A randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Escalation and Dose-Confirmation Study to Evaluate the Safety and Efficacy of Rivaroxaban in Combination with Aspirin Alone or with Aspirin and a Thienopyridine in Subjects with Acute Coronary Syndromes

Published: 05-12-2006
Last updated: 10-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON30638

Source
ToetsingOnline

Brief title
The ATLAS ACS TIMI 46 Trial

Condition

- Coronary artery disorders

Synonym
acute coronary syndrome, heart infarction

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: de opdrachtgever van het onderzoek (zie ook B6)

Intervention

Keyword: anti-Xa, cardiovascular, efficacy, rivaroxaban

Outcome measures

Primary outcome

Stage (Phase) 1 Dose Escalation

The primary objective of Stage 1 of this study is to evaluate the safety of rivaroxaban in subjects with recent ACS (including STEMI, NSTEMI, or UA) who are treated with aspirin alone or aspirin plus a thienopyridine. The dose, dosing regimen and background therapy strata with a promising benefit:risk profile will be selected based on the results of Stage 1 for a more extensive efficacy evaluation in Stage 2.

Stage (Phase) 2: Dose Confirmation

The primary objective of Stage 2 of this study is to evaluate the ability of rivaroxaban to reduce the combined incidence of death, MI (or reMI), stroke (ischemic, hemorrhagic or unknown), or severe recurrent ischemia requiring revascularization in subjects with recent ACS (including STEMI, NSTEMI, or UA) who are treated with aspirin alone or aspirin plus thienopyridine after medical therapy or PCI as acute treatment.

Secondary outcome

Stage 1: Dose Escalation

· to evaluate primary and secondary efficacy endpoints to enable a benefit:risk assessment

· to evaluate the PK/PD of rivaroxaban assessing drug exposure using rivaroxaban plasma concentrations and exposure/response relationships using factor Xa activity and PT

· to evaluate the ability of rivaroxaban to reduce thrombin generation, as assessed by biomarkers such as fragment F1.2 levels

· to assess the overall safety of rivaroxaban treatment

Stage 2: Dose Confirmation

· to evaluate the ability of rivaroxaban to reduce the composite of death, MI, or stroke through 6 months of treatment

· to evaluate the ability of rivaroxaban to reduce the composite of death, MI, stroke or severe recurrent ischemia through 6 months of treatment

· to assess the net clinical benefit of rivaroxaban by measuring the composite of death, MI, stroke, severe recurrent ischemia requiring revascularization, TIMI major bleed or TIMI minor bleed through 6 months

· to evaluate the ability of rivaroxaban to reduce each component of the primary composite efficacy endpoint

· to evaluate the ability of rivaroxaban to reduce ischemia as measured by continuous ST segment monitoring in a subset of subjects

· to evaluate the ability of rivaroxaban to reduce the incidence of left ventricular (LV) thrombus at Day 10 to 14 after randomization in a subset of

subjects presenting with anterior STEMI

· to assess the overall safety or rivaroxaban treatment

Study description

Background summary

Heart and blood vessel disease is one of the major causes of death in the western world. After having a myocardial infarction and unstable angina (pain on the chest in rest), anti-coagulant medication is prescribed (*bloodthinners*) to prevent the formation of new bloodclots which can block the (coronary) arteries again. The coronary arteries are the vessels which transport blood to the heart.
Aspirin is one of the most prescribed medications after a myocardial infarction and unstable angina. Besides aspirin a number of other blood thinners is prescribed with different modes of action (eg. thienopyridines). Often, combinations of blood thinners are prescribed.
Rivaroxaban is a member of the category of factor Xa inhibitors (factor Xa plays a part in blood clotting). In this trial it will be investigated whether rivaroxaban can make a substantial contribution to the prevention of new myocardial infarctions, unstable angina or strokes when it is given in combination with aspirin alone or in combination with aspirin and a thienopyridine. The trial consists of 2 phases (see also question 5), where in phase I the dose with the most optimal benefit-risk profile is being assessed, after which in fase II this dose is further investigated and in which it will be investigated if rivaroxaban is an effective medication to prevent new myocardial infarctions, strokes, etc. in patients with acute coronary syndrome.

