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

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The primary objective of this study is to:* To determine the PD profiles for treatment doses of dalteparin in pediatric subjects of different ages with or without cancer and VTE, using anti-Xa levels and a population PD analysis methodology;* To...

Ethical review	Not approved
Status	Will not start
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON46293

Source
ToetsingOnline

Brief title
FRAGMIN

Condition

- Embolism and thrombosis

Synonym
blood clot in the vein, VTE

Research involving

Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: pharmaceutical industry

Intervention

Keyword: Children, FRAGMIN, Venous thromboembolism

Outcome measures

Primary outcome

Primary Endpoints:

* Determine the median dose of dalteparin (IU/kg) associated with the

achievement of the therapeutic anti-Xa level (0.5-1.0 IU/mL) among subjects

that achieved their therapeutic anti-Xa level duringthe dose adjustment phase,

for each age cohort group;

* Anti-Xa activity versus time profile following dalteparin treatment will be

explored using a population PD analysis methodology.

Population PD parameters such as clearance, volume of distribution, absorption

rate constant will be estimated based on anti-Xa levels collected during dose

adjustment phase, PD phase and follow-up phase. Age and other relevant

covariates will be explored in the population PD analysis.

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Secondary outcome

Efficacy Endpoints (all are secondary):

* Proportion of subjects achieving an anti Xa therapeutic range of 0.5 to 1.0

IU/mL during the Dose Adjustment Phase;

* Proportion of subjects with objectively documented new or progressive

symptomatic VTE during dalteparin treatment;

* Proportions of subjects with progression, regression, resolution, or no

change in the qualifying VTE during dalteparin treatment;

* Time to first episode of recurrent VTE during dalteparin treatment.

Safety Endpoints

(all are secondary):

* Proportion of subjects with major bleeding during dalteparin treatment;

* Proportion of subjects with minor bleeding during dalteparin treatment;

* Relationship between major bleeding event and the Anti-Xa level during

dalteparin treatment if data permits;

* Description of subjects' adverse events (AE) throughout the study period;

* Summary of chemistry, hematology, vital signs and physical examinations;

* Time to first major bleeding events during dalteparin treatment.

Study description

Background summary

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

The FDA indicated that a post-approval study to investigate the safety and efficacy of dalteparin in a pediatric cancer population requiring anticoagulation was warranted.Following a Type C Meeting with FDA on October 5, 2015, this study now includes both pediatric patients with and without cancer. This phase II pharmacodynamic (PD) study is intended to provide information to guide the conditions under which dalteparin may be used for the acute treatment and secondary prophylaxis of recurrent VTE in children with or without cancer.

Study objective

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

Study design

A prospective, multicenter, open-label cohort study in North America and Europe Divided into three phases: Dose Adjustment Phase, PD Phase and Follow- up Phase.

Intervention

The initial doses of the study drug (FRAGMIN® dalteparin sodium) are:

* Participants who are ages newborn to less than 8 weeks will receive an initial dose of 125 IU/kg twice-daily.
* Participants who are greater than or equal to 8 weeks up to less than 2 years (infant) will receive an initial dose of 150 IU/kg twice-daily.
* Participants who are greater than or equal to 2 years through less than 12 years (pre-school through school) will receive an initial dose of 125 IU/kg twice-daily.
* Participants who are ages greater than or equal to 12 years and less than 19 years (teen) will receive an initial dose of 100 IU/kg twice-daily.

After the initial dose of FRAGMIN® is given, there is a Dose Adjustment phase which will determine if this initial dose is adequate to dissolve the clot.

Study burden and risks

Most of the procedures described in the protocol are also part of standard treatment of VTE in paediatric patients. The following may be done extra as part of this study:
-a physical examination at the beginning of the study.

-There will be more blood draws compared to standard treatment The total amount of blood drawn will be approximately 90 - 120 ml throughout the 3 months of this study, depending on the child*s age and weight
-The study drug will be injected twice a day instead of once a day.
-There may also be more hospital visits compared to what a patient normally would have, especially if the patient isn't hospitalized.
-time investment for the patient or the parents for the phone follow-up.

As to the risks of the study drug, the benefit-risk profile of dalteparin is well known and favorable for the approved therapeutic indications. There are no quantitative or qualitative findings that suggest the safety profile in paediatric patients to be different from the overall safety profile for dalteparin.The combination of the published data and recognition that for more than 10 years children worldwide have been treated with Low Molecular Weight Heparins including dalteparin for VTE, outside of the approved indication, supports the safety of the recommended doses in children in this trial.

