A Randomised, Double-Blind, Placebo-Controlled Study of the Safety and Tolerability of E5555, and its Effects on Clinical Events and Biomarkers in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome

Published: 11-12-2007
Last updated: 11-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Observational non invasive

Summary

ID

NL-OMON34002

Source
ToetsingOnline

Brief title
LANCELOT 202

Condition

- Coronary artery disorders

Synonym
ACS, Acute Coronary Syndrome

Research involving

Human

Sponsors and support

Primary sponsor: PRA Belgium BVBA
Source(s) of monetary or material Support: EISAI Limited

Intervention

Keyword: Acute coronary syndrome, Angina pectoris

Outcome measures

Primary outcome

see study objectives

Secondary outcome

see study objectives

Study description

Background summary

The inappropriate aggregation of platelets at sites of disrupted atherosclerotic plaques contributes significantly to occlusive vascular disorders such as unstable angina, myocardial infarction, and stroke. Exposure of Tissue Factor in the lipidrich
core of the plaque initiates coagulation, which leads to local thrombin generation. Thrombin, a potent platelet agonist, stimulates platelet activation and recruits additional platelets to the site of vascular injury. Because thrombin plays a central role in arterial thrombogenesis, one of the goals of most atherothrombosis treatment regimens is blockade of
its generation or inhibition of its activity.
Thrombin-triggers platelet activation through a series of G protein-coupled protease-activated
receptors (PARs). In man, PAR-1 is the major thrombin receptor molecule, although PAR-4 is also present on the platelet surface.
E5555 reversibly inhibits the thrombin-mediated activation of PAR-1 by binding to PAR-1, presumably at or near the tethered ligand-binding site.

Study objective

The primary objectives of the study are to investigate the safety and tolerability of E5555 at three dose levels in patients admitted to hospital with symptoms of Acute Coronary Syndrome (ACS). This will be assessed for a period of up to 16 weeks (112 days).
* To assess the effect of E5555 on overall bleeding (major, minor, or minimal) outcome at 1, 4, 12, and 16 weeks (7, 28, 84, and 112 days) of E5555 administration.
The secondary objectives are:
* To determine the effect of E5555 on major adverse cardiac events (MACE, which includes cardiovascular death, acute myocardial infarction [MI], stroke, refractory ischemia) and platelet aggregation (only in selected sites) at 1, 4, 12, and 16 weeks (7, 28, 84, and 112 days) following ACS.
* To assess the effect of E5555 on high-sensitivity C-Reactive Protein (hsCRP) levels.
* 12-lead continuous ECG monitoring (Holter) will be obtained for the initial 48 hours following randomisation.
* To provide data that can be used to help determine the safe and effective clinical dose/dose range.
* The pharmacokinetic (PK) and pharmacodynamic (PD) objectives will be investigated at selected sites. The objectives are to describe the PK of E5555 and its active metabolites in the patient population using an appropriate parametric PK model, and to obtain an evaluable dataset of individual patient exposures for exploration of exposure-response relationships with safety and efficacy outcomes. Additional exploratory analyses aim to identify significant patient-specific covariates with PK variables and determine the relationships between E5555 exposure and (inhibition of) platelet aggregation, and markers of endovascular inflammation.
* The exploratory objectives, are to investigate the effect of E5555 on markers of endovascular inflammation including but not limited to soluble ligand CD40 [sCD40L], Lipoprotein-associated phospholipase A2 [Lp-PLA2], myeloperoxidase [MPO], placental growth factor [PlGF] and cytokines such as interleukin 6 and 18 [IL-6 and IL-18].

Study design

This is a multicenter, randomized, double-blind, placebo-controlled study. Approximately 200 qualified sites in the US, Canada, Europe, Israel, South Africa, Australia, and South America will be selected for participation.
600 patients in 4 treatment arms: loading dose 400mg (drug or placebo)
1.E5555 50 mg (one 50 mg active and two 100 mg placebo tablets) po once daily for 24weeks (168 days)
2.E5555 100 mg (one 50 mg placebo, one 100 mg active, and one 100 mg placebo tablets) po once daily for 24 weeks (168 days)
3. E5555 200 mg (one 50 mg placebo and two 100 mg active tablets) po once daily for 24 weeks (168 days)
Control arm:
4. Placebo (one 50 mg placebo and two 100 mg placebo tablets) po once daily for

24 weeks (168 days)

Study burden and risks

In animal studies, E5555 was found to bind melanin (substance in the eye that protects one*s sight from the sun*s UV radiation) in the eye. In the studies in healthy volunteers, some subjects reported adverse events related to the eye (see below).
310 healthy volunteers have taken at least 1 dose of E5555 in 10 previous research studies. The most common side effects seen with the use of E5555 up to 600 mg/day include headache, dizziness, pharyngolaryngeal pain (sore throat), cough, chest pain, bruising, dry lips and nausea. The majority of these events were of mild severity.
The following eye disorders were reported infrequently as adverse events during clinical trials and are considered mild: blurred vision, eye redness, conjunctivitis (red itchy eye with a discharge), eye pain, eye itch and eye irritation.

E5555 is a platelet inhibitor which means that it may increase the risk of bleeding, especially in people that need to have an invasive medical procedure. There is no medication that can stop or prevent the effects of E5555 on platelets. However, for some people a platelet transfusion might reverse the effects of E5555 on platelets, if necessary. If you need to have an invasive medical procedure during the Study, please tell the study doctor or study staff.

The number of reported bleeding events in these 10 previous research studies in healthy volunteers was very low; however nosebleeds, eye redness, gum bleeding, increased bruising and prolonged oozing of blood from sites used for venous access (where the blood was drawn from) have been reported. All these events were of mild severity.

