A Clinical Outcomes Study to Compare the Incidence of Major Adverse Cardiovascular Events in Subjects Presenting with Acute Coronary Syndrome Treated with Losmapimod Compared to Placebo (PM1116197, LATITUDE STUDY)
(Short title: LosmApimod To Inhibit p38 MAP kinase as a TherapeUtic target and moDify outcomes after an acute coronary syndromE (LATITUDE)-TIMI 60)

Published: 12-03-2014
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Primary: To evaluate the efficacy of oral losmapimod compared to placebo added to standard of care in subjects with ACS on the time to first occurrence of adjudicated MACE (defined as CV death, MI, or severe recurrent ischemia requiring urgent...

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

Summary

ID

NL-OMON41191

Source
ToetsingOnline

Brief title
PM1116197 (LATITUDE)

Condition

- Coronary artery disorders

Synonym
heart attack; acute coronary syndrome

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline BV

Intervention

Keyword: ACS, losmapimod, MACE, STEMI/NSTEMI

Outcome measures

Primary outcome

Composite of adjudicated MACE that includes the time to first occurrence of CV death, MI or severe recurrent ischemia requiring urgent coronary artery revascularization.

Secondary outcome

Principal endpoint only: Time to first occurrence of the composite of CV death or MI.

Study description

Background summary

p38 mitogen-activated protein kinase (MAPK) is an important mediator of inflammation that leads to activation of cytokine production during acute coronary syndrome (ACS). Evidence suggests that p38 MAPK inhibition may potentially interrupt the inflammatory processes in the vascular wall, thus

stabilizing atherosclerotic plaques, and reducing the risk of subsequent plaque rupture.
Losmapimod is a selective inhibitor of p38 MAPK. It is being developed in several indications, e.g. COPD and ACS. The safety of losmapimod for 12 weeks, and its effects on systemic inflammation, infarct size and cardiac function was evaluated in a Phase II placebo-controlled study in 526 subjects with non-ST-segment elevation myocardial infarction (NSTEMI). Acute increases in inflammatory biomarkers during the in-hospital period were significantly attenuated on losmapimod versus placebo. Although the trial was not powered to assess clinical outcomes, there was a non-significant trend toward lower incidence of major adverse cardiovascular events (MACE) compared to placebo, which was driven by a reduction in myocardial infarction. A subgroup of subjects who underwent cardiac MRI had statistically significant improvements in left ventricular ejection fraction and left ventricular volumes at Week 12 versus placebo.
This Phase III trial will compare the effects of losmapimod for 12 weeks versus placebo when added to standard of care on the incidence of MACE in subjects with ACS (NSTEMI and STEMI).

Study objective

Primary: To evaluate the efficacy of oral losmapimod compared to placebo added to standard of care in subjects with ACS on the time to first occurrence of adjudicated MACE (defined as CV death, MI, or severe recurrent ischemia requiring urgent coronary artery revascularization through 12 weeks of therapy.
Principal secondary: to evaluate the efficacy of losmapimod on the time to first occurrence of adjudicated CV death or MI.

Study design

Multicenter randomized double blind phase III parallel group study.
Randomization 1:1 to:
* Oral losmapimod 7.5mg BID
* Placebo.
On top of standard care.
Treatment period 12 weeks, follow-up period 12 weeks.
The study has3 parts.
Part A: Subjects will be randomized to provide an initial assessment of safety and exploratory efficacy (~200 reports of primary endpoint events) before progressing to Part B1. Efficacy data from Part A of the study will not be used in the primary efficacy analysis of the trial.
Upon completion of treatment of Part A, summary level unblinded efficacy and safety data from Part A will be reviewed by a limited group involved in study conduct, who will make a decision on whether or not to proceed to Part B1. Continuation needs endorsement from the IDMC. It is expected that the protocol will not bemodified when progressing from part A to part B1. A decision to

proceed to Part B2 can only be made with endorsement with respect to safety from the IDMC. This review will occur prior to initiation of recruitment in Part B2.
Part B: will be event driven to provide the main assessment of efficacy with an event target of 1,400 adjudicated primary endpoint events, and 1,000*1,200 adjudicated CV death/MI.
25.500 patients (3.500 in part A and part B1 each and 18.500 in part B2). NL: 870 (170 in part A, 700 in B).
NB: For question C9 (participating centers and nr. of pats) for NL the data for part A have been entered. For part B additional centers will be added in due time and the total number of pats per center will be fixed.
Independent Data Monitoring Committee.

Intervention

Treatment with losmapimod or placebo.

Study burden and risks

Risk: Adverse effects of study medication.
Burden:
3 visits after hospital discharge (in part B2 possibly 1 visit and 2 telephone calls). Hospital stay not prolonged by study.
After discharge: 2 (in B2 possibly 1) times physical examination and 2 (in B2 possibly 1) times ECG.
In total max 6 (in B2 possibly 4) blood draws for study purposes (5-50 ml/occasion) plus 3 (in B2 possibly 2) times pregnancy test.
Renal substudy (optional): 2 extra visits after discharge from hospital. In total 2 extra blood draws for study purposes.

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

* Patients 35 years and above.
* Hospitalization for NSTEMI or STEMI (see protocol page 30-31 for details).
* At least one of the predictors of cardiovascular disease (see protocol page 31 for details).

Exclusion criteria

* Unable to be randomized prior to coronary revascularization or fibrinolysis for the qualifying MI.
* Severe heart failure or shock (New York Heart Association [NYHA] class III or IV, or Killip class III or IV).
* Ongoing clinical instability (see protocol page 32 for details).
* History of chronic liver disease or severe renal impairment (see protocol page 32 for details).
* Known active tuberculosis, HIV, active opportunistic or other active life threatening infections.
* Vaccination with a live attenuated vaccine within 6 weeks of randomization.
* Pregnancy, lactation.
* Use of another investigational product (see protocol page 33 for details).

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):	03-06-2014
Enrollment:	870
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	losmapimod
Generic name:	losmapimod

Ethics review

Approved WMO Date:	12-03-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	23-05-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	30-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-12-2014
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-10-2015
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
Other	clinicaltrials.gov, registratienummer n.n.b.
EudraCT	EUCTR2013-000657-50-NL
CCMO	NL48045.060.14