Randomized, double-blind, triple-dummy trial to compare the efficacy of otamixaban with Unfractionated Heparin + eptifibatide, in patients with Unstable angina/Non ST segment Elevation Myocardial infarction scheduled to undergo an early invasive strategy

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Primary: To demonstrate the superior efficacy (composite of all-cause death + Myocardial infarction) of otamixaban to unfractionated heparin (UFH) + eptifibatideSecondary:• To demonstrate the superior efficacy (composite of all-cause death +...

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

Summary

ID

NL-OMON35026

Source
ToetsingOnline

Brief title
TAO

Condition

- Coronary artery disorders

Synonym
(imminent) Myocardial Infarction, Acute Coronary Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: sponsor

Intervention

Keyword: ACS, Non-ST elevation, Otamixaban, Percutaneous Coronary Intervention

Outcome measures

Primary outcome

All-cause death + Myocardial infarction from randomization to day 7.

Secondary outcome

- All-cause death + myocardial infarction + any stroke from randomization to

day 7

- Rehospitalization or prolongation of hospitalization due to a new episode of

myocardial ischemia / myocardial infarction from randomization to day 30

- All cause death from randomization to day 30

- Safety of otamixaban as compared to UFH + eptifibatide

- Procedural thrombotic complications during the index PCI

Study description

Background summary

Acute coronary syndrome (ACS) remains a major cause of death and disability. ACS is the result of a complex interaction of activation of coagulation and platelet aggregation, superimposed on a disruptive atherosclerotic plaque. For many years unfractionated heparin (UFH) has been the cornerstone of antithrombotic therapy for ACS for patients presenting with a non STE elevation acute coronary syndrome There are multiple disadvantages of this treatment,

heparin resistance and an unpredictable pharmacodynamic and pharmacokinetic effects as a result of interactions are two examples. The optimal anti-thrombotic regimen for ACS patients with unstable angina / non ST-elevation myocardial infarction scheduled to undergo an early invasive strategy remains, therefore, to be determined. A direct inhibitor of factor Xa could be an effective therapy for these ACS patients, therefore otamixaban, a direct factor Xa inhibitor could be an appropriate therapy.

Study objective

Primary: To demonstrate the superior efficacy (composite of all-cause death + Myocardial infarction) of otamixaban to unfractionated heparin (UFH) + eptifibatide
Secondary:
• To demonstrate the superior efficacy (composite of all-cause death + Myocardial infarction + any stroke) of otamixaban as compared to UFH + eptifibatide
• To document the effect of otamixaban on Rehospitalization or prolongation of hospitalization due to a new episode of myocardial ischemia/myocardial infarction as compared to UFH+ eptifibatide
• To document the effect on mortality (all cause mortality) of otamixaban as compared to UFH + eptifibatide
• To document the safety of otamixaban as compared to UFH + eptifibatide
• To document the effect of otamixaban on Thrombotic procedural complications during the index PCI as compared to UFH + eptifibatide
• To characterize otamixaban pharmacokinetics over the entire dosing interval and to evaluate otamixaban exposure-response (safety and efficacy) in the target population.
A single blood sample will be drawn if a subject participates in the pharmacogenetic substudy. This sample may be used to determine a possible genetic effect on response to treatment with otamixaban, efficacy, safety and/or metabolism of otamixaban.

Study design

Randomized, double blind, triple-dummy study with two parallel groups; one control arm of UFH + eptifibatide and one otamixaban arm. In two arms at randomization patients will be assigned to receive blinded study medication A (otamixaban /placebo), B (placebo/UFH) and in case of a PCI Drug C (placebo/eptifibatide). In the otamixaban arms Drug A will be a bolus and an infusion of active otamixaban, and Drug B and C will be a bolus and infusions of placebo. In the UFH + eptifibatide arm Drug A will be a bolus and an infusion of placebo, Drug B a bolus and a infusion of active UFH, and Drug C a bolus and an infusion of active eptifibatide. Drug A (otamixaban or its placebo) and drug B (UFH or placebo) will be administered from the time of randomization until the end of the PCI or hospital discharge. Eptifibatide or

