Clinical Study Report Synopsis	
Drug Substance	AZD8601
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A Randomised, 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

Study dates:

First subject enrolled: 05 February 2017

Last subject last visit: 30 June 2021

Date of early study termination and reason: 04 March 2021 due to low patient recruitment

The analyses presented in this report are based on a clinical data lock date of 23 July 2021

Phase of development:

Therapeutic exploratory (IIa)

[redacted]

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted by 4 investigators at 2 sites in Finland and 2 sites in Germany.

Publications

Anttila V, Saraste A, Knuuti J, Jaakkola P, Hedman M, Svedlund S et al. Synthetic mRNA Encoding VEGF-A in Patients Undergoing Coronary Artery Bypass Grafting: Design of a Phase 2a Clinical Trial. Mol Ther Methods Clin Dev. 2020;18464-72

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary-Safety	
• To investigate safety and tolerability of AZD8601 following epicardial injection in patients undergoing CABG surgery with moderately impaired systolic function	• AEs/SAEs • Vital signs (blood pressure, pulse) • ECG • LVEF • Physical examination • Laboratory assessments (haematology, clinical chemistry and urinalysis) • Assessment of haemopericardium and/or tamponade
Exploratory	
• To assess the effect of AZD8601 on baseline cardiac function	• Regional and global sMBF measured with 15O PET imaging • Regional and global quantitative MPR measured with 15O PET • LVEDV, LVESV and global LVEF by echocardiography • Regional myocardial wall motion measured by echocardiography and strain analysis (GLS)
• To assess the effect of AZD8601 on adenosine-induced stress cardiac function	• Stress cardiac function measured by echocardiography.
• To assess the effect of AZD8601 on clinical symptoms	• NYHA class, SAQ and KCCQ [a]
• To assess the effect of AZD8601 on markers of cardiac damage	• Change from baseline in terms of [redacted] related to AZD8601 treatment
• Determination of VEGF-A protein in plasma after epicardial injection of AZD8601or placebo	• Concentration of VEGF-A protein in plasma

[a] KCCQ quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life as an overall score

Adenosine-induced stress cardiac function was to be assessed by echocardiography but data were only collected for 2 participants and not reported in this CSR. Collection of plasma samples was made for potential future investigation of VEGF-A downstream markers, [redacted] (AZD8601) and assessment of ADA.

15O PET; Oxygen[15] positron emission tomography; ADA, anti-drug antibody(ies); AE, adverse event; CABG, coronary artery bypass grafting; CSR, Clinical study report; ECG, electrocardiogram; GLS; global longitudinal strain; [redacted] KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MPR, myocardial perfusion reserve; [redacted]; NYHA, New York Heart Association; SAE, serious adverse event; SAQ, Seattle Angina Questionnaire; sMBF, stress myocardial blood flow; VEGF-A, vascular endothelial growth factor A

Study design

The proposed indication for AZD8601 is the treatment of ischaemic heart disease. This was a randomised, double-blind, placebo-controlled, sequential design, multicentre study to investigate safety and tolerability of AZD8601 following epicardial injections. Exploratory objectives were also planned to address the capability of AZD8601 to improve global and local myocardial perfusion and/or left ventricle function as well as patient reported outcome(s) (PRO[s]).

Participants, investigators, and the contract research organisation responsible for site monitoring were blinded to investigational product (IP). Participants were identified by screening of hospital medical and eligible participants were randomly assigned using the AstraZeneca randomisation solution after the outcome of a pre-operative cardio-thoracic surgery conference.

The study was to include two dose cohorts, which were to receive a total dose of [redacted] of AZD8601. Dosing for each dose cohort was to proceed using three sentinel cohorts. In the first and second sentinel cohorts, 2 patients were to be randomised to placebo or [redacted] AZD8601 at a ratio of 1:1. In the third sentinel cohort, 8 patients were to be randomised to placebo or [redacted] AZD8601 at a ratio of 1:3. However, due to low recruitment levels, only 7 participants receiving a total dose of [redacted] AZD8601 and 4 participants receiving placebo completed dosing, according to the randomisation scheme, and the study.

