Once-daily oral direct factor Xa rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis or pulmonary embolism. The Einstein-Extension study.

Published: 29-12-2006
Last updated: 14-05-2024

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

Summary

ID

NL-OMON31783

Source
ToetsingOnline

Brief title
The Einstein-Extension Study

Condition

- Embolism and thrombosis

Synonym
venous thromboembolism

Research involving
Human

Sponsors and support

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

Intervention

Keyword: anticoagulants, pulmonary embolism, venous thrombosis

Outcome measures

Primary outcome

The primary efficacy outcome is symptomatic recurrent VTE, i.e., the composite

of recurrent DVT or fatal or non-fatal PE. The primary efficacy analysis is

based on the time to the first symptomatic recurrent VTE event.

The principal safety outcome is major bleeding.

Secondary outcome

Other safety outcomes include all deaths and other vascular events

Study description

Background summary

Patients with idiopathic PE or DVT and those with persistent risk factors remain at risk for recurrent thromboembolic events.(5) This risk is most pronounced in the first months after the acute episode and diminishes slowly over subsequent years. The bleeding risk with VKA therapy is usually stable over years with a tendency
to increase with advancing age and the occurrence of comorbid conditions. Therefore, the decision to prolong VKA therapy is a challenge to the physician who should balance the risk of disease progression or recurrence with that of bleeding, against the background of the impact of this therapy on the patient*s daily life.
Therefore there remains equipoise about the optimal duration of VKA therapy in various categories of PE or DVT patients. This is reflected in a grade

2Arecommendation by the American College of Chest Physicians guidelines for antithrombotic therapy, the *2* indicating that the risk/benefit of extended treatment is not clear. Rather than restrict prolonged treatment to a variably-defined selected group, it would be worthwhile to evaluate a broad group of patients in whom treatment might be discontinued, and to study prolonged treatment with a placebo comparator. In the decision to provide extended anticoagulant treatment another aspect would be if it were safer than warfarin and provided efficacy. A new therapeutic agent with an equal or improved efficacy profile combined with a lower risk of bleeding could allow for a longer treatment duration, especially if this can be achieved with easier treatment logistics.
Rivaroxaban is a novel, direct oral factor Xa-inhibitor which plays its role at the intersection of the extrinsic and the intrinsic pathways for thrombin generation.
It requires no monitoring of its effect and has high benefit-risk ratio.
In the present study rivaroxaban will be compared to placebo. Placebo control is needed because there remains equipoise about the optimal treatment duration after the initial treamnet period (see above). If the present study shows that this new treatment is effective without compromising patient's safety, extended anticoagulant therapy with easy logistcs might be avialable for patients

Study objective

The purpose of this study is to show that the incidence of new thrombotic events during an additional 6 or 12 months of treatment with rivaroxaban is lower when compared to placebo and that the likely advantage of an extended effect is not offset by an increase of bleeding complications.

Study design

This is a multicenter, randomized, double-blind, placebo-controlled, event-driven, superiority study for efficacy.
Patients with confirmed symptomatic DVT or PE who completed 6 to 14 months of treatment with VKA (warfarin or acenocoumarol) outside the VTE treatment study or who completed 6 or 12 months of treatment with VKA or rivaroxaban in the 11702 study, are eligible for this trial.
Therefore, patients who participated in the Einstein VTE program (rivaroxaban/11702) and also patients treated outside
that program for 6 to 14 months with warfarin or acenocoumarol following the initial diagnosis of PE or DVT and continued up to the moment of randomization,are potential candidates. The treatment duration is 6 or 12 months and should be indicated prior torandomization. The last patient will be treated for at least 3 months once the required number of events has been reached.All patients will have a 30-day observational period after cessation of studytreatment. Allocation to treatment will be done centrally by interactive voice response system and will be stratified by 1) country, 2) previous

treatment
(rivaroxaban or VKA), and 3) intended treatment duration.
All suspected recurrent VTE, deaths and all episodes of bleeding and vascular events will be evaluated by a central, blinded, independent adjudication committee. Adjudication results will be the basis for the final analyses.
An independent data and safety monitoring board will monitor the patients* safety during the study and give recommendations to the executive committee.
The study is event-driven and requires 30 confirmed recurrent thromboembolic events. The expected number of patients required per group is 650.
A 24-hour emergency telephone service will be available throughout the study.