its placebo (drug C) will be initiated after the angiography, immediately prior tot the PCI start andgiven up to 18-24 hour post PCI or until hospital discharge.
During the initial hospitalization if a bailout use of GP IIb/IIIa is needed (i.e. only as required because of a significant recurrent ischemia, procedural complication or other clinical instability) patients will receive a blinded bolus of Drug D followed by an infusion of open label eptifibatide in case they already received Drug C. Then in the otamixaban arm the Drug D bolus will be a bolus of active eptifibatide. In the UFH+eptifibatide the Drug D bolus will be a placebo of eptifibatide. When the patient did not yet receive Drug C an open-label bolus of eptifibatide will be given. In all arms the bolus will be followed by an infusion of open label eptifibatide and the Drug C will be stopped.
All patients will be treated with aspirin (75-325mg daily) as recommended in the ACC/AHA and ESC guidelines. In addition to aspirin patients should be treated from randomization by clopidogrel or prasugrel according to their respective labelling. After discharge all patients will have a Day 30 follow up visit and a visit or a telephone follow up at 3 Month and 6 Month.

Intervention

Patients will be divided into two medication arms. Patients will receive intravenous infusion of otamixaban and placebos or an intravenous infusion of UFH (plus eptifibatide in case of a PCI) and placebo. Otamixaban or UFH and its placebo will administered by one infusion system via a multifold.

Study burden and risks

Patients can experience otamixaban related side effects, of which bleedings was the most frequent in previous studies. Pyrexia, headache, nausea and hypotension were common side effects too.

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

- Patient with non ST-segment elevation Acute Coronary Syndrome with the following symptoms:
- Ischemic symptoms (chest pain or equivalent) at rest >=10 minutes within 24 hours of randomization
-One of the two following criteria:
*New ST-segment depression >=0.1 mV (>=1 mm), or transient (<30 minutes) ST-segment elevation >=0.1 mV (>=1 mm) in at least 2 contiguous leads on the ECG, OR
*Elevation of cardiac biomarkers within 24 hours of randomization, defined as elevated troponin T, troponin I, or CK-MB level above upper limit of normal
- Planned to have a coronary angiography (followed, when indicated, by PCI) as early as possible (after at least 2 hours of treatment with study drug) and within 36 hours (at the latest on Day 3, if justified)

Exclusion criteria

7.3.1.1 General
- High likelihood of being unavailable for the Day 180 follow up
- Age <18 years old
- Pregnancy, as evidenced by a positive urine pregnancy test performed prior to randomization (applicable only to women of childbearing potential, ie, women who are pre-menopausal or <2 years post-menopausal)/ Breastfeeding
- Treatment with other investigational agents (including placebo) or devices within 30 days prior to randomization, or planned use of investigational agents or devices during the study duration

- Revascularization procedure already performed for the qualifying event.
- Acute ST-segment elevation MI
- Patient having received curative dose of anticoagulant treatment (including UFH, LMWH, or bivalirudin) for more than 24 hours prior to randomization.
- Inability to discontinue current anticoagulation in order to transition to Investigational Products according to the specified transition timing
- Patient who cannot be treated with aspirin and clopidogrel (or any other oral antiplatelet agent), eptifibatide or UFH according to the national labeling
- Allergy to otamixaban

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:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-11-2010
Enrollment:	145
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Heparin Sodium
Generic name:	Heparin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Integrilin

Generic name:	eptifibatide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	Otamixaban

Ethics review

Approved WMO Date:	23-02-2010
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	26-04-2010
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	27-05-2010
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	07-06-2010
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	16-08-2010
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	17-01-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	25-02-2011
Application type:	Amendment

Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	25-10-2011
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 25630
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2009-016568-36-NL
CCMO	NL30308.075.10
Other	Zie sectie J
OMON	NL-OMON25630