NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

Study information

Title	A Retrospective Chart-Review Study to Evaluate the Safety, Effectiveness and Dosing of Dalteparin for Treatment of Venous Thromboembolism (VTE) in Neonates
Protocol number	A6301097
Protocol version identifier	1.1
Date	June 4, 2020
EU Post Authorization Study (PAS) register number	EUPAS42367
Active substance	Dalteparin sodium ATC code: B01AB04
Medicinal product	Fragmin
Research objectives	Neonates (≤ 28 days old and ≥ 35 weeks gestation) treated for VTE with dalteparin: • Characterize the safety profile of dalteparin by examining evidence of major and minor bleeding and deterioration in hematological biomarkers (hemoglobin levels, platelet counts, prothrombin time, and partial thromboplastin time) among other serious events • Characterize the effectiveness of dalteparin by examining changes in relevant factor anti-Xa levels and VTE status • Describe dosing (starting dose and optimal therapeutic dose) of dalteparin and corresponding anti-Xa assay levels
Country (-ies) of study	The United States (US) is the country of focus. If feasible, sites in the United Kingdom (UK) and Canada may be recruited to achieve the study sample size.

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
AESI	Adverse Event of Special Interest
CBC	Complete Blood Count
CIOMS	Council for International Organizations of Medical Sciences
CPA	Conventional Pulmonary Angiogram
CPT	Current Procedural Terminology
CT	Computer Tomography
CTV	Computed Tomography Venography
CUD	Compression Ultrasound with Doppler
CVAD	Central Venous Access Device
CVC	Central Venous Catheter
CRF	Case Report Form
CRA	Clinical Research Associate
CSM	Clinical Study Monitor
DMP	Data Management Plan
DVT	Deep Vein Thrombosis
DCT	Data Collection Tool
eCRF	Electronic Case Report Form
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EDC	Electronic Data Capture
EMR	Electronic Medical Records
EHR	Electronic Health Records
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
ICD-9	International Classification of Disease, Ninth Edition

ICD-10	International Classification of Disease, Tenth Edition
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IQR	Interquartile Range
LMWH	Low Molecular Weight Heparin
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRV	Magnetic Resonance Venography
NIS	Non-Interventional Study
NICU	Neonatal Intensive Care Unit
VTE	Venous Thromboembolism
PASS	Post Authorization Studies
PE	Pulmonary Embolism
PMC	Post-Marketing Commitment
RCT	Randomized Controlled Trial
RWD	Real-World Data
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCTA	Spiral Computed Tomographic Angiography
SD	Standard Deviation
SDV	Source Data Verification
UK	United Kingdom
US	United States
V/Q scan	Ventilation–Perfusion Scan
WHO-DD	World Health Organization Drug Dictionary
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Marketing Authorization Holder:

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Principal Investigator(s) of the Protocol

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4. ABSTRACT

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

Rationale and background: Fragmin (dalteparin sodium) is a low molecular weight heparin (LMWH) initially approved by the U.S. Food and Drug Administration (FDA) for prophylaxis and treatment of VTE in adults in 1994. In May 2019, Fragmin became the first FDA-approved therapy to treat VTE in pediatric patients 1 month and older based upon data from a clinical trial in pediatric patients with VTE that was completed in 2018. This study was granted priority review status due to the urgent need for an FDA-approved treatment for VTE in pediatric patients. Due to the low VTE incidence specifically in neonates (≤ 28 days old), treatment with dalteparin has not been formally examined in this age group.

This non-interventional study (NIS) utilizing secondary (i.e., existing) data from routine clinical care is designed to characterize the safety, effectiveness and dosing of dalteparin in neonates treated for VTE. This NIS is designated as a Post-Authorization Safety Study (PASS) and is a Post-Marketing Requirement (PMR) to the FDA.

Research question and objectives: Neonates (≤ 28 days old and ≥ 35 weeks gestation) treated with dalteparin for VTE:

- Characterize the safety profile of dalteparin by examining evidence of major and minor bleeding and deterioration in hematological biomarkers (hemoglobin levels, platelet counts, prothrombin time, and partial thromboplastin time) among other serious events.
- Characterize the effectiveness of dalteparin by examining changes in relevant factor anti-Xa levels and VTE status.
- Describe dosing (starting dose and optimal therapeutic dose) of dalteparin and corresponding anti-Xa assay levels.

