs in the safety population. Both all-causality and treatment related adverse events will be assessed. The latest Pfizer Data Standard (PDS) will be used for reporting.

### **3.4.1. Adverse Events**

An adverse event is considered treatment emergent if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment, or
- the event was seen prior to the start of treatment but increased in severity during treatment.

The effective duration of treatment is determined by the lag time (30 days). Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is attributed to the previous treatment period.

### **3.4.2. Laboratory Data**

To determine if there are any clinically significant laboratory abnormalities, the hematological and clinical biochemistry and other safety tests will be assessed against the criteria specified in the Pfizer reporting standards. This assessment will take into account whether each subject's baseline test results are within or outside the laboratory reference range for the particular laboratory parameter.

## **4. ANALYSIS SETS**

The main subject populations to be used for the analysis are a pharmacodynamics (PD) population and a safety population.

The PD population will be the analysis population for efficacy.

### **4.1. PD Analysis Set**

The PD analysis set (PD population) will include all subjects who receive at least one dose of study drug and achieve therapeutic range of anti-Xa during dose adjustment phase.

### **4.2. Safety Analysis Set**

The safety analysis set (safety population) will include all the subjects who receive at least one dose of study drug.

### **4.3. Protocol Deviations**

Protocol deviations relevant to the PD population and the safety population will be summarized.

## **5. GENERAL METHODOLOGY AND CONVENTIONS**

The final primary analysis will be performed at database release after last subject last visit.



## **5.1. Hypotheses and Decision Rules**

Because of the descriptive nature of this study, there will be no statistical hypotheses tested and decisions rules. Two-sided 95% confidence interval (CI) will be provided to aid decision making.

## **5.2. General Methods**

The following sub-sections contain the descriptions of the methods that will be used in the analysis of the various endpoints in this study. The choice of analysis method will be dependent on the endpoint of interest (eg, whether the endpoint is a primary or secondary, or whether the endpoint is efficacy or safety). The analysis methods to be used for each endpoint will be covered in the following section.

### **5.2.1. Analyses for Binary Endpoints**

Response rates (eg, proportion of subjects with objectively documented new or progressive symptomatic VTE) will be presented with exact 95% confidence intervals for binomial proportion, using the Clopper-Pearson method (Collett 1991).

### **5.2.2. Analyses for Continuous Data**

Continuous data are variables that are continuous or considered continuous for the purpose of analysis, the following descriptive statistics will be provided at each visit (including the baseline, when applicable): N, mean, median, standard deviation (SD), minimum and maximum.

### **5.2.3. Analyses for Categorical Data**

Categorical data will be presented with frequency and percentage.

### **5.2.4. Analyses for Time to Event Data**

Time-to-event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Kaplan-Meier graphs will describe the number of patients at risk over time. In addition, the Cox Proportional Hazard Regression model will be employed to assess the hazard ratio of the event with prognostic factors.

## **5.3. Methods to Manage Missing Data**

For efficacy endpoints, missing data will not be imputed.

## **6. ANALYSES AND SUMMARIES**

All statistical analyses will be performed using SAS<sup>®</sup> (Version 9.1 or higher), and statistical tests will be assessed at the two-sided 0.05 level of significance.

### **6.1. Endpoint(s)**

#### **6.1.1. PD Endpoints**

Unless otherwise noted, all PD endpoints will be analyzed within the PD population.

#### **6.1.1.1. Primary PD Endpoint**

- Anti -Xa activity versus time profile following dalteparin treatment in pediatric subjects of different ages with VTE (detailed in a separated population modeling analysis plan [PMAP-EQDD-A630c-DP4-560]).
- Median dose required to achieve an anti-Xa level of 0.5 to 1.0 IU/mL during the dose adjustment phase.

The median dose will be presented overall and by each age group for patients who achieved an anti-Xa level of 0.5 to 1.0 IU/mL during the dose adjustment phase.

#### **6.1.1.2. Secondary PD Endpoints**

- Proportion of subjects achieving an anti-Xa therapeutic range of 0.5 to 1.0 IU/mL during the Dose Adjustment Phase.

The count and proportion will be summarized overall and by each age group within the safety population, along with the two-sided exact 95% CI.

- Proportion of subjects who remain within therapeutic range at each visit during the follow up phase (Visit 5, Visit 6 and Visit 7).

The count and proportion will be summarized overall and by each age group, along with the two-sided exact 95% CI.

- The percentage of anti-Xa levels measured 4 hours post dose  $\pm 1$  hour that are outside the target range will be calculated at each visit during the follow up phase of study (Visit 5, Visit 6 and Visit 7).

The count and percentage will be summarized overall and by each age group, along with the two-sided exact 95% CI.

- The maintenance dose, time to achieve the target range, and number of dose adjustment during dose adjustment phase.

The maintenance dose, time to achieve the target range, and number of dose adjustments will be summarized overall and by each age group.

#### **6.1.2. Efficacy Endpoints**

All efficacy endpoints will be analyzed within the PD population.

##### **6.1.2.1. Efficacy Analysis**

- Proportion of subjects with objectively documented new or progressive symptomatic VTE during dalteparin treatment.

The count and proportion will be summarized overall and by each age group, along with the two-sided exact 95% CI.