Study objective

There are two phases in this trial with 2 objectives:
In phase I of the trial it will be assessed which dose of rivaroxaban is the most safe and effective (most optimal benefit:risk profile). In phase II this dose will be further investigated to evaluate if rivaroxaban is an effective medication to prevent new myocardial infarctions, strokes etc. in patients with acute coronary syndromes.

Study design

This is an international, randomized, multicenter, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of rivaroxaban in subjects with recent ACS (STEMI, NSTEMI, or UA) who are receiving background low dose aspirin therapy (75 to 100 mg/day) without the

intention to use a thienopyridine therapy (Stratum 1, aspirin only) or with thienopyridine therapy (Stratum 2, aspirin plus a thienopyridine). The trial consists of 2 phases:
Phase I: In Phase I the dose of rivaroxaban with the most optimal benefit:risk profile will be assessed.
Phase II: In Phase II the most optimal dose as assessed in Fase I will be further investigated and it's role in the prevention of recurrence of acute coronary sydrome.

Each phase has a screening/baseline phase within the 6 days prior to randomisation or on the day of randomisation (day 1). The double-blind treatment period lasts for 6 months, with an endvisit planned at the end of this period or at the time a patient will leave the trial prematurely. Approximately 30 days after the last dose of study drug, a posttreatment follow-up visit will occur and will include assessment of any new adverse events and follow-up of any ongoing adverse events. The total duration of the study will be approximately 216 days. Subjects in each stratum will follow the same Time and Event Schedule for each stage of the study, unless otherwise specified.

Per stratum and dose level, there are always 3 treatment groups: placebo, rivaroxaban in a twice daily dose and rivaroxaban in a once daily dose. See also pages 48 and 49 of the protocol for a schematic overview. Patients will be randomized with a chance of 1 in 3 to one of the 3 treatment groups.

Intervention

In both phases and in both strata patients receive ór placebo, ór rivaroxaban in a twice daily dose, ór rivaroxaban in a once daily dose.

The total daily doses tested in phase I are 5, 10 and 20 mg. The most optimal dose from phase I will be further investigated in phase II.

During the trial extra treatment groups may be added (rivaroxaban in a 15 mg and 30 mg total daily dose).

Study burden and risks

Burden to the patient: patients will be for a maximum of 216 days in the trial (including screening and follow-up period). After discharge from the hospital, patients need to visit the hospital for trial visits for 7 times and will undergo a number of trial procedures (a.o. blooddrawings, ECG and completion of questionnaires).
Risks: the side effects of aspirin and thienopyridines are known.
In earlier trials with healthy volunteers no differences were seen in the incidence of mild side effects between subjects treated with rivaroxaban and

subjects treated with placebo. Side effects which were reported in more than 2% of these subjects are abdominal distension, upper abdominal pain, nausea, heartburn, fatigue, headache, rash and sore throat. Rivaroxaban is a bloodthinner which can make it more difficult for the blood to clot in case of a bleeding. Therefore, there is a risk of a haemorrhage. The patient will get an extensive screening vist, before the patient will be randomized. During the trial, the patient will be followed closely. In case of side effects, extra visits will be planned to follow up the patient. In case of bleeding, the guidelines on page 85 of the protocol are given.
Risks of blooddrawing are minimal.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Man/women between 18 and 75 years of age
- Diagnosis of STEMI (ST-segment elevation myocardial infarction) or a diagnosis of NSTEMI (non-ST-segment elevation myocardial infarction) or UA (unstable angina) with at least 1 of the following: elevated cardiac enzyme marker, ><= 1 mm ST-segment deviation or TIMI risk score ><= 3 (see protocol page 50)
- symptoms suggestive of ACS lasting at least 10 minutes at rest occurring within 7 days of randomization

Exclusion criteria

- conditions that may increase the risk of bleeding
- conditions that may increase the risk of intracranial hemorrhage
- required drugs or procedures (need for continued treatment with anticoagulant drugs, planned PCI within 30 days of randomization)
- severe concomitant diseases (such as cardiogenic shock, anemia)
- general (eg. allergy to aspirin, pregnant, employees of the study center)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-06-2007
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	rivaroxaban
Generic name:	rivaroxaban

Ethics review

Approved WMO Date:	05-12-2006
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-01-2007
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-05-2007
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-09-2007
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-11-2007
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-05-2008
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	10-06-2008
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	EUCTR2006-004449-40-NL
ClinicalTrials.gov	NCT00402597
CCMO	NL15332.060.06