Study design: This will be a descriptive NIS in neonates (aged ≤ 28 days; ≥ 35 weeks gestation) treated with dalteparin for VTE. The study will utilize existing data from medical records dating back to 2010 at pediatric hospitals with demonstrated neonatology expertise.

Study population: Neonates aged ≤ 28 days exposed to dalteparin for the treatment of VTE will constitute the study population.

Inclusion and exclusion criteria:

The following are the inclusion criteria:

- Neonates aged ≤ 28 days at the time of dalteparin initiation and born at gestational age ≥ 35 weeks
- Diagnosis of VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), based on acceptable imaging modalities including compression ultrasound with doppler (CUD), computed tomography with/without venography (CT/CTV), magnetic

resonance imaging with/without venography (MRI/MRV), conventional venography (CV), conventional pulmonary angiogram (CPA), ventilation-perfusion (V/Q) scan, spiral CT angiography (SCTA)

- Received ≥ 1 dose of dalteparin for the treatment of VTE

The following is the exclusion criterion:

- Patients with bleeding disorders, including, but not limited to platelet dysfunction, disseminated intravascular coagulation, hemophilia, idiopathic thrombocytopenic purpura, or von Willebrand disease

Index date and follow up: The index date will be the date that the first dose of dalteparin was administered. Eligible patients will be followed from the index date to whichever of the following occurs first: 28 days after the last dose of dalteparin, death, lost to follow up based on documentation in medical records, or end of study period (i.e., 31 December 2020).

Variables: The study will be designed to collect data on demographic and clinical characteristics, as well as dosing, safety, and effectiveness of dalteparin. Definitions of variables that will be collected or derived for analyses will be included in the Statistical Analysis Plan (SAP).

Data sources: Study data will be collected from medical charts which meet the study criteria at pediatric hospitals in the US as well as potentially from the United Kingdom (UK) and Canada.

Study size: The goal is to collect data for at least 12 neonates who were treated with dalteparin for VTE.

Data analysis: Analyses will be descriptive in nature (i.e., no hypothesis will be tested) and conducted using SAS statistical software (version 9.3 or higher). All variables will be summarized descriptively through tabular displays of means, medians, interquartile ranges (IQRs), and standard deviations (SDs) for continuous or discrete variables, with frequencies and percentages reported for categorical variables. A detailed description of statistical methodology and analyses for this study will be documented in a separate Statistical Analysis Plan.

Milestones: It is anticipated that data collection will begin in January 2021. The final study report is expected to be submitted to the FDA by December 31, 2022. This planned timeline is, however, dependent on the FDA's review and endorsement of the study protocol.

5. AMENDMENTS AND UPDATES

Not applicable

6. MILESTONES

Milestone	Planned timeline
Registration in the EU PAS register	Prior to starting the data collection
Start of data collection*	01 January 2021
End of data collection*	30 June 2022
Final study report to the FDA*	31 December 2022

*The planned timeline will depend on FDA's review and endorsement of the study protocol

7. RATIONALE AND BACKGROUND

Venous Thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is an acute medical condition that occurs in both adult and pediatric patients that requires immediate medical attention. The incidence of thromboembolic disorders in pediatric patients is reported to be low, compared with adults (Jung H, 2016). The overall incidence of VTE is estimated to be 0.07 – 0.49 per 10,000 children. However, higher incidence rates have been observed in specific populations including hospitalized children, those with central venous catheters (CVCs) and patients convalescing from a major surgery (Mahajerin A, 2017). In a Pediatric Health Information System (PHIS) database, retrospective cohort study conducted from 2001 - 2007, the incidence of VTE increased from 34 hospital admissions (per 10,000 admissions) in 2001 up to 75 in 2007. This increase was observed in neonates, infants, children and adolescents with neonates and infants younger than a year-old accounting for about 50% of VTE in children (Raffini L, 2007). A 2008 systematic database review study found that occurrence of neonatal VTE has been estimated as high as 24 per 10,000 intensive care admissions (Young G, 2008). It has been reported that the rise in VTE incidence in pediatric patients could in part be due to a combination of improved supportive care for serious life-threatening illnesses, increased use of CVCs, and improved diagnostic techniques (Tarango C, 2017).

