A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of 2 Doses of RO4905417 (R1512) Administered to Patients with Non ST-Elevation Myocardial Infarction (Non-STEMI) Undergoing Percutaneous Coronary Intervention (PCI)

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The primary efficacy objective of this study is:• To evaluate the efficacy of RO4905417 in reducing the procedural damage during PCIThe secondary efficacy and safety objectives of this study are: • To evaluate the changes in other cardiac and renal...

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

Summary

ID

NL-OMON35644

Source
ToetsingOnline

Brief title
BP25619

Condition

- Myocardial disorders

Synonym
non- STEMI / Myocardial Infarction

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffmann La Roche Inc.

Intervention

Keyword: 2 doses RO4905417, Efficacy and Safety, Non ST Elevation Myocardial Infarcti, Percutaneous Coronary Intervention

Outcome measures

Primary outcome

The primary efficacy objective of this study is:

• To evaluate the efficacy of RO4905417 in reducing the procedural damage

during PCI

Secondary outcome

The secondary efficacy and safety objectives of this study are:

• To evaluate the changes in other cardiac and renal biomarkers

• To evaluate the safety of RO4905417 by monitoring of adverse events and the

incidence of MACEs at 30 and 120 days after PCI after a single dose of study

drug

Study description

Background summary

Cardiovascular disease (CVD) is the leading cause of death according to the American Heart Association*s 2010 Heart Disease and Stroke statistics and

coronary artery disease (CAD) is the most common form of CVD. As CAD progresses, narrowing and obstruction of the lumen of coronary blood vessels occurs, restricting the flow of oxygenated blood to the myocardium. Blockages of the arteries to the heart may lead to angina pectoris, and ultimately myocardial infarction. The two primary interventions for patients with multivessel CAD are coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI).

Percutaneous coronary intervention has become a standard revascularization procedure for patients with coronary artery disease. Since its introduction into clinical practice in 1977, remarkable technological advances have rendered PCI a safe procedure used to treat increasingly complex lesions in patients with both stable and unstable coronary artery disease. Nevertheless, periprocedural myocardial damage has been estimated to occur in between 4 % and 50 % of patients and importantly, can even occur after seemingly uneventful PCI procedures. PCI may result in myocardial infarction, need for emergent or urgent repeat revascularization, or even death.

The pathophysiology of post-PCI myocardial damage is multifactorial, but inflammation appears to play a pivotal role. Hyperplasia of the arterial intima at the site of intervention remains one of the major causes of late failure of PCI. Damage to the vascular wall during intervention leads to activation of leukocytes, endothelial cells, and smooth muscle cells. Importantly, inflammatory and cellular changes after PCI are not restricted to the injured arterial intima and the proximal adventitia but are also present in perivascular tissue extending several millimeters away from the artery wall. Following angioplasty of porcine coronary arteries, neutrophils and macrophages have been detected deep within the myocardium. Adhesion molecules such as P-selectin, VCAM-1 and E-selectin are expressed by endothelial cells of the myocardial microvessel. These animal studies are consistent with clinical observations that activated neutrophils are present in the coronary sinus after PCI. Release of proteolytic enzymes and generation of reactive oxygen species by these activated neutrophils may in turn aggravate endothelial damage during PCI. Concentrations of various inflammatory markers including tumor necrosis-factor alpha, C-reactive protein, and IL-6 also rise in response to PCI and PCI has also been associated with platelet activation as demonstrated by increased soluble P-selectin (sP-selectin) concentrations.

Cumulatively, these data suggest that PCI stimulates an extensive inflammatory and proliferative response in the vasculature that may ultimately result in injury to the myocardium and/or later restenosis.

Restenosis has also remained a major limitation of the clinical usefulness of PCI. Despite primary success rates as high as 90 %, the incidence of chronic restenosis after PCI has been reported to be as high as 40 % within 6 months. Migration of leukocytes across the endothelium, platelet aggregation and thrombus formation seem to be major reasons for restenosis after PCI. Heider et al. observed that patients that developed restenosis after PCI by six months, had significantly higher concentrations of the adhesion molecules P-selectin, E-selectin, and VCAM-1 up to 30 days following PCI than patients who did not develop restenosis.

P-selectin, a cell adhesion molecule expressed on activated endothelial cells and platelets plays a critical role in leukocyte tethering and rolling on the vessel wall and subsequent diapedesis. Following activation of endothelial cells, P-selectin can be rapidly translocated from Weibel-Palade bodies to the membrane surface to mediate leukocyte rolling by interacting with sialylated, fucosylated ligands such as P-selectin glycoprotein ligand 1 (PSGL-1). When expressed on the endothelial surface, P-selectin affects hemostasis and thrombosis. P-selectin also promotes platelet rolling and adhesion to stimulated vessel walls, supports leukocyte recruitment to thrombi and enhances fibrin formation. Furthermore, P-selectin induces formation of procoagulation microparticles and mediates microparticle recruitment to thrombi, which promotes thrombus growth and stabilization. The vessel is transformed into a proinflammatory, hypercoagulable state, which contributes to lesion growth and instability. On activated platelets, P-selectin facilitates the adhesion of monocytes to injured endothelium or subendothelial matrix.
Recent studies in apolipoprotein E-deficient mice have suggested that transient inhibition of P-selectin with either anti-P-selectin antibodies or anti-PSGL-1 antibodies significantly decreased macrophage content of atherosclerotic plaque as well as neointima formation after arterial injury. These data indicate that inhibition of P-selectin can reduce vascular injury in an animal model of atherosclerosis and may also decrease myocardial injury following PCI.

