# A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Tolerability of E5555, and its Effects on Markers of Intravascular Inflammation in Subjects with Coronary Artery Disease

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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-OMON33893

**Source**
ToetsingOnline

**Brief title**
E5555-G000-201

### Condition

- Coronary artery disorders

**Synonym**
Coronary Artery Disease

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** Atherosclerosis, coronary artery disease, PAR

## Outcome measures

### Primary outcome

see objectives

### Secondary outcome

see 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 assess the safety and tolerability of E5555 in subjects with coronary artery disease (CAD) (Revised per Amendment

01).
The secondary objectives are to determine the effect of E5555 on (a) the incidence of major adverse cardiovascular events (MACE) (cardiovascular death, myocardial infarction, stroke, and refractory ischemia) and (b) platelet aggregation inhibition (in qualified sites in subjects willing to take part in this component of the study) (Revised per Amendments 01 and 02).
The exploratory objective being pursued is to determine the effect of E5555 on the endovascular inflammatory processes that are believed to be integral to the pathogenesis of CAD.
In addition, the pharmacokinetics of E5555 and its metabolites will be determined; qualified sites will conduct comprehensive plasma sample collection for measurement of levels of E5555 and its metabolites to evaluate the relationship between E5555 pharmacokinetics and pharmacodynamics (Revised per Amendments 01 and 02).

## Study design

This is a multicenter, randomized, double-blind, placebo-controlled study.
Approximately 140 qualified sites in the US, Canada, Europe, Israel, India, Australia, and South America will be selected for participation.
600 patients in 4 treatment arms:
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

1. Age 45 * 80 years, inclusive
2. Males or Females (females of childbearing potential must use adequate contraception)
3. Confirmed coronary artery disease defined as one of the following:
a. Post-ACS (>4weeks) or MI (>4 weeks) or Post PCI (>4 weeks) or
CABG (>12 weeks) or
b. Angina pectoris with documented (ECG or imaging study) ischemia or
c. Angiographically documented lesion occluding *70% of a coronary
vessel
and at high risk as defined as one or more of the following:
a. Screening hsCRP *3.0 mg/L
b. History of diabetes mellitus, under Rx treatment
c. Documented history of peripheral arterial disease
d. Documented history of thrombo-embolic TIA or stroke >1 year prior to
screening
e. Documented history of carotid artery disease
4. All subjects must be receiving low dose aspirin (75-325 mg) and/or clopidogrel
75 mg once daily. Ticlopidine 250 mg twice daily with or without low dose aspirin
once daily is also allowed. These medications must have been taken for at least
1 month prior to Screening.

## Exclusion criteria

1. Unwilling or unable to provide informed consent
2. History of acquired or congenital bleeding disorder, coagulopathy, or platelet
disorder
3. Recent trauma or major surgery in the past 30 days prior to Screening
4. Evidence of active pathological bleeding at screening or history of bleeding

(such as gastrointestinal or genitourinary) within the 6 months prior to Screening, unless the cause has been definitely corrected
5. History of intracranial bleeding (eg, hemorrhagic stroke, subdural hematoma, subarachnoid hemorrhage) or history of hemorrhagic retinopathy
6. History of ischemic stroke or transient ischemic attack within the past year prior to Screening or known structural cerebral vascular lesion (eg, arterial venous malformation, aneurysm)
7. Hematological abnormalities: INR >1.5 or PTT >1.5 X ULN, Platelet count <100 x 103/*L (<100 x 109/L), Hemoglobin <10 g/dL at Screening
8. History of New York Heart Association class 3 or 4 congestive heart failure or history of severe, uncontrolled cardiac arrhythmias at Screening
9. Significant (as determined by the Investigator) cardiovascular events in the 30 days prior to the Screening Visit or newly prescribed or dose adjustments made to cardiovascular medications in the 30 days prior to the Screening Visit
10. Planned elective surgical operation or major invasive procedure from 30 days before 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)
11. Unstable diabetes requiring frequent adjustments to medications (other than insulin) in the 30 days prior to the Baseline Visit
12. Documented history of chronic liver disease and/or Screening ALT or AST >3 x ULN or Total Bilirubin >1.5 x ULN (unless the abnormal bilirubin level is secondary to Gilbert*s syndrome)
13. Documented presence of rheumatologic or autoimmune diseases requiring continuous treatment with anti-inflammatory agents
14. Significant renal impairment, defined as creatinine clearance <30 mL/min (Revised per Amendment 02)
15. History of cancer (other than basal cell carcinoma of the skin, cervical carcinoma in situ, or low-grade prostate cancer), unless adequately treated with no evidence of disease recurrence for at least 2 years
16. Recent (within 14 days prior to Baseline Visit) significant infection or history of chronic infections with a recurrence <14 days prior to the Screening Visit and/or requiring continuous antibiotic treatment
17. Use of any of the following drugs in the 30 days prior to Screening and for the duration of the study:
* Oral anti-thrombotics other than low dose aspirin (daily aspirin dose of 325 mg or lower) and/or clopidogrel (75 mg) and/or ticlopidine (250 mg bid)
* Anticoagulants (eg, coumadin, warfarin)
* Fibrinolytics (eg, TPA, streptokinase, urokinase)
* NSAIDs, other than occasional use
* COX-2 inhibitors, other than occasional use
* Potent and moderate CYP (global) 3A4 inhibitors (see Appendix 8):
Selected CYP 2D6 substrates: (See Appendix 8)
* Herbals with antiplatelet properties:
* ginkgo biloba
* Horse chestnut (Aesculus hippocastanum)

18. Use of another investigational drug within 30 days prior to the Screening Visit or use of an investigational device (eg, unapproved stent) within 12 weeks prior to the Screening Visit
19. Pregnancy, or nursing women
20. Use of illicit drugs or alcohol abuse 3 months prior to the screening or during the course of the study.
21. A marked prolongation of QT/QTc interval (>500 ms or >60 msec over baseline) at the Screening (Day -21 to -1) or Baseline visits (Day 1).

# Study design

## Design

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| 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): | 19-05-2008 |
| Enrollment: | 24 |
| Type: | Actual |

## Medical products/devices used

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

# Ethics review

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| Approved WMO Date: | 11-12-2007 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| Approved WMO Date: | 13-03-2008 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| Approved WMO Date: | 26-08-2008 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| Approved WMO Date: | 13-01-2009 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| Approved WMO Date: | 17-03-2009 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| Approved WMO Date: | 27-04-2009 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| Approved WMO Date: | 29-07-2009 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| Approved WMO Date: | 21-09-2009 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |

## 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 | EUCTR2005-006029-94-NL |
| CCMO | NL20255.098.07 |