NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: A Retrospective Chart-Review Study to Evaluate the Safety, Effectiveness and Dosing of Dalteparin for Treatment of Venous Thromboembolism (VTE) in Neonates

Date: 15 September 2022

Name and affiliation of the main author: Muhammad Younus
Non-interventional Study Lead, Safety Surveillance Research, Worldwide Medical and Safety, Pfizer Inc.

Keywords: venous thromboembolism, dalteparin, neonates, non-interventional study

Rationale and background:
Venous Thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is an acute medical condition that occurs in both adult and pediatric patients that requires immediate medical attention. In general, recommendations for evaluation, treatment, and management of pediatric patients with VTE are primarily based on extrapolation of data from adult patients. In May 2019, Fragmin (dalteparin sodium) became the first Food and Drug Administration (FDA)-approved therapy to treat VTE in pediatric patients aged ≥ 1 month. Upon approval, a Post Marketing Requirement (PMR 923-1) was requested to the sponsor (Pfizer Inc) to conduct a non-interventional, retrospective medical record review study to characterize the safety of dalteparin treatment in neonates with VTE using real-world evidence in at least 12 neonates receiving dalteparin. Therefore, this non-interventional study (NIS) is a post-marketing commitment to the FDA, utilizing secondary data from routine clinical care aimed to examine safety, effectiveness, and dosing of dalteparin among neonates treated for VTE.

Research question and objectives: Among neonates (≤ 28 days old, and ≥ 35 weeks gestation) treated with dalteparin for VTE, characterize the safety profile, effectiveness and describe dosing of dalteparin in real-world settings.

Study design: The study utilized available existing data from medical records dating back to 2010 at pediatric hospitals in the United Kingdom with demonstrated neonatology expertise.

Setting: Data from medical records were collected at the participating sites in the UK for eligible patients who were admitted to the hospital between January 2010 and December 2021. Data abstraction started in January 2022 and ended in April 2022.

Patient data was collected from the date of initiation of dalteparin dosing i.e., the index date, as documented in the medical records. Eligible patients were then followed from the index date to whichever of the following occurred first: 28 days after the last dose of dalteparin, death, lost to follow-up, end of study period (i.e., 31 December 2021).

Subjects and study size, including dropouts: The study aimed to enroll 12 patients from approximately ten sites with demonstrated expertise in treating neonates with VTE. A feasibility assessment was conducted to identify pediatric hospitals across the United States, the UK and Canada, with potentially eligible study patients. Out of 500 sites across the three countries that were contacted, 406 sites did not respond, and 47 institutions declined to participate. In the United States and Canada, no sites willing to participate were identified. Thus, a total of 18 patients were screened across 7 sites in the UK for this study. Of these, 16 patients were enrolled from five sites.

Variables and data sources: Data on exposure variables (dalteparin dose, date and time of dose, duration, indication), data on safety (major and minor bleeding events, deterioration in hematological biomarkers [platelets, hemoglobin, prothrombin time, and partial thromboplastin time]), treatment and effectiveness outcomes were collected from medical records retrospectively.

Results: Complete data were available for 13 patients while 3 patients were lost to follow-up. The majority of patients were female (56.3%) and White (81.3%). The mean age (±standard deviation [SD]) at first dalteparin dose was 14.5 (±5.9) days. A total of 15 patients (93.8%) had at least one comorbid disease or non-drug allergy. The most common comorbid disease was sepsis, followed by hyperinsulinism. A total of 12 patients (75.0%) were documented with use of at least one concomitant medication and the medication was initiated prior to first dalteparin dose.

The qualifying diagnosis for all 16 patients was deep vein thrombosis (DVT) and none of them had pulmonary embolism (PE). Overall, ten patients (62.5%) had a specific VTE risk factor. The most common risk factors were a central venous catheter and hospitalization (7 patients, 43.8% each), followed by acute medical condition (6 patients, 37.5%). The mean (±SD) duration of hospitalization due to a VTE was 40.1±24.4 days. Central venous access device (CVAD) was present in eight patients (50.0%) and was related to the VTE in four of these patients. The mean (±SD) daily dose of dalteparin at initiation was 364.88±196.39 IU/kg.

No patient experienced a bleeding event during treatment with dalteparin and through follow-up. One patient experienced a serious event of hypoglycaemic brain injury. This patient's medical history was documented with hyperinsulinism (ongoing at study entry i.e., at first dalteparin dose) and confirmed late onset sepsis (not ongoing). This event was documented as ongoing and with a duration of 531 days. No drastic differences were found in laboratory test results 30 days pre-dalteparin initiation and 30 days post-dalteparin initiation. Four patients had resolution of VTE. All 16 patients initiated dalteparin treatment, experienced a dose or frequency change, then permanently discontinued treatment. The mean (±SD) duration of dalteparin treatment was 62.44±30.04 days. A total of 82 changes in dalteparin treatment were documented across 16 patients of this study. The most reported main reason for a change in dalteparin treatment were the anti-Xa levels (61 updates, 74.4%) for 15 patients, followed by treatment course completed (11 updates, 13.4%) for 11 patients.

Discussion: The main objective of the study was to characterize the safety profile of dalteparin by examining evidence of major and minor bleeding, deterioration in hematological biomarkers, and other serious events.

No patients experienced a bleeding event during treatment with dalteparin and follow-up. One patient experienced a serious event of hypoglycaemic brain injury. No other serious events were documented, and no patients died.

The study provides pertinent data on dalteparin dosing in the neonatal population treated for VTE and permits the identification of safety signals for further refinement. Furthermore, this study provides a cross-sectional overview of real-world data on current patient management and outcomes in the UK. However, there was no control group in this study, therefore, comparisons with neonates who were not treated with dalteparin was not possible. Additionally, generalizability of the findings may be limited due to small number of patients that were included using a convenient sample. Limitations are also inherent to the retrospective observational study design, which may increase the likelihood of incomplete data and does not allow causal inferences to be drawn. The current study did not obtain sufficient data to assess effectiveness of dalteparin in neonates.

Conclusions: Overall, no safety concerns were identified. The data obtained from the study were insufficient to assess the effectiveness of dalteparin. Study limitations such as potential for inaccuracies and limited generalizability should be considered when interpreting the data given that this was a small observational study using retrospective data from medical records.

Names and affiliations of principal investigators:

Muhammad Younus, MBBS, PhD
Senior Director, Safety Surveillance Research, Worldwide Medical and Safety, Pfizer Inc.

Nancy Sherman
Senior Director, Post Approval Commitment Clinical Development Global Product Development, Pfizer Inc.