Oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep-vein thrombosis or pulmonary embolism using a strong CYP 3A4 inducer.

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

Summary

ID

NL-OMON32634

Source
ToetsingOnline

Brief title
13238/The Einstein CYP cohort study

Condition

- Embolism and thrombosis

Synonym
venous tromboembolism

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Het farmaceutisch bedrijf: Bayer HealthCare AG

Intervention

Keyword: CYP 3A4 inducer, deep-vein thrombosis, pulmonary embolism, rivaroxaban

Outcome measures

Primary outcome

The primary objective is to characterize the population PK/PD of an adapted

rivaroxaban dose regimen in patients with acute, proximal deep-vein thrombosis

(DVT) or acute pulmonary embolism (PE) and concomitant use of a strong CYP 3A4

inducer.

Secondary outcome

The occurrence of symptomatic recurrent venous thromboembolism and major and

clinically relevant non-major bleeding will be documented.

Study description

Background summary

Rivaroxaban is a new anticoagulant drug that is currently being tested in a large group of patients with DVT or PE. Under normal circumstances, the dose of rivaroxaban for the treatment of DVT or PE is 15 mg twice daily for 3 weeks followed by 20 mg once daily for a longer period of time. However, the effect of rivaroxaban can be influenced by medication that belongs to the group of the so-called strong CYP 3A4 inducers. Examples of strong CYP 3A4 inducers are carbamazepine, phenytoin, rifampicin/rifampin, and rifabutin. If a patient uses such a strong CYP inducer in combination with rivaroxaban, then the effect of rivaroxaban will be substantially less, possibly making the treatment of DVT or PE less effective. The aim of this study is to demonstrate that in patients who use a strong CYP inducer, the rivaroxaban dose needs to be higher than normal for achieving the same therapeutic effect as in patients who use rivaroxaban in

the absence of a strong CYP 3A4 inducer.

Study objective

The purpose of this study is to demonstrate that in patients with DVT or PE who use a strong CYP 3A4 inducer, the use of this higher rivaroxaban dose results in a similar rivaroxaban concentration in the blood and a rivaroxaban induced blood thinning effect than observed in patients that use the normal rivaroxaban dose in the absence of a strong CYP 3A4 inducer.

Additionally, the occurrence of symptomatic recurrent venous thromboembolism and major and clinically relevant non-major bleeding will be documented.
After the whole study is finished, your doctor will be informed on the study results in general. Your doctor will discuss these with you if requested. If there are issues concerning your particular health status your doctor will be discuss these with you. This will not happen immediately after you have finished taking part in the study but will take some time due to the analysing of results.

Study design

De Einstein CYP 13238 study is a multicentre cohort study evaluating an adapted rivaroxaban dose regimen in patients with acute, proximal deep-vein thrombosis or acute pulmonary embolism and concomitant use of a strong CYP 3A4 inducer for the entire 3-month study duration.

Intervention

After inclusion all participating patients receive 30 mg twice daily during 3 weeks followed by rivaroxaban 20 mg twice daily. All patients will have a 30-day observational period after cessation of treatment.

Study burden and risks

For this study, participating patients will be asked to attend the center for 6 study visits; during these visits blood samples will be taken: on day 1 (1 blood sample), day 15 (3 blood samples), day 30 (1 blood sample), day 60 (2 blood samples), day 90 (1 blood sample). Day 121 a follow-up is planned; on day 8 a contact by telephone.
Each study visit takes approximately 2 to 3 hours; the visit on day 15 (3 blood samples) may take 3 to 4 hours.

The study treatment takes 3 months, followed by an observational period of 1 month.

Since rivaroxaban is a blood thinner it may be associated * like all other

blood thinners - with an increased risk of bleeding. These bleedings might be minor and insignificant but, in rare cases, bleeding can involve an organ and can be severe or even fatal. The risk of bleeding may be increased in patients with high blood pressure (i.e. arterial hypertension) and/or on concomitant drugs which also prevent the clotting of blood (including drugs like Aspirin and other common drugs to relieve pain).

Rivaroxaban has already been tested in healthy volunteers and patients. The dose of rivaroxaban which will be used in this study appeared to be as effective and safe as the standard way of treatment without the need for regular laboratory monitoring of the anti-clotting effect. Rivaroxaban may turn out to be more or less effective than the standard treatment with enoxaparin and warfarin or acenocoumarol. If rivaroxaban is less effective, this will be noticed as soon as possible and the treatment will be changed immediately by the investigator.

The safety of rivaroxaban 10 mg has been evaluated in several studies including three phase III studies in patients undergoing major orthopedic surgery of the legs (total hip replacement or total knee replacement) treated during up to 39 days. In these studies, rivaroxaban was compared to enoxaparin, a commonly used blood thinner. Commonly (>1%) reported adverse drug reactions were anemia, nausea, increase in liver enzymes (like ALT, AST, GGT) and bleeding complications after surgery. Less frequently, an increase was found in bilirubin (a blood break-down product) and in enzymes (i.e. lipase and amylase) which break down food components.

It is not yet known if the study drug could affect an unborn child. Women who are able to conceive and who decide to take part must agree to take adequate contraception throughout the study and be checked for pregnancy using urine tests.

As the study drug is under development there may be side effects that are not yet known and have not yet been reported. Therefore the patient is asked to notify your doctor, or any of the study staff, of any new symptoms that may appear.

Contacts

Public
Bayer

Bayer HealthCare AG
51368 Leverkusen
Duitsland

Scientific
Bayer

Bayer HealthCare AG
51368 Leverkusen
Duitsland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Confirmed acute symptomatic proximal DVT and/or PE
2. Concomitant use of a strong CYP 3A4 inducer, (i.e., carbamazepine, phenytoin, rifampicin/rifampin, or rifabutin) during the entire 3-month study period
3. Written informed consent

Exclusion criteria

1. Legal lower age limitations (country specific)
2. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE
3. Other indication for VKA than DVT and/or PE
4. More than 36 hours of treatment with therapeutic dosages of anticoagulant treatment or more than a single dose of VKA prior to inclusion
5. Participation in another pharmacotherapeutic study within 30 days
6. Creatinine clearance < 30 ml/min
7. Significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or ALAT > 3 x ULN
8. Bacterial endocarditis
9. Life expectancy <3 months
10. Active bleeding or high risk for bleeding contraindicating treatment with

enoxaparin or VKA
11. Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg
12. Childbearing potential without proper contraceptive measures (i.e. a method of contraception with a failure rate < 1 % during the course of the study (including the observational period). These methods of contraception according to the note for guidance on non-
clinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH/286/95, modification) include consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing intrauterine devices, surgical sterilization, sexual abstinence and vasectomy), pregnancy or breast feeding.
13. Concomitant use of strong CYP3A4 inhibitors (e.g., HIV protease inhibitors, systemic ketoconazole)
14. Use of the strong CYP 3 A4 inducers phenobarbital/primidone or St John*s Wort

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2008
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet aanwezig
Generic name:	Rivaroxaban

Ethics review

Approved WMO Date:	09-12-2008
Application type:	First submission
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
Approved WMO Date:	12-03-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2010
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	EUCTR2008-003303-31-NL
CCMO	NL25826.018.08