Study objective

The primary efficacy objective of this study is:
• To evaluate the efficacy of RO4905417 in reducing the procedural damage during PCI
The secondary efficacy and safety objectives of this study are:
• To evaluate the changes in other cardiac and renal biomarkers
• To evaluate the safety of RO4905417 by monitoring of adverse events and the incidence of MACEs at 30 and 120 days after PCI after a single dose of study drug

Study design

Three arms, multi-center, randomized, double-blind, placebo-controlled, study comparing 5 mg/kg dose and 20 mg/kg dose of RO4905417 versus a matching placebo. Patients will be randomized to receive either:
-Placebo administered as at least 1 hour infusion prior to PCI
-5 mg/kg of RO4905417 administered as at least 1 hour infusion prior to PCI
-20 mg/kg of RO4905417 administered as at least 1 hour infusion prior to PCI

The infusion should be completed at least one hour and not more than 24 hours before the planned PCI procedure. The patients will be assessed at 8 hours post-PCI, 16 hours post-PCI, and 24 hours post-PCI (or time of discharge, whichever is earlier). Baseline will correspond to assessments and blood

sampling performed before the infusion (before the procedure). The patients will have a safety visit at 30 and 120 days after the infusion. Patients who receive infusion, but do not undergo the planned PCI procedure will be followed for assessment of safety only.

Intervention

Patients who are eligible for the study will be treated with RO4905417 according to the schedule of assessments, outlined on page 8 and 9 in the protocol.

Study burden and risks

Risks in other studies:

RO4905417 was well tolerated up to the highest dose administered (20 mg/kg) and for up to 3-month treatment (once monthly administration) in both healthy volunteers and PAD patients.
Eight serious adverse events (SAEs) have been reported in phase I studies; rhabdomyolysis (possibly related to study medication) in a healthy subjects treated with 0.1 mg/kg, hypopharyngeal cancer (unrelated to the study medication) in a PAD patient treated with 3 mg/kg, acute hepatitis B leading to death (unrelated to the study medication) in a PAD patient treated with 0.3 mg/kg and five SAEs in patients treated with placebo, including four cardiovascular SAEs (transient ischemic attack, acute myocardial infarction, angina pectoris and intermittent claudication) and one major thrombocytopenia
Most other adverse events (AEs) were of mild/moderate intensity and resolved without sequelae. The most frequently reported AEs were headache and upper respiratory tract infection in healthy volunteers, diarrhea, hypoaesthesia and fatigue in PAD patients. Overall, the pattern and nature of AEs were similar in the placebo and the active treated groups.
No clinically significant or dose-related abnormalities were reported on ECG and vital signs. No dose-related abnormalities were reported in laboratory parameters. Elevated CPK values were the most commonly reported laboratory abnormality, but without showing dose related pattern.
Bleeding time and platelet aggregation were not affected by treatment with RO4905417, in healthy subjects as well as in PAD patients treated with aspirin or clopidogrel.
Out of 114 subjects and patients treated with RO4905417, two healthy subjects tested positive for antibodies against RO4905417. The presence of HAHA had however no impact on their safety, pharmacokinetic and pharmacodynamic profiles

Risks of research procedures:

The research procedures can also entail risks and discomfort. There is a slight

chance of pain or bruising from blood samples. Some people faint when a blood sample is taken. See also a list of all study activities on pages 8 and 9 of the Protocol or the answers to question E4, E6 and E9 of this form

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. Patients > 18 years old and < 85 years
2. Patients must be diagnosed with Non STEMI event
3. Woman of childbearing potential will be allowed only if using two acceptable methods of contraception
4. Body mass index (BMI) <40 kg/m2

Exclusion criteria

Acute ST-elevation myocardial infarction (STEMI) ;Culprit coronary lesion with a total thrombotic occlusion or a lesion requiring the use of distal embolization protection or thrombectomy devices ;Percutaneous coronary intervention (PCI) within the past 72 hours ;Thrombolytic therapy within the past 7 days ;Major surgery within the past 3 months ;History of cerebral vascular disease or stroke in the past 3 months ;Bleeding disorders ;Inadequately controlled severe hypertension ;Prior coronary artery bypass graft (CABG) surgery ;Decompensated heart failure (oedema and/or rale) ;Acute infection at screening or active chronic infection within 3 months prior to PCI ;Patients known to be HIV positive, patients receiving antiretroviral drugs, or immuno-suppressed patients ;Uncontrolled diabetes mellitus (HbA1C > 10%) at baseline

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:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-03-2012
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	16-12-2011

Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	08-02-2012
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	02-04-2012
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	21-08-2012
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	EUCTR2011-001365-40-NL
CCMO	NL38478.099.11
Other	zodra studie is goedgekeurd is de studie te vinden op www.rochetrials.com