Reduced-dosed rivaroxaban and standard-dosed rivaroxaban versus ASA in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis and/or pulmonary embolism The Einstein Choice Study

Published: 16-04-2014
Last updated: 20-04-2024

1. The primary efficacy objective is to evaluate whether rivaroxaban, in doses of 10 mg or 20 mg, is superior to ASA 100 mg in the prevention of the primary efficacy outcome (i.e. fatal or non-fatal symptomatic recurrent venous thromboembolism).2....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON41605

Source
ToetsingOnline

Brief title
The Einstein Choice-study

Condition

- Embolism and thrombosis

Synonym
Symptomatic venous tromboembolism / Blood clots

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Sponsor: Bayer

Intervention

Keyword: Acetylsalicyclic acid (ASA), Rivaroxaban, venous thromboembolism

Outcome measures

Primary outcome

The primary efficacy objective is to evaluate whether rivaroxaban, in doses of 10 mg or 20 mg, is superior to ASA 100 mg in the prevention of the primary efficacy outcome (i.e. fatal or non-fatal symptomatic recurrent venous thromboembolism).

The principal safety objective is to document the incidence of the principal safety outcome (i.e. major bleeding).

Secondary outcome

The secondary efficacy objective is to evaluate whether rivaroxaban 10 mg and rivaroxaban 20 mg are superior to ASA 100 mg in the prevention of the secondary efficacy outcome (i.e. fatal or non-fatal symptomatic recurrent venous thromboembolism, myocardial infarction, ischemic stroke, systemic non-CNS embolism).

The secondary safety objective is to document the incidence of the secondary safety outcome (i.e. clinically relevant non-major bleeding).

Additional study objectives are to evaluate

a. the composite of non-fatal symptomatic venous thromboembolism and all cause

mortality

b. the composite of major bleeding and recurrent venous thromboembolism

c. the composite of major bleeding, recurrent venous thromboembolism,

myocardial infarction, ischemic stroke and systemic non-CNS embolism

Study description

Background summary

Acute VTE, i.e. DVT or PE is a common disorder with an annual incidence rate of approximately 1-2 per thousand. Based on the reported incidence rates for VTE, the VITAE study described the extent of the health burden attributed to VTE in France, Germany, Italy, Spain, Sweden and the UK as a total of 460,000 incident and recurrent non-fatal DVT, 300,000 PE, and 370,000 VTE related deaths per year. VTE is not only a burden for healthcare systems due to its high mortality and considerable morbidity in terms of recurrent VTE, but also due to the associated risk of long-term sequelae of post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension. Treatment of DVT and PE has two aims: To prevent the extension of the existing thrombus and to prevent recurrent VTE. Treatment with vitamin K antagonists (VKAs) is challenging because of multiple drug and food interactions and because it requires ongoing coagulation monitoring leading to subsequent dose adaptations. The incidence rate of recurrent VTE is around 5*10% in the year after discontinuation of VKA and is around 30% after 8 years. The annual risk of major bleeding with VKAs is1-2% after the first year of treatment. As a result of the very high risk for recurrent VTE after the presentation of acute, symptomatic DVT and/or PE, there is a wide consensus among physicians to treat patients with therapeutic-dosed anticoagulants, despite the well documented high risk for major bleeding. After the first months of treatment, the risk of recurrent VTE diminishes as does the risk of major bleeding. During this period, the focus of physicians and patients deviates from prevention of recurrent venous thromboembolism to minimizing the risk of (anticoagulantinduced) bleeding, and the general burden of monitored and adjusted dose anticoagulant treatment. The duration of treatment with anticoagulants is recommended to be individualized for as long as the balance between the risk for recurrent VTE, the associated bleeding risk, and the burden of anticoagulation remains favorable. The current American College of Chest Physicians (ACCP) guidelines recommend long-term treatment in

conjunction with periodic benefit-risk assessment in patients with first unprovoked PE or proximal DVT, second unprovoked VTE or VTE in active cancer and low-moderate bleeding risk.

Study objective

1. The primary efficacy objective is to evaluate whether rivaroxaban, in doses of 10 mg or 20 mg, is superior to ASA 100 mg in the prevention of the primary efficacy outcome (i.e. fatal or non-fatal symptomatic recurrent venous thromboembolism).

2. The secondary efficacy objective is to evaluate whether rivaroxaban 10 mg and rivaroxaban 20 mg are superior to ASA 100 mg in the prevention of the secondary efficacy outcome (i.e. fatal or non-fatal symptomatic recurrent venous thromboembolism, myocardial infarction, ischemic stroke, systemic non-CNS embolism).

