# A randomized, double-blind, placebo-controlled, multi-centre, sequential design, phase IIa study to evaluate safety and tolerability of epicardial injections of AZD8601 during coronary artery bypass grafting surgery.

Published: 28-11-2018
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Primary Objective; To investigate safety and tolerability of AZD8601 following epicardial injection in patients undergoing Coronary Artery Bypass Grafting (CABG) surgery with moderately impaired systolic function. In addition, exploratory objectives...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Heart failures |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON49505

**Source**
ToetsingOnline

**Brief title**
EPICCURE

### Condition

- Heart failures

**Synonym**
heart failure, ischaemic heart disease

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Astra Zeneca
**Source(s) of monetary or material Support:** opdrachtgever/sponsor AstraZeneca

## Intervention

**Keyword:** Coronary artery bypass grafting surgery, Epicardial injections, Heart Failure, VEGF-A165- modified RNA

## Outcome measures

### Primary outcome

To investigate safety and tolerability of AZD8601 following epicardial

injection in patients undergoing Coronary Artery Bypass Grafting (CABG) surgery

with moderately impaired systolic function.

Outcome measures:

- Adverse Events/Serious Adverse Events (AEs/SAEs)

- Vital signs (blood pressure, pulse)

- Electrocardiogram (ECG)

- Left Ventricular Ejection Fraction (LVEF)

- Physical examination

- Laboratory assessments (hematology, clinical chemistry and urinalysis)

### Secondary outcome

NA

# Study description

## Background summary

Coronary artery disease (CAD) is characterized by constrictions in the coronary arteries of the heart causing insufficient oxygen-rich blood to flow to the heart muscle. This causes damage to the heart muscle, which prevents the heart from functioning properly. In addition, CAD is a primary cause of heart failure. This is due to a reduced squeezing force of the left ventricle causing less blood to be pumped out of the heart.

Despite all possible treatments (revascularization, medication, new devices such as resynchronization therapy) there remains an unmet medical need because these treatments are usually unable to restore the full physiological functionality and that makes innovative treatments essential for this population.

The study will investigate the safety and tolerability of AZD8601 (versus placebo). AZD8601 is VEGF-A165 modRNA under development as a novel modality for local production of human VEGF-A protein and is developed for the treatment of ischemic heart disease through stimulation of angiogenesis. The study examines the effects of AZD8601 given as epicardial injections in patients with stable CAD with decreased left ventricular ejection fraction (LVEF) going through elective CABG.

Primarily the safety and tolerability of AZD8601 in increasing doses in patients going through CABG will be assessed. In addition, exploratory objectives that address the capabilities of AZD8601 to improve global and local myocardial perfusion and/or left ventricle function in the studied patient cohort will be explored.

## Study objective

Primary Objective; To investigate safety and tolerability of AZD8601 following epicardial injection in patients undergoing Coronary Artery Bypass Grafting (CABG) surgery with moderately impaired systolic function.

In addition, exploratory objectives that address the capabilities of AZD8601 to improve global and local myocardial perfusion and/or left ventricle function in the studied patient cohort will be explored (patients with stable CAD with decreased left ventricular ejection fraction (LVEF) going through elective CABG).

## Study design

This is a randomized, double-blind, placebo-controlled, sequential design, multicentre study in patients with moderately impaired systolic function undergoing CABG surgery.

The study will include two cohorts of 12 patients each, which will receive either a low or high dose of AZD8601 (see Section 7.2 of the protocol) in a sequential, dose ascending fashion. Within each cohort 8 patients will be randomized to receive AZD8601 and 4 to placebo.

Each cohort will be divided into 3 sentinel dosing cohorts. See Figure 1 section 1.4. The two first will include 2 patients each * 1 patient randomized to placebo and 1 to AZD8601. The third sentinel cohort will include the 8 remaining patients on that dose level; 2 placebo, 6 AZD8601. After each sentinel cohort, before proceeding dosing the next, safety data from up to 1 month post dose (Visit 5) from the current cohort and the available data from previous cohorts, will be reviewed. The same applies before continuing to the high dose cohort. The procedure will be repeated in the same way within the high dose cohort.

**Intervention**

subjects will receive either AZD8601 or placebo. AZD8601 will be administered as epicardial injections. Thirty injections of either 0.1 mg (3 mg per subject) or 1 mg (30 mg per subject) will be given on a single occasion with approximately 1 cm injection distance and 200 *L per injection.

Placebo for AZD8601 will be administered in the same manner as AZD8601 and in a volume and injection distance to match AZD8601.

