Dalteparin Sodium Injection (FRAGMIN®), Multicenter, Open Label, Single-Arm, Long Term (52 weeks) Study for Understanding Safety and Efficacy in Subjects with Malignancies and symptomatic Venous Thromboembolism

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON33828

Source
ToetsingOnline

Brief title
FRAG-A001-401

Condition

- Miscellaneous and site unspecified neoplasms benign
- Embolism and thrombosis

Synonym
blood clot, cancer

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: The Sponsor;Eisai Inc;will finance this clinical trial.

Intervention

Keyword: Malignancy, Phase IV, Safety, Thromobembolism

Outcome measures

Primary outcome

The primary safety endpoint is a comparison of the rates of major bleeding events for the intervals of 2-6 months and 6-12 months.

Primary efficacy endpoint is to evaluate the proportion of subjects with symptomatic, new or recurrent, lower limb DVT, PE, or CVT occurring while the subject is on treatment with dalteparin.

Secondary outcome

The secondary safety endpoints are to evaluate the rate of major and minor bleeding events at monthly intervals. Secondary efficacy endpoints includes to evaluate the time to symptomatic, objectively documented DVT, PE, or CVT and the time from the date of first treatment to the date of first objective documentation of VTE

Study description

Background summary

Dalteparin sodium (Fragmin®) is a low molecular weight heparin (LMWH), produced

by degradation of heparin, a member of the glycosaminoglycan family of biological entities found in the intestinal mucosa. Dalteparin was first approved in the US in December 1994 for primary prophylaxis of deep vein thrombosis (DVT) in subjects undergoing abdominal surgery. On May 1, 2007, the FDA approved dalteparin for the extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or PE), to reduce the recurrence of VTE in subjects with cancer. The pathogenic mechanisms of thrombosis in subjects with cancer involve a complex interaction between the tumor cell, the subject, and the hemostatic system. When compared to subjects without cancer, cancer subjects are far more prone to develop venous thromboembolism (VTE); in fact, VTE may represent the initial presenting finding for an otherwise occult cancer. Multiple retrospective studies have shown that cancer-associated thrombosis (CAT) is a significant entity previously under-recognized and under-treated. Relative to cancer-free subjects with symptomatic VTE, cancer subjects with VTE are more prone to recurrence and to treatment-related bleeding complications. VTE has been reported in up to 30% of subjects with cancer at autopsy. 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 clear 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.
As there are currently no data on dalteparin treatment beyond six months in this patient population, this study will evaluate the safety and efficacy of dalteparin treatment for up to 52 weeks in subjects with cancer and VTE.

Study objective

The primary objective of the study is to determine the rate of major bleeding events in cancer subjects receiving extended treatment with dalteparin (> 6 months and up to 12 months) for prevention of recurrent symptomatic venous thromboembolism (VTE). Major bleeding event rates will be evaluated for all subjects.
Secondary objectives will be to determine for all Subjects: 1) the rate of recurrent VTEs during treatment; 2) time to symptomatic recurrent VTE; 3) the rate of minor bleeding events; 4) time to first major bleeding event; 5) time to first bleeding event (any bleeding event); and 6) the safety and tolerability of extended treatment with dalteparin.
Additional secondary objectives include evaluating the utility of measuring anti Factor Xa (anti-Xa) activity to manage dose adjustment in subjects who present with or develop severe renal impairment (CrCl < 30 mL/min).

Study design

This is a 52 week open-label study to evaluate the safety and efficacy of dalteparin sodium
(Fragmin®) in cancer subjects receiving extended treatment with dalteparin. All subjects
enrolled will receive 200 IU/kg of dalteparin once daily for the first four weeks. The dose should
then be decreased to 150 IU/kg for the duration of the study (up to 48 weeks).

Intervention

Dalteparin will be administered once daily at a dosage of 200 IU/kg for the first 4 weeks (28 ± 5 days) and then reduced to 150 IU/kg for the duration of the study (up to 48 weeks). Dalteparin sodium (Fragmin) will be provided as multidose vials of 25,000 IU/mL and single dose pre-filled syringes. Total daily dose should not exceed 18,000 IU.
Treatment will be continued for a maximum of 12 months (52 weeks) or until any of the following occurs: 1) new or recurrent VTE; 2) development of central venous thrombosis of the upper limb(s), neck, or chest; 3) bleeding necessitating permanent discontinuation of anticoagulant therapy; 4) other adverse event necessitating discontinuation of study drug; or 5) withdrawal of informed consent, or 6) removal of subject by primary investigator for any other significant medical reason