3. The principal safety objective is to document the incidence of the principal safety outcome (i.e. major bleeding).

4. The secondary safety objective is to document the incidence of the secondary safety outcome (i.e. clinically relevant non-major bleeding).

5. Additional study objectives are to evaluate
a. the composite of non-fatal symptomatic venous thromboembolism and allcause mortality
b. the composite of major bleeding and recurrent venous thromboembolism
c. the composite of major bleeding, recurrent venous thromboembolism, myocardial infarction, ischemic stroke and systemic non-CNS embolism

Study design

This is a multicenter, randomized, double-blind, double-dummy, active-comparator, eventdriven study. Patients with confirmed symptomatic DVT and/or PE who completed 6 to 12 months (± 1 month) of anticoagulant treatment and did not interrupt anticoagulation for longer than 1 week are eligible for this study. Patients will be allocated by interactive voice/web response system (IxRS) to a 12-month duration of either once-daily:
1. rivaroxaban 10 mg,
2. rivaroxaban 20 mg, or
3. ASA 100 mg.
Randomization will be stratified by country and by index event (i.e. DVT or PE±DVT). All efficacy and safety analyses are based on time to first event. All patients who prematurely stop study treatment need to be observed until the end of the 12-month treatment period. All suspected recurrent VTEs, myocardial infarctions, ischemic strokes, systemic non-CNS embolisms, deaths and all

episodes of bleeding will be evaluated by a central, blinded, independent adjudication committee. Adjudication results will be the basis for the final analyses. An independent data monitoring committee (DMC) will monitor the patients* safety during the study and give recommendations to the steering committee. The study is event-driven and requires at least 80 confirmed primary efficacy outcomes. The expected number of patients required per group is 950. The patients randomized last into the study will receive study medication for 6 months and will not receive a second supply at visit 4. A 24-hour emergency telephone service will be available throughout the study. An observation visit is planned for all patients 30 days after stopping study medication. Only SAEs need to be reported with the exemption of all efficacy and safety outcomes. Furthermore, all patients with Hb <10 g/dl (also if not related to overt bleeding), white blood cells <3.0 x 109/l and /or neutrophils < 0.5 x 109/l, platelets <50 x 109/l, and allergic skin
reactions, allergic systemic reactions, if possibly related to study drug (even if not considered serious), need to be reported. These adverse events (AEs) must be reported within 24 hours. Any pregnancy in a patient or in the patient*s partner, and the outcome of the pregnancy need
to be reported.

Intervention

NA

Study burden and risks

1. Risks and Discomforts Associated with Rivaroxaban
The most common side effect of rivaroxaban is bleeding from anywhere in your body, which usually is not severe and stops when the medication is stopped. Bleeding from rivaroxaban can rarely be fatal (less than 1 person per 1000). Other side effects that may be seen with rivaroxaban are: nausea, abdominal and stomach pains, increase of some of the liver enzymes or allergic reactions including skin rash, hives (urticaria), itching and swelling of eyelids, face, lips, mouth or throat.

2. Risks and Discomforts Associated with Aspirine

Bleeding, bruising, nausea, vomiting, pain or discomfort in stomach, ringing / buzzing in the ears, allergic reactions including skin rash, hives (urticaria), itching, swelling of eyelids, face, lips, mouth or tongue and difficulty in breathing.

3. Risks and Discomforts Associated with study procedures

Taking of blood samples may cause discomfort at the injection site and dizziness when having blood drawn.

Contacts

Public
Bayer

Parc Eurasanté - avenue de la Recherche 220
Loos 59120
FR
Scientific
Bayer

Parc Eurasanté - avenue de la Recherche 220
Loos 59120
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients with confirmed symptomatic PE and/or DVT who have been treated for 6 to 12 months and did not interrupt anticoagulation for longer than 1 week
2. Written informed consent

Exclusion criteria

1. Legal lower age limitations (country specific)
2. Indication for therapeutic-dosed anticoagulants
3. Hypersensitivity to investigational or comparator treatment
4. Any other contraindication listed in the local labeling for investigational or comparator treatment

5. Indication for antiplatelet therapy or a conventional non-steroid anti-inflammatory drug (NSAID)
6. Hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk
7. Calculated creatinine clearance <30 mL/min
8. Active bleeding or high risk for bleeding contraindicating anticoagulant therapy
9. Life expectancy <6 months
10. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, i.e. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically
11. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding
12. Participation in a study with an investigational drug or medical device within 30 days prior to randomization

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-09-2014
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NVT

Generic name:	Aspirin 100mg
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NVT
Generic name:	Rivaroxaban 10mg
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NVT
Generic name:	Rivaroxaban 20mg
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-000619-26-NL
CCMO	NL47415.018.14