In general, recommendations for evaluation, treatment, and management of pediatric patients with VTE are primarily based on extrapolation of data from adult patients (Monagle P, 2008). Low molecular weight heparins (LMWHs) constitute the mainstay of anticoagulant therapy for pediatric patients with VTE (Raffini L, 2007). Fragmin (dalteparin sodium) is a LMWH initially approved by the Food and Drug Administration (FDA) for prophylaxis and treatment of VTE in adults in 1994. In May 2019, Fragmin became the first FDA-approved therapy to treat VTE in pediatric patients aged ≥ 1 month. The FDA's approval of Fragmin for VTE in pediatric patients ≥ 1 month of age was supported by the results of a Phase II clinical trial, "Fragmin for the Treatment of Acute VTE in Pediatric Cancer Patients (NCT00952380)." This clinical trial was granted priority review status due to the urgent need for an FDA-approved treatment for VTE in pediatric patients. The clinical trial was a single-arm open-label trial in pediatric patients up to 18 years of age with or without malignancies enrolled from 5 countries: United States (US), Norway, Russia, Spain, and Slovenia. Of a total of 38 patients (1 of these patients was a neonate) enrolled in the study, 21 (61.8%) patients achieved a clinical response of resolution with no clinical responses of progression in the qualifying VTE, 7 (20.6%) showed signs of regression, and 2 did not exhibit any substantial changes. No new safety concerns were identified, and the overall safety profile of dalteparin was consistent with the established safety profile in adults. Dalteparin is being used to treat neonates with VTE by pediatricians in the US. However, the efficacy and safety of dalteparin in neonates (aged≤ 28 days) treated for VTE have not been formally examined in randomized controlled trials (RCTs), as conducting an adequately powered study with a sufficient sample size may not be feasible due to very low VTE incidence in this age group. Further, it is likely that the prospective recruitment of neonates with VTE would result in an inadequate sample size even over an extended period.

Therefore, a non-interventional study (NIS) utilizing secondary (i.e., existing) data from routine clinical care has been designed to examine safety, effectiveness and dosing of dalteparin among neonates treated for VTE. This study design offers certain advantages. First, it evaluates the treatment of VTE with dalteparin in a real-world setting, which offers greater generalizability of study findings than a clinical trial with stringent eligibility criteria. Second, a study utilizing retrospective/existing data can be completed in less time when compared with a prospective study. Additionally, the use of real-world evidence to inform regulatory decisions is consistent with the 21st Century Cures Act (Cures Act).

This NIS is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing requirement (PMR) to the FDA.

8. RESEARCH QUESTION AND OBJECTIVES

Neonates (≤ 28 days old, and ≥ 35 weeks gestation) treated with dalteparin for VTE:

- Characterize the safety profile of dalteparin by examining evidence of major and minor bleeding and deterioration in hematological biomarkers (hemoglobin levels, platelet counts, prothrombin time, and partial thromboplastin time) among other serious events
- Characterize the effectiveness of dalteparin by examining changes in relevant factor anti-Xa levels and VTE status
- Describe dosing (starting dose and optimal therapeutic dose) of dalteparin and corresponding anti-Xa assay levels

9. RESEARCH METHODS

9.1. Study design

This will be a descriptive NIS among neonates (≤ 28 days old and ≥ 35 weeks gestation) treated with dalteparin for VTE. The study will utilize available existing data from medical records dating back to 2010 at pediatric hospitals with demonstrated neonatology expertise.

9.2. Setting

This study will be conducted in up to 10 sites with demonstrated neonatology expertise. These are likely to be large pediatric hospitals that treat critically ill neonates and will be identified through a site feasibility assessment. Major pediatric hospitals in the US will be first targeted to recruit the study eligible patients. If feasible, patients from pediatric hospitals in the United Kingdom (UK) or Canada may also be recruited to achieve the study sample size. A feasibility assessment designed to identify pediatric hospitals with potentially eligible study patients will be conducted. The feasibility assessment will also evaluate institutional review board (IRB)/Ethics Committee (EC) requirements (e.g. local versus central IRB/EC) and review/approval timing, electronic medical record EMR)/electronic health record (EHR) capabilities for completing chart abstraction via an electronic data capture (EDC) system, and the individual site's experience with similar studies (i.e., non-interventional secondary data collection/chart review studies).