Study burden and risks

The following are some of the side effects that might occur for patients receiving FRAGMIN®:
Patients may start bleeding, although this is rare when the normal doses are given.
Certain substances produced by the liver may increase, but this has not been shown to cause you any harm.
If the patient has an artificial heart valve, treatment with FRAGMIN® might not be sufficient to prevent a blood clot, and you might develop a clot in the heart valve.
Special care is needed if the patient is receiving FRAGMIN® for the prevention of blood clots and have to have a spinal or epidural anesthetic.
The patient may develop a bruise where he/she has been injected. Very rarely, when FRAGMIN® is used at the time as spinal anesthesia or puncture, bruising of the spine may occur. For this reason, patients must tell a doctor immediately if any of the following occur: back pain, tingling, numbness or weakness in the legs, bowel or bladder problems.
In rare cases there may be a decrease in the number of clotting cells (platelets) in the blood.
Osteoporosis (a reduction in bone density leading to bones which may fracture

easily) has occurred after long term treatment with a similar medicine called heparin. It is possible that this could happen with FRAGMIN®.
Medicines like FRAGMIN® can rarely cause temporary muscle weakness, loss of feeling, or changes in the patients' heartbeat.
Allergic reactions can occur rarely (some patients have reported slight hair loss, rashes, or itching). Severe allergic reactions have occurred in a few cases. Symptoms of any allergic reaction can include a rash, hives, itching, and/or difficulty breathing, closing of the throat, swelling of the lips, tongue or face, and rarely death.
Other Risks:
If a CT scan is performed, the patient will be exposed to a small amount of radiation. The MRI scan does not expose the patient to x-ray radiation. However, during the MRI the patient will have to lie still on the back in the MRI scanner, which is a tight space. This may be difficult for patients with claustrophobia.
Risks associated with drawing blood include: possibility of discomfort while the blood is being drawn or for a short time afterward, possibility of bruising or bleeding at the needle puncture site, and rarely, infection at the needle puncture site. Other possible side effects from blood draws include lightheadedness and/or fainting.

Reproductive Risks
There are no adequate and well-controlled studies in pregnant women with FRAGMIN®. The effects of the study drug on an unborn baby are unknown. Females who are sexually active and/or are capable of becoming pregnant are asked to follow an acceptable method of birth control such as abstinence, oral contraceptive (the pill), injectable contraceptive, implantable contraceptive, IUD or double barrier method (e.g., a condom and foam) throughout the study. Females who become pregnant may remain in the study if the study doctor feels that the potential benefit is greater than any potential risk to the unborn child.

Contacts

Public
Eisai

100 Tice Blvd.
Woodcliff Lake, NJ 07677
US
Scientific
Eisai

100 Tice Blvd.

Woodcliff Lake, NJ 07677
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age range: subjects must be >= 18 years of age.
2. Male and female subjects will be eligible for enrollment.
3. Females should be either of non-childbearing potential as a result of surgery, radiational therapy, menopause (one year post onset), or of childbearing potential and willing to adhere to an acceptable method of contraception
4. Subjects must be newly diagnosed, symptomatic proximal deep-vein thrombosis of the lower extremity, pulmonary embolism, or both.
5. Subjects must have active malignancy defined as a diagnosis of cancer (excluding basal cell or squamous cell carcinoma of the skin) within six months before enrollment, having received any treatment for cancer within the previous six months, or having documented recurrent or metastatic cancer.
6. Prior to enrollment, subjects must not have received therapeutic doses of anticoagulant therapy (including LMWH) for > 48 hours (or > 4 doses within 48 hours). Subjects must not have received unfractionated heparin within 4 hours prior to enrollment.
7. ECOG performance status of 0, 1 or 2.
8. Subjects must have a life expectancy of > 6 months.
9. Subjects must have a platelet count of > 75,000 mm3.
10. The subject must not be on any oral anticoagulant therapy for concomitant diseases.
11. Subjects must have no active or serious bleeding episodes within two weeks prior to study entry.
12. Subjects must be able to comply with scheduled follow-ups.
13. Subjects must give written informed consent

Exclusion criteria

1. Subjects who have a high risk of serious bleeding (e.g. recent neurosurgery, history of intracranial hemorrhage, acute gastroduodenal ulcer, etc.).
2. Subjects who are on hemodialysis.
3. Subjects who have a prior placement of a greenfield filter or other device to prevent embolization of DVTs.
4. Subjects with a known contraindication to the use of heparin (e.g. heparin-induced thrombocytopenia).
5. Subjects with a known hypersensitivity to heparin, dalteparin, other LMWHs or pork products.
6. Subjects who are currently participating in another clinical trial involving anticoagulation therapy (with the exception of aspirin), participating in a clinical trial involving anticoagulation therapy (with the exception of aspirin) in the 30 days prior to study entry, or who is actively using any investigational drugs/treatments 30 days prior to study entry involving anticoagulation therapy (with the exception of aspirin x 3).
7. Subject is pregnant or breast feeding.
8. Subjects with uncontrolled hypertension characterized by a sustained systolic pressure > 170 mmHg and/or diastolic pressure > 100 mmHg.
9. Subjects with a serious concomitant systemic disorder (for example, active infection including HIV or cardiac disease) that in the opinion of the investigator, would compromise the subject*s ability to complete the study.
10. Any condition that makes the subject unsuitable in the opinion of the investigator.
11. Subjects with acute leukemia.
12. Subjects with a genetic predisposition to clotting.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	11-08-2010
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fragmin
Generic name:	Dalteparin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-01-2009
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-09-2009
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-11-2009
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-03-2010
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2008-005236-32-NL
CCMO	NL26280.060.08