A Phase 3, Randomized, Double-Blind, Evaluation of the Safety and Efficacy of Apixaban In Subjects with a Recent Acute Coronary Syndrome

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Primary Objective: to determine if Apixaban is superior to placebo for preventing the composite of cardiovascular death, myocardial infarction, or ischemic stroke, in subjects with a recent acute coronary syndrome (ACS).

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

Summary

ID

NL-OMON33485

Source
ToetsingOnline

Brief title
Appraise II

Condition

- Coronary artery disorders

Synonym
Acute coronary syndrome; coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb

Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: Acute Coronory Syndrome, Apixaban, Composite endpoint, Placebo-controlled

Outcome measures

Primary outcome

Primary efficacy outcome: Time to first occurrence of cardiovascular death,

myocardial infarction, or ischemic stroke.

Primary safety outcome: Time to first occurrence of TIMI major bleeding.

Secondary outcome

Secondary efficacy outcomes: Time to first occurence:

• Cardiovascular death, myocardial infarction, unstable angina or ischemic

stroke.

• Cardiovascular death, fatal bleeding, myocardial infarction or stroke

(ischemic or hemorrhagic).

• Death (all-cause), myocardial infarction or stroke (ischemic or hemorrhagic).

Secondary safety outcome: Time to first occurrence of ISTH major bleeding.

Study description

Background summary

This trial studies extended oral anticoagulation in subjects with a recent ST-segment elevation or non-ST-segment elevation ACS event. These patients have recurrent ischemic events. Studies of the use of vitamin K antagonists after ACS have demonstrated a significant reduction in recurrent ischemic events with therapeutic anticoagulation (INR 2-3) compared to aspirine alone. Factor Xa plays a pivotal role in blood coagulation. Apixaban is an orally active, direct

factor Xa inhibitor. Chronic oral anticoagulation with Apixaban in moderate to high risk patients who have had a recent episode of ACS has the potential to further reduce the frequency of major adverse cardiac events. The need for alternative antithrombotic agents with acceptable risk-benefit rations for chronic use in the ACS population is clear. Apixaban does not require therapeutic monitoring and has a wide therapeutic index.

Study objective

Primary Objective: to determine if Apixaban is superior to placebo for preventing the composite of cardiovascular death, myocardial infarction, or ischemic stroke, in subjects with a recent acute coronary syndrome (ACS).

Study design

Appraise II will be a randomized, placebo-controlled, parallel arm superiority study to evaluate the efficacy and safety of apixaban compared with placebo in subjects with recent ACS and at least 2 additional risk factors for recurrent ischemic events. Subjects will be randomized 1:1 to either apixaban 5 mg BID or matching placebo following cessation of parenteral anticoagulation therapy. Patients with a calculated creatinine clearance < 40 mL/min at the time of randomization will receive apixaban 2.5 mg BID or matching placebo. Randomization will be stratified by the investigator's intension to continue single or dual antiplatelet therapy. The primary efficacy outcome will be the composite of cardiovascular death, myocardial infarction or ischemic stroke. The last randomized subject will be treated for a minimum of three months. All randomized subjects will be followed until the targeted number of primary events (938) occur in the study with one month post study-drug discontinuation safety follow-up. The estimated study duration is approximately 28 months but the final study duration will be determined by the time required to accrue 938 primary efficacy outcome events.

Intervention

Oral apixaban/placebo tablets 5 mg or 2.5 mg BID. After 938 primary events, the last randomised patient will receive study medication for 3 months.

Study burden and risks

In case of participation of 28 months:

9 x ECG
9 x heart rate and blood pressure
1 x length and heigth
4 x blood drawn of 12.5 mL

Time of visits to the hospital and phone visits:
ca. 6 hours during 8 months

For woman of child-bearing potential, 8 pregancy tests will be performed (urine).

Possible side effects of Apixaban are:
An increased risks of bleedings, nausea, obstipation, fever, vomiting, swellings, joint pain, poor sleep, dizziness, xxx, rash, headache, fatigue, stomach pain.

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

1) An acute coronary syndrome within 7 days characterized by:
a) Symptoms of myocardial ischemia at rest lasting at least 10 minutes
And either
b) Elevation in cardiac biomarkers above the local upper limit of normal
Or
c) Dynamic ST-segment deviation (depression or elevation >= 0.1 mV (1.0 mm))
2) Completion of parenteral anticoagulation therapy for the index ACS event.
3) Clinically stable, receiving standard of care for ACS, including single or dual antiplatelet therapy, at the discretion of the treating physician.
4) Two or more of the following risk factors
a) Age >= 65 year
b) Diabetes mellitus
c) Prior myocardial infarction (other than the qualifying event) within 5 years
d) Ischemic cerebrovascular disease
e) Peripheral vascular disease (symptoms of claudication and/or peripheral revascularization, and/or ankle-brachial index (ABI) < 0.9)
f) Heart failure or left ventricular ejection fraction < 40% associated with the index ACS event
g) Impaired renal function (calculated CrCl < 60 mL/min)
h) No revascularization for index ACS event.

Exclusion criteria

1. Persistent severe hypertension (SBP * 180 mmHg of DB * 110 mmHg)
2. Calculated CrCl < 20 mL/min or on dialysis for end-stage renal disease
3. Active bleeding or high risk for major bleeding
4. Known coagulopathy
5. Acute pericarditis
6. Recent (<7 days) ischemic stroke
7. NYHA Class IV heart failure at time of randomization
8. Any history of intracranial bleeding
9. Active and/or significant, known hepatobiliary disease
10. Required ongoing treatment with a parenteral or chronic oral anticoagulant (eg, mechanical valve, recent DVT or pulmonary embolism, known left ventricular thrombus)
11. Required ongoing treatment with a strong inhibitor of CYP3A4, macrolide antibiotics, protease inhibitors.

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:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-09-2009
Enrollment:	150
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine

Ethics review

Approved WMO Date:	28-04-2009
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	16-07-2009
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	30-07-2009
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO	

Date:	11-11-2009
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	30-12-2009
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	03-02-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	13-04-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	14-05-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	28-05-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	24-08-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

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	EUCTR2008-008298-77-NL
ClinicalTrials.gov	NCT00831441
CCMO	NL27334.094.09