Target population and sample size

The target population was participants aged > 18 years with moderately reduced global LVEF at rest (30% ≤ LVEF ≤ 50%) from medical records, undergoing elective coronary artery bypass grafting (CABG) surgery and enrolled at least 15 days before the planned surgery. CAD should have been stable for at least 3 months prior to surgery and they should have had no history of ventricular arrhythmia (≥ Lown III) and be without an Implantable Cardiac Defibrillator (ICD). History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which was symptomatic or required treatment and current atrial fibrillation as well as paroxysmal atrial fibrillation were also contraindicated.

The sample size was not based on formal statistical considerations but it was estimated that 24 patients (8 per arm) needed to be randomised and receive treatment in order to achieve

21 evaluable patients (7 per arm). Ultimately, this sample size was not achieved due to low levels of recruitment, and 7 participants receiving a total dose of [redacted] AZD8601 and 4 participants receiving placebo completed the study with no participants assigned to the [redacted] AZD8601 treatment group.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

AZD8601 ([redacted]), supplied as a [redacted] solution for injection ([redacted]), was administered as [redacted] epicardial injections [redacted] on a single occasion, total dose [redacted] The matching placebo was supplied as a solution for injection ([redacted]9) and administered as [redacted] epicardial injections ([redacted]) on a single occasion.

Duration of Treatment

Single dose.

Statistical Methods

Data were analysed using mixed model repeated measures (MMRM) (fixed factors: treatment, visit, treatment*visit interaction with baseline, also considered as fixed, as a covariate) or ANCOVA (fixed factor: treatment with baseline, considered as fixed, as a covariate).

15O PET data was analysed for changes from baseline at Visit 6 and echocardiography data was analysed for changes from baseline at Visit 7 using MMRM.

Study Population

In total, 15 participants were enrolled from 4 sites in 2 countries and 11 patients were randomised into the study: 7 patients to the [redacted] AZD8601 group and 4 patients to the placebo group. Eight participants were randomised at 2 centres in Finland (total 4 each in the [redacted] AZD8601 and placebo treatment groups). Three participants were randomised in Germany, all of whom were randomised to the [redacted] AZD8601 treatment. There were no randomised participants withdrawn or discontinued from the study. All participants completed treatment and completed the study up to Visit 7 at the 6 month follow-up visit. Treatment groups were balanced in terms of participants' age with a similar proportion of participants ≥ 65 years. All participants were white, not Hispanic or Latino, and in the AZD8601 treatment group all were male, whereas in the placebo treatment group there were equal numbers of male and female participants

Summary of Efficacy Results

There were no primary or secondary efficacy objectives in this study, but a number of exploratory analyses were performed to assess cardiac function. None of these assessments were statistically different between treatment groups. Numerical improvements were observed

when comparing change from baseline for AZD8601 [redacted] versus placebo for a number of efficacy parameters, including LVEF, NT-proBNP and patient reported outcomes.

Summary of Safety Results

All of the 7 patients randomised to the [redacted] AZD8601 treatment group and the 4 participants randomised to the placebo treatment group completed the study. There were no deaths recorded, no discontinuations and none of the 7 serious adverse events reported (2 on-treatment, 4 in follow-up in the AZD8601 treatment group and 1 in follow-up in the placebo group) were assessed as treatment related. The adverse events were balanced between groups and were as expected for this patient population and CABG surgery.

No clinically significant symptoms were observed for vital signs, clinical laboratory results, or 12-lead electrocardiograms. No malignant arrhythmias were observed, and there was no negative impact on LVEF or %GLS (measures of the pumping capacity of the heart) up to 6 months after epicardial injection.

Conclusion(s)

- Epicardial administration of investigational product was well tolerated and all of the 7 participants randomised to the [redacted] AZD treatment group and the 4 randomised to the placebo treatment group completed the study.
- It was not possible to draw definitive conclusions as to efficacy of AZD8601 in any of the exploratory assessments numerical improvements for some parameters. An adequately powered study is needed in order to draw any conclusions from these observations.