In a small clinical study conducted in human volunteers that used very high doses of the E5555 study drug (including 800 and 1200 mg), some of the volunteers had irregular heart rhythm seen on electrocardiogram (ECG), which is also known as a *QT prolongation.* This finding was observed in a small number of the volunteers who were given a higher dose of E5555 study drug that ranged from 4-24 times the doses you could receive during your participation in this clinical study. None of the subjects in the study experienced a side effect associated with the irregular heart rhythm.
Large increases in the QT interval prolongation have been shown to be associated with serious defects of the heart rhythm (arrhythmias) and may lead to death in very rare cases.

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

* Men and women (women of child-bearing potential must use adequate contraception)
* Presenting with features of non-ST segment elevation ACS (unstable angina or MI without persistent ST elevation). There must be new onset or a worsening pattern of characteristic ischemic chest pain or ischemic symptoms occurring at rest or with minimal activity (lasting longer than 5 minutes or requiring sublingual nitroglycerin for relief of the pain)
* Randomisation and treatment possible within 72 hours of symptoms. Every effort should be made to randomize and treat eligible subjects as soon after hospital admission as possible.
* Age 18*80 years inclusive
* and at least one of the following two criteria on admission:
- Troponin T or I * ULN or CKMB * ULN for the local institution
- ECG changes compatible with ischemia (i.e. ST depression at least 1 mm in 2

contiguous leads or T wave inversion > 3 mm or any dynamic ST shift or transient ST elevation)

Exclusion criteria

* Unwilling or unable to provide informed consent
* History of acquired or congenital bleeding disorder, coagulopathy or platelet disorder
* Recent trauma or major surgery (within the 30 days prior to screening/baseline)
* Recent (within 14 days prior to screening/baseline) significant infection or history of chronic infections with a recurrence < 14 days prior to screening/baseline visit and/or requiring continuous antibiotic treatment
* Evidence of active pathological bleeding at screening/baseline or history of bleeding (such as gastrointestinal or genitourinary) within the last 6 months prior to screening/baseline visit, unless the cause has been definitely corrected
* History of intracranial bleeding e.g. hemorrhagic stroke, subdural hematoma, subarachnoid hemorrhage) or history of hemorrhagic retinopathy
* History of ischemic stroke or transient ischemic attack, within the past year prior to screening/baseline or known structural cerebral vascular lesion (eg, arteriovenous malformation [AVM], aneurysm)
* Haematological abnormalities: platelet count <100 x 103 /
*L, haemoglobin < 10 g/dL at screening/baseline visit (day 1)
* History of NYHA class III or IV congestive heart failure or history of severe, uncontrolled cardiac arrhythmias at screening/baseline
* Patients with ST-segment changes at baseline attributed to left ventricular hypertrophy with repolarisation changes, bundle branch block and digoxin will be excluded.
* A marked prolongation of QT/QTc interval (>500 ms) at the screening/baseline visit (Day 1)
* Percutaneous cardiac intervention or coronary artery surgery in the previous 12 weeks prior to the screening/baseline visit
* Significant (as determined by the investigator) cardiovascular events (such as a Q wave MI) within the past 30 days prior to the screening/baseline visit
* Planned elective surgical operation or major invasive procedures planned from 30 days prior to screening to completion of the study (the decision of what constitutes a major invasive procedure will be at the discretion of the investigator in conjunction with review and approval by the Medical Monitor)
* Unstable diabetes requiring frequent adjustments to medications (other than insulin) in the 30 days prior to the screening/baseline visit
* Documented history of chronic liver disease and/or screening/baseline ALT or AST > 3 x ULN or total bilirubin > 1.5 x ULN (unless the abnormal bilirubin is secondary to Gilbert*s syndrome)
* History of rheumatologic or autoimmune diseases
* Significant renal impairment, defined as creatinine clearance of < 30mL/min
* History of cancer (other than basal cell carcinoma, cervical carcinoma in situ, or lowgrade prostate cancer), unless adequately treated with no evidence of disease recurrence for at least 2 years
* Use of any of the following drugs in the 30 days prior to the screening / baseline visit and

for the duration of the study:
o Oral anti-thrombotics other than aspirin (daily aspirin dose of 325 mg or lower) and/or clopidogrel (75 mg chronically; loading dose allowed) and/or Ticlopidine (250mg BID)
o Anticoagulants (e.g. coumadin, warfarin)
o Fibrinolytics (eg, tPA, streptokinase, urokinase)
o NSAIDs, other than occasional use
o COX-2 inhibitors (other than occasional use)
o Potent and moderate CYP (global) 3A4 inhibitors (please refer to Appendix 6)
o Select ed CYP 2D6 subtrates (please refer to Appendix 6)
o Herbals with anti-platelet properties:
* ginkgo biloba
* Horse chestnut (Aesculus hippocastanum)
* Use of another investigational drug or device within previous 30 days (12 weeks for investigational devices, eg, unapproved stents) prior to sceening/baseline visit
* Pregnanct or nursing women
* Use of illicit drugs or alcohol abuse 3 months prior to the screening or during the course of the study.

Study design

Design

Study phase:	2
Study type:	Observational non invasive
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):	23-10-2008
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	E5555
Generic name:	/

Ethics review

Approved WMO Date:	11-12-2007
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	13-03-2008
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-08-2008
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	26-08-2008
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	13-01-2009
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	17-03-2009
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	27-04-2009
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	25-05-2009
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2006-000296-15-NL

Register	ID
CCMO	NL20342.098.07