9.2.1. Inclusion criteria

Patients must meet all of the following criteria to be eligible for inclusion in the study:

- Neonates aged ≤ 28 days at the time of dalteparin initiation and born at gestational age ≥ 35 weeks
- Diagnosis of VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), based on acceptable imaging modalities including compression ultrasound with doppler (CUD), computed tomography with/without venography (CT/CTV), magnetic resonance imaging with/without venography (MRI/MRV), conventional venography (CV), conventional pulmonary angiogram (CPA), ventilation-perfusion (V/Q) scan, spiral CT angiography (SCTA)
- Received ≥ 1 dose of dalteparin for the treatment of VTE

9.2.2. Exclusion criteria

Patients meeting the following criterion will not be included in the study:

- Patients with bleeding disorders, including, but not limited to platelet dysfunction, disseminated intravascular coagulation, hemophilia, idiopathic thrombocytopenic purpura, or von Willebrand disease

9.3. Index date and follow-up

The index date will be the date of initiation of dalteparin dosing, as documented in the medical records. The study eligible patients will be followed from the index date to whichever of the following occurs first:

- Twenty-eight (28) days after the last dose of dalteparin,
- Death,
- Lost to follow up based on documentation in medical records, or
- End of study period (i.e., 31 December 2020)

9.4. Lost to follow-up

Lost to follow-up is defined as no follow-up visit documented in medical records at or beyond 28 days after the last dose of dalteparin if a patient is discharged soon (i. e., ≤ 28 days) after the last dose.

Note: Once exposed to dalteparin, patients will be considered exposed until the end of follow-up, as described above, regardless of dalteparin discontinuation or a switch to another anticoagulant.

9.5. Variables

This section describes the exposure, outcomes, and other study variables that will be collected and analysed in this study.

9.5.1. Exposure variable

The following data on dalteparin will be collected (if available) from each patient's medical chart:

- Each dose, date and time of dose
- Dose interruption, discontinuation or switching to another anticoagulant with respective dates (including reasons for interruption or discontinuation, if documented)
- Duration of dalteparin use (start and stop dates)
- Indication/use of dalteparin (e.g. VTE)

9.5.2. Outcome variables

Data on safety endpoints, treatment, and effectiveness outcomes will be collected from medical records, as described below.

Safety endpoints

Data on the following safety events of interest, irrespective of causal relationship to therapy, will be collected in this study:

- Major or minor bleeding events, and deterioration in hematological biomarkers, including platelets, hemoglobin, prothrombin time, and partial thromboplastin time
- Serious events are undesirable events that result in death, are life-threatening, require hospitalization, prolongation of hospitalization, or result in persistent or significant disability/incapacity

Effectiveness assessment/endpoints

To assess effectiveness of dalteparin, the data abstractor will review medical records (e.g., daily progress notes from treating physicians, laboratory data, and radiology/imaging, as available), abstract data pertinent to clinical response to dalteparin treatment, such as progression, regression, resolution, recurrence, or no change in VTE, and changes in anti-Xa levels after treatment initiation, and enter these data into the electronic case report form (eCRF). Training will be provided to participating sites regarding key data to be collected and investigator data validation.

9.5.3. Covariates

Data on demographic and clinical variables will be collected including:

- Year of birth / age (days) at the time of first dose
- Gender
- Race / ethnicity
- Hospital admission and discharge dates, including the neonatal intensive care unit (NICU) / intensive care unit (ICU) admissions
- Length and weight at birth and at the time of dalteparin initiation

- Diagnosis of VTE (including method of diagnosis, date of diagnosis, and results of assessment)
- Presence of comorbidities at the time of dalteparin first dose
- Concomitant medications (medications administered from birth through end of follow-up)
- Targeted laboratory results, including results on platelets, hemoglobin, prothrombin time, and partial thromboplastin time before and after treatment with dalteparin
- Central venous access device (CVAD) at baseline and during follow-up
- Endotracheal intubation at baseline and during follow up
- Procedure / surgery at baseline and during follow-up
- Use of mechanical ventilator including start and stop dates

9.6. Data sources and collection

All data on dalteparin use, safety, and effectiveness, as well as other demographic and clinical variables, will be retrospectively collected from eligible patient medical records at the participating sites admitted between January 2010 and December 2020. Chart abstraction will be performed at a single time point for each enrolled patient. The data will be entered into the eCRF by the data abstractors at each participating site.