**Study burden and risks**

The subject is asked to visit the site at least 6 times. 5 visits time will last maximally 5 hours, 1 visit will be the hospitalization for elective CABG. The subject will be contacted by telephone 1 time. This telephone contact will last maximally 10 minutes. Blood samples will be taken in this study. The total volume of blood that will be collected is approximately 450 ml. The subject will undergo physical examinations at every hospital visit. The subject will undergo 3 times a 15O PET/CT Scan. The subject will be asked to fill out 2 questionnaires at 4 hospital visits. Women must be non-child bearing potential confirmed at screening. The subject will undergo 5 times an echography. The subject will undergo 2 times a stress echocardiography. The subject will receive the studymedication 1 time on a single occasion. The taking of bloodsamples may cause some discomfort. The administration by epicardial injections may cause some side effects as cardiac arrhythmia.

In a ongoing phase 1 trial where AZD8601 is administered as intradermal injections, AZD8601 was well tolerated without SAE`s. In terms of AE`s the most common was local transient injection site reaction which is completely reversible.

Riskreduction:After each sentinel cohort, before proceeding dosing the next, safety data from up to 1 month post dose (Visit 5) from the current cohort and the available data from previous cohorts, will be reviewed. The same applies before continuing to the high dose cohort. The procedure will be repeated in the same way within the high dose cohort.
Two parallel safety reviews will be done:
* Blinded safety review board (SRB) consisting of study investigators and AZ personnel
* Study independent unblinded safety review committee (SRC) consisting of internal AZ expertise

## Contacts

**Public**
Astra Zeneca

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Astra Zeneca

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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. Provision of signed and dated informed consent prior to any study specific procedures
2. Males and females:
a. Males must be surgically sterile or using an acceptable method of contraception (see Section 3.8.5)
b. Females must be of non-childbearing potential confirmed at screening by fulfilling one of the following criteria a) postmenopausal defined as amenorrhoea for at least 12 months or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels in the postmenopausal range, b) documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
3. Age >18 years
4. Indication for elective CABG surgery enrolled at least 15 days before the planned surgery
5. Moderately reduced global LVEF at rest (30% * LVEF * 50%) from medical records
6. If patient is on statin, ACE inhibitor/ARB, and/or beta-blocker, the dose should be stable at least 2 weeks prior to Visit 1
7. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of AZD8601.

## Exclusion criteria

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
2. Previous randomisation in the present study
3. Participation in another clinical study with an investigational product during the last 3 months
4. BMI > 35 kg/m2 OR poor image window for echocardiography
5. Need for CABG emergency operation. (Emergency operation is defined as significant symptom status worsening in CAD, such as crescendo angina, unstable angina or ACS requiring rescheduling the revascularization. CAD should be stable at least 3 months prior to Visit 3.)
6. History of ventricular arrhythmia (* Lown III) without Implantable Cardiac Defibrillator (ICD)
7. History of any clinically significant disease or disorder which, in the opinion of the PI, may either put the patient at risk because of participation in the study, or influence the results or the patient*s ability to participate in the study
8. Severe co-morbidities that can interfere with the execution of the study, interpretation of study results or affect the safety of the patient, in

judgement of the investigator
9. eGFR * 30 mL/min (derived from creatinine clearance, calculated by local lab)
10. For CFVR (Visit 1) and sMBF (Visit 2) measurement:
- Known severe adverse reactions to adenosine
- Known elevated intracranial pressure
- AV block * second degree and/or sick sinus syndrome in patient without pacemaker
- Heart rate < 40 bpm (ECG verified)
- Systolic blood pressure < 90 mmHg
- Asthma or COPD with strong reactive component in judgement of investigator
- Treatment with dipyridamole (e.g. Persantin or Asasantin), theophyllamine or fluvoxamine that cannot be paused
11. Inability to comply with the protocol
12. History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity to drugs with a similar chemical structure or class as study drugs
13. Patients unable to give their consent or communicate reliably with the investigator or vulnerable patients e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order
14. Positive hepatitis C antibody hepatitis B virus surface antigen or hepatitis B virus core antibody or human immunodeficiency virus, at Visit 1
15. Known history of drug or alcohol abuse
16. Any concomitant medications that are known to be associated with Torsades de Pointes
17. History of QT prolongation associated with other medications that required discontinuation of that medication
18. Congenital long QT syndrome
19. History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3).
20. Current atrial fibrillation as well as paroxysmal atrial fibrillation.

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |

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| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

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| Recruitment status: | Will not start |
| Enrollment: | 5 |
| Type: | Actual |

## Ethics review

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|---|---|
| Approved WMO Date: | 28-11-2018 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-03-2019 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 10-05-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 20-06-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 20-01-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO | |

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|---|---|
| Date: | 26-02-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 23-03-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 25-05-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 05-06-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# 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 | EUCTR2017□002690□19-NL |
| ClinicalTrials.gov | NCT03370887 |
| CCMO | NL67762.056.18 |