The use of dalteparin is well established in current paediatric clinical practice. The available efficacy and safety data characterizing the use of dalteparin in paediatric patients suggest a benefit for the use of dalteparin in paediatric patients. These data and guidelines also provide clinicians with target anti-Xa ranges and corresponding dalteparin doses to initiate and guide both prophylaxis and treatment of VTE in paediatric patients. Importantly, however, no specific dose can be recommended for all paediatric patients at this time. The correct dose for these patients remains adaptable and mostly driven by the target anti-Xa range. The paediatric subjects in this trial receive a treatment for their VTE under close clinical supervision and monitoring of their anti-Xa-levels. The subjects will further benefit from the individual dose adjustments, based on age and weight, to achieve the anti-Xa therapeutic goal range of 0.5 to 1.0 International Units [IU]/mL.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Subjects meet inclusion if all of the following are true:;1. Have been objectively diagnosed with a venous thrombotic event documented using one of the following acceptable imaging modalities within 4 days of the Screening Visit:
* - Compression ultrasound with Doppler [CUD];;* - Computed tomography with/without venography [CT/CTV];;* - Magnetic resonance imaging with/without venography [MRI/MRV];;* - Conventional venography [CV];;*- Ventilation-perfusion scan [V/Q] (for pulmonary artery);;* - Spiral CT angiography [SCTA];;* - Conventional pulmonary angiogram [CPA].;2. Are judged clinically to require anticoagulation therapy.;3. Are in the age range of *36 weeks gestation and <19 years at Screening.;4. Have given signed informed consent (and assent, as appropriate) to participate prior to Screening Visit.;5. For cancer patients, a diagnosis of active malignancy (currently under treatment), other than basal cell or squamous cell carcinoma of the skin.
6. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.
7. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
8. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:
a. Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or psychiological cause; [status may be confirmed with/and have] a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;

b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
c. Have medically confirmed ovarian failure
9. All other female subjects (including female subjects with tubal ligations) are considered to be of child bearing potential.

Exclusion criteria

Subjects are excluded if any one of the following apply:;1. Weight *3.0 kg or >100 kg at Screening Visit;2. Platelet count * 50,000/mm (despite appropriate medical measures to support platelet count).;3. Received oral anticoagulant (OAC) therapy within 3 days of the Screening Visit.;4. History of administration of therapeutic doses of LMWH (low molecular weight heparin) or unfractionated heparin for a period of > 4 days (or > 8 doses of LMWH) for the qualifying VTE.;5. Received unfractionated heparin within 3 hours, or LMWH within 12 hours, of the first dose of dalteparin.;6. Acute VTE intervention which includes thrombolytic therapy.;7. Subjects with major bleeding or bleeding disorders such as Platelet Dysfunction, Protein Deficiency, Disseminated Intravascular coagulation (DIC), Factor Deficiency, Hemophilia, Idiopathic Thrombocytopenic Purpura (ITP) or Von Willebrand Disease at the time of the Screening Visit or an
unacceptably high risk of bleeding, at the discretion of the investigator, should not be considered candidates.;8. Activated partial thromboplastin time (aPTT) *5 seconds above upper limit of normal (ULN), and that corrects to within normal limits upon 1:1 mixing with normal plasma.;9. Prothrombin time (PT) *2 seconds above ULN, and that corrects to within normal limits upon 1:1 mixing with normal plasma.;10. Creatinine clearance < 60mL/min/1.73m2 in subjects > 1 month of age.;11. Uncontrolled hypertension characterized by a sustained systolic pressure or diastolic pressure > 99th percentile of age- and heightrelated norms.;12. History of heparin-induced thrombocytopenia (HIT).
13. Any condition in which the investigator feels the subject is unsafe or inappropriate for study participation.
14. Participation in other clinical studies involving investigational drug(s) within the past 30 days.
15. Insufficient subcutaneous tissue to facilitate subcutaneous drug administration.
16. Pregnant female subjects; breastfeeding female subjects; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of assigned treatment.
17. Unable or unwilling to comply with scheduled follow-up visits.

Study design

Design

Study phase: 2

Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	FRAGMIN
Generic name:	Dalteparin Sodium
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	01-03-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Not approved

Date:	21-03-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000394-21-NL
ClinicalTrials.gov	NCT00952380
CCMO	NL58046.041.16