To ensure quality data collection, pilot testing of the eCRF will occur during qualitative telephone interviews with at least 3 specialty pediatric clinicians prior to the start of data collection. The pilot testing will evaluate whether or not the eCRF content and wording can be easily and correctly understood by the specialty clinicians. If feasible, 1-2 participating study investigators will also test the eCRF within the database to ensure utility and that the final eCRF is capturing the necessary data appropriately prior to the start of data collection.

9.7. Study size

This is a descriptive study and is not intended to test a formal hypothesis. The goal is to collect data for at least 12 neonates who were treated with dalteparin for VTE.

9.8. Data management

All study data collected from medical records will be stored within a validated electronic data capture (EDC) system at secure servers and maintained by trained data study personnel ensuring compliance with all applicable regulations. The collected data will be evaluated by checking variable distributions to ensure they are within expected ranges, verifying that any skip logic in the eCRF has functioned correctly, and any screening items to confirm that only data from patient charts meeting all inclusion (and no exclusion) criteria have been collected. For any computed or recoded variables, crosstabulations and frequencies will be periodically checked against the original variables to verify the accuracy of the computed/recoded variables. SAS (v9.3 or higher) will be used to conduct the statistical analyses.

9.8.1. Case report forms (CRFs)/Electronic data record

As used in this protocol, the term CRF/Data Collection Tools (DCTs) should be understood to refer to an electronic data record.

A CRF/DCT is required and should be completed for each included patient. The completed original CRFs/DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. Kantar shall ensure that the CRFs/DCTs, within the EDC, are securely stored at their research location within encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

Kantar has ultimate responsibility for the collection and reporting of all data entered on the CRFs/DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs/DCTs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs/DCTs are true. Any corrections to entries made in the CRFs/DCTs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents for this study are within the medical records for the appropriate patient's chart only. In these cases, data collected within the CRFs/DCTs must match those charts.

All data will be collected retrospectively from patient charts. Data will be directly entered into a standardized eCRF by qualified staff at the study sites. Missing or implausible data will be queried, and the data will be validated. The fields and variables subject to edit checks are to be agreed upon prior to implementing. Any record change will be available to be audited in an audit trail file. All data will be stored centrally in an EDC database with restricted access that is maintained according to all current standards for hardware and software security as dictated by applicable data protection legislation. Secure logins will be assigned to all staff members who are involved in data collection. An EDC system that is validated according to FDA 21 Code of Federal Regulations Part 11 will be used.

Every effort will be made to protect patient confidentiality. Only appropriate site study staff and the assigned Clinical Research Associate (CRA), whom will monitor the study site source data to ensure quality and correctness of the data, will be able to identify patients based on the patient identification code. No confidential information will be disclosed to Pfizer Inc.

Baseline comorbidities, safety events of interest such as minor and major bleeding events and surgeries will be coded using the current version at time point of patient data transcription to the eCRF of the Medical Dictionary for Regulatory Activities (MedDRA), and prior and concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD).

A data management plan (DMP) will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation.

9.8.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Kantar agrees to keep all study-related records, e.g., CRFs/DCTs, copies of all CRFs/DCTs, appropriate regulatory documents, safety reporting forms, source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by Kantar according to local regulations or as specified in the research agreement, whichever is longer. Kantar must ensure that the records continue to be stored securely for so long as they are retained.

If Kantar becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Kantar and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

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

9.9. Data analysis

A brief overview of the analyses planned for the current study is described below. Details on statistical methodology and analyses will be provided in the Statistical Analysis Plan (SAP). Descriptive analyses (no formal hypothesis-testing) will be conducted to address all study objectives. Frequencies and percentages to describe categorical variables and means and SDs (or medians with IQRs, where appropriate) for continuous or discrete variables will be calculated.

Imputation of missing data is not currently planned. Rather, all variables will include a category for missing values, and the frequency and percentage of missing data on each variable will be reported, if applicable. However, the extent of the missing data will be evaluated at the time of data analysis. In case of substantial missing data, appropriate statistical techniques for imputing missing data will be considered and documented in the final study report, if applicable.