Intervention

After randomization,patients allocated to rivaroxaban will receive rivaroxaban 20 mg once-daily, patients allocated to placebo will receive a matching placebo tablet once-daily

Study burden and risks

In the present study there are 2 strata depending on the treatment duration which is determined by the investigator prior to randomization
Depending on this treatment duration the number of visits is scheduled.
For the 6 month treatment period, 7 assessments are planned: 6 of these need to be hospital visits and each time a blood sample will be taken (about 10-20 ml per blood sample). The assessment at day 8 may be a telephone contact.
For the 12 month treatment period, 9 assessments are planned: 8 of these need to be hospital visits and each time a blood sample will be taken (about 10-20 ml per blood sample). The assessment at day 8 may be a telephone contact.
If during the course of the study re-occurrence or worsening of deep-vein thrombosis or pulmonary embolism is suspected, diagnostic testing will take place. There is also an additional blood collection (about 10 ml). If suspected pulmonary embolism or deep-vein thrombosis is confirmed, the study medication will be discontinued and replaced by another therapy at the discretion of your doctor. For this purpose, you will receive a booklet detailing what to do if you develop symptoms suggestive for recurrent pulmonary embolism/ deep vein thrombosis or bleeding. In case of any abnormal laboratory values, or clinical signs and symptoms, an appropriately close monitoring will be performed until complete normalisation. A blood sample (about 10 ml) will also be collected in case of a bleeding complication.
Before treatment begins, your doctor will document your current health status and you will have blood samples taken to check your kidney and liver function. One of the blood tubes taken will be stored and evaluated only in case you will develop unexpected complications or if requested by a health authority.
Female patients of childbearing potential will also have a urine pregnancy test to exclude a pregnancy.
Hence, compared to standard treatment there will be more blood samples, and

out-patient visits . The risks associated with bloodsampling is low and the extra effort required for out-patient visits is acceptable in view of the trial.

Contacts

Public
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-
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Duitsland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with confirmed symptomatic PE or DVT who have been treated for 6 to 14 months with VKA (either warfarin or acenocoumarol) outside of the Einstein VTE treatment program (study 11702) or who have been treated for 6 or 12 months with VKA or rivaroxaban in the 11702 study.

Exclusion criteria

1. Legal lower age limitations (country specific)
2. Indication for VKA other than DVT and/or PE
3. Patients in whom anticoagulant treatment for their index PE or DVT should be continued
4. Significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or ALAT > 3 x ULN
5. Creatinine clearance < 30 ml/min
6. Bacterial endocarditis
7. Active bleeding or high risk for bleeding.
8. Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg
9. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding
10. Participation in another pharmacotherapeutic study other than the Einstein VTE program (rivaroxaban/11702) within the prior 30 days
11. Life expectancy <3 months
12. Concomitant use of strong CYP3A4 inhibitors (e.g., HIV protease inhibitors, systemic ketoconazole) or strong CYP3A4 inducers like rifampicin

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	30-01-2007
Enrollment:	200
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	placebo
Product type:	Medicine
Brand name:	nog niet aanwezig
Generic name:	rivaroxaban

Ethics review

Approved WMO Date:	29-12-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-11-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date: 20-12-2007

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 28-02-2008

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 25-03-2008

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 27-05-2008

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 11-09-2008

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 16-10-2008

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 03-12-2008

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 21-01-2009

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 27-01-2009

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date:	23-02-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2009
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	EUCTR2006-004494-96-NL
CCMO	NL15701.018.06