- Relationship between objective documented new or progressive symptomatic VTE assessed by investigators and the anti-Xa level during dalteparin treatment.

Logistic regression for new/progressive VTE assessed by investigators on anti-Xa level at end of dose adjustment and other prognostic factors (eg, age, baseline tumor status), will be performed. For each of the covariates, the odds ratio, and the corresponding 95% CI, will be displayed.

Subjects who experience at least one new or progressive VTE while on study will be counted as Yes.

- Time to event (first episode of recurrent VTE) during dalteparin treatment.

The time to event (first recurrent VTE) will be described by using the Kaplan-Meier method. In addition, the Cox Proportional Hazard Regression model will be employed to assess the hazard ratio of the event with prognostic factors.

See [Appendix 1](#) for a general description of censoring of time-to-event variables.

- Proportions of subjects with progression, regression, resolution and no change in the qualifying VTE (in comparison with the assessment at study entry) during dalteparin treatment.

The count and proportion will be summarized overall and by each age group, along with the two-sided exact 95% CI.

## **6.2. Baseline and Other Summaries and Analyses**

### **6.2.1. Demography and Baseline Summaries**

The demographic characteristics will be summarized, overall and by each age group, within the safety population and the PD population. This will include age, gender, race, height, and baseline weight.

All baseline disease characteristics will be summarized overall and by each age group based within the safety population and the PD population. This will include diagnosis of cancer, previous history of VTE, risk factors for VTE and qualifying episodes of VTE.

### **6.2.2. Study Conduct and Subject Disposition**

Study conduct and subject disposition will be summarized within the safety population. The number of subjects screened, randomized, treated, completing and discontinuing from the study, as well as the number of subjects in each analysis set will be summarized overall and by each age group. For subjects who did not complete the study, the reasons for withdrawal from the study will be presented.

### **6.2.3. Study Treatment Exposure**

Duration of treatment will be summarized, overall and by each age group, within the safety population and the PD population.

#### **6.2.4. Concomitant Medications and Non-Drug Treatments**

All concomitant medications as well as non-drug treatments will be summarized overall and by each age group within the safety population.

### **6.3. Safety Endpoint Summaries and Analyses**

The safety summaries below will be performed within the safety population.

#### **6.3.1. Safety analysis**

- Proportion of subjects with major bleeding assessed by investigators during dalteparin treatment.

The count and proportion will be summarized overall and by each age group, along with the two-sided exact 95% CI.

- Relationship between major bleeding event and the Anti-Xa level during dalteparin treatment.

Logistic regression for major bleeding event assessed by investigators on anti-Xa level observed at the end of dose adjustment and other prognostic factors (eg, age, gender), will be performed. For each of the covariates, the odds ratio, and the corresponding 95% CI, will be displayed.

Subjects who experience at least one major bleeding event while on study will be counted as Yes.

- Proportion of subjects with minor bleeding events during dalteparin treatment.

The count and proportion will be summarized overall and by each age group, along with the two-sided exact 95% CI.

- Time to first major bleeding event during dalteparin treatment.

The time to first major bleeding event assess by investigators will be described by using the Kaplan-Meier method. In addition, the Cox Proportional Hazard Regression model will be employed to assess the hazard ratio of the event with prognostic factors.

See [Appendix 1.1](#) for a general description of censoring of time-to-event variables.

#### **6.3.2. Adverse Events**

All adverse events will be coded using the most current version of the MedDRA dictionary available at the time of database lock. Frequencies of adverse events will be presented by system organ class, preferred term, and severity level.

- All causality treatment emergent adverse events will be summarized overall and by each age group.

- Treatment related treatment emergent adverse events will be summarized overall and by each age group.
- Adverse events and serious adverse events will be listed by subjects for all age groups.
- Adverse events leading to discontinuation or temporary dose reduction will be presented.

Adverse events will be reported in accordance with the Pfizer Data Standards for safety reporting.

### **6.3.3. Laboratory Data**

Descriptive statistics will be summarized overall and by each age group as well as median change from baseline for laboratory parameters.

All laboratory data will be reported in accordance with Pfizer Data Standards for safety reporting.

### **6.3.4. Vital Signs and Physical Examination**

All vital sign and physical exam data will be reported in accordance with the Pfizer Data Standards for safety reporting.

## **7. INTERIM ANALYSES**

In August 2014, analyses for an interim report were performed by the previous study sponsor, Eisai Inc. on the data available at that time. The corresponding interim report was submitted to the FDA for review by Eisai Inc. These analyses did not contain any provisions for early stopping of the study.

## **8. REFERENCES**

1. Collett, D. (1991), *Modelling Binary Data*, London: Chapman & Hall.

## **9. APPENDICES**

### **Appendix 1. STATISTICAL METHODOLOGY DETAILS**

#### **Appendix 1.1. Time to Event**

For this analysis, time to event will be measured from the first dose of study medication in days. For subjects who have event, time to event is defined as:

$$T = \text{date of event} - \text{first treatment date} + 1$$

Subjects who do not have the event of interest will be censored at the latest date in the database. Time to event is defined as:

$$T = \text{latest date in the database} - \text{first treatment date} + 1$$

The latest date is expected to be the date of the End of Study visit.