Analysis Populations

Safety population

All eligible patients will be included in the analysis of safety outcomes.

Dosing and effectiveness population

Study.

9.10. Quality control

Kantar will follow their standard procedures to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data.

For the monitoring activities, Kantar will prepare a Monitoring/Quality Review Plan describing all site-related quality review. A combination of on-site and remote monitoring visits will be performed to obtain information on chart review status and related entry criteria confirmation, discuss any issues that might arise during data collection, and ensure quality and data completeness supported by programmed edit checks in the EDC.

The source data verification (SDV) will be determined after approximately 50% of the study data is collected, to ensure accurate sampling of the study data across sites. It is planned to have every site receive at least one on-site visit. Kantar will conduct approximately 20% on-site SDV (20% of the available data on site at the time of each visit) to validate that the original record (i.e. source document) of the patient chart matches the data that has been entered the EDC. Any discrepancies will be queried by the CRA and resolved by the site investigator as appropriate within the eCRF system. If determined the site meets a threshold of significant discrepancies, outlined in the study monitoring plan or they are high enrollers for the study there may be cause for additional visits.

9.11. Strengths of the research methods

Limited data are available on dalteparin use among neonates treated for VTE. Although the study is not intended for hypothesis testing, this study will examine the safety, effectiveness and dosing of dalteparin in this patient population.

The study is expected to utilize real-world data (RWD) on dalteparin use among neonates from several pediatric hospitals. Medical record abstractions provide a unique opportunity to collect and analyze RWD outside of the highly controlled setting of clinical trials. In addition, this methodology allows for the collection of information on clinical characteristics, treatment patterns, and outcomes that might not otherwise be available in alternative administrative data sources, such as insurance claims. Other strengths of this study are defined by the assessment of treatment patterns and outcomes in a standardized manner across all participating sites to maximize validity of results.

9.12. Limitations of the research methods

Small sample size and large variability in patient characteristics/variables, may pose a challenge for the meaningful interpretation of the data. Nonetheless, the study will provide pertinent data on dalteparin dosing in the neonatal population treated for VTE and permit the identification of safety signals for further refinement. There is no control group in this study; therefore, comparisons with neonates who were not treated with dalteparin is not possible.

The intent of this study is to describe safety, effectiveness, and dosing data among neonates treated with dalteparin without testing a formal hypothesis.

Inter-individual variability in performing chart abstraction could lead to a difference in the way in which safety and/or effectiveness endpoints and dosing data will be collected. However, training the CRA and data abstractors along with a structured eCRF for all sites, will help to maintain data abstraction consistency across sites and minimize data ascertainment bias. The assigned CRA will also be fully trained on the eCRF in order to guide the sites regarding data collection and ensure data quality.

It is also possible that treatment protocols among institutions might differ, leading to differences in patient management across sites. That said, this study will provide a cross-sectional overview of RWD on current patient management and outcomes. Limitations are also linked to the retrospective observational study design, which may increase the likelihood of incomplete data and does not allow causal inferences to be drawn. However, every effort will be made to collect all relevant data in a consistent way across sites.

9.13. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

All data will be obtained retrospectively from patient charts. Thus, no additional diagnostic, therapeutic, or monitoring processes are required for patients participating in this study.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer Inc. is not required.

10.3. Institutional review board (IRB)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs. All correspondence with the IRB must be retained. Copies of IRB approvals must be forwarded to Pfizer Inc.

10.4 Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP), Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, Council for International Organizations of Medical Sciences (CIOMS), International Ethical Guidelines for Epidemiological Studies, and the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

11. REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires a human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer Inc. drug that appears in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the NIS adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appears in the reviewed information must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form

- Scenarios involving drug exposure, medication error, overdose, including exposure during pregnancy, exposure during breast feeding, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must

be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form

For AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered valid in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (MM/YYYY) format, rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer Inc. training requirements:

- "Your Reporting Responsibilities (YRR) Training for Vendors Working on Pfizer Inc. Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*"*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer Inc.

Re-training must be completed on an annual basis using the most current YRR training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered at the EU PAS Register, and the results will also be posted at this register after completion. The study may potentially lead to manuscripts that will be submitted to peer-reviewed scientific journals.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by any applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer Inc. product, Pfizer Inc. should be informed immediately.

13. REFERENCES

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