mRNA Encoding VEGF-A in Patients Undergoing Coronary Artery Bypass Grafting: Results of the Phase 2a EPICCURE Clinical Trial

Vesa Anttila MD PhD
Heart Center, Turku University Hospital and University of Turku, Turku, Finland

Co-authors: Antti Saraste, Juhani Knuuti, Marja Hedman, Pekka Jaakkola, Karl-Ludwig Laugwitz, Markus Krane, Kenneth R Chien, Anders Jeppsson, Jaya Rosenmeier, Pernilla Zingmark, Anna Rudvik, Pavlo Garkaviy, Christina Watson, Mene Pangalos, Anna Collén, Regina Fritsche Danielson, Li-Ming Gan

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Background

Endogenous VEGF-A production by mRNA shown to stimulate epicardial progenitor cells in vitro\(^1\)

A single cardiac administration of VEGF-A mRNA (AZD8601) improves cardiac function after MI in pigs\(^2\)

VEGF-A is made within the cells and secreted into the neighboring microenvironment

MI, myocardial infarction; mRNA, messenger ribonucleic acid; VEGF-A, vascular endothelial growth factor A

Phase 1 Study

Intradermal injection of AZD8601 was safe and tolerable and showed a dose-dependent VEGF-A protein production and transient vasodilation

Microdialysis sampling of VEGF-A protein

Dose-dependent protein production following single injection of VEGF-A mRNA (AZD8601)

mRNA, messenger ribonucleic acid; VEGF-A, vascular endothelial growth factor A
EPICCURE Study Objectives

Primary
• To evaluate the safety and tolerability of the first therapeutic VEGF-A mRNA AZD8601, in a cardiac indication

Exploratory
• To explore potential effects of AZD8601 on cardiac-related intermediate endpoints, such as ejection fraction, NT-proBNP, and patient reported outcomes
Methods

• EPICCURE was a randomized, double-blind, placebo-controlled, sequentially designed study for intracardiac delivery of a naked VEGF mRNA, AZD8601 formulated in citrate saline buffer

• Inclusion criteria
  • Age ≥ 18 years
  • Indication for elective CABG surgery enrolled at least 15 days before planned surgery
  • Moderately reduced global LVEF at rest (LVEF 30–50%)
  • Stable medication at least 2 weeks prior to enrollment

CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; mRNA, messenger ribonucleic acid; VEGF-A, vascular endothelial growth factor A
### Methods

<table>
<thead>
<tr>
<th>Screening/enrolment</th>
<th>Treatment</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td><strong>Baseline</strong>&lt;br&gt;15O water PET&lt;br&gt;Echo&lt;br&gt;Biomarkers Questionnaires</td>
<td><strong>CABG surgery dosing</strong>&lt;br&gt;AZD8601 (3 mg) as 30 injections or placebo as 30 injections</td>
<td><strong>1 month</strong>&lt;br&gt;15O water PET Echo Biomarkers Questionnaires</td>
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<td><strong>Cardiac surgery conference</strong>&lt;br&gt;• Individual injection map agreed&lt;br&gt;• Randomization</td>
<td><strong>3 months</strong>&lt;br&gt;15O water PET Echo Biomarkers Questionnaires</td>
<td><strong>6 months</strong>&lt;br&gt;Echo Biomarkers Questionnaires</td>
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11 patients enrolled: AZD8601, 7 patients; Placebo, 4 patients

CABG, coronary artery bypass graft; PET, positron emission tomography
**Methods**

15O PET imaging was used to create tailored injection maps in patients.

30 direct intracardiac injections of total 3 mg into ischemic but viable myocardium.

PET, positon emission tomography
Results

Safety and tolerability

• There were no deaths or treatment-related serious adverse events
• Two participants in each of the AZD8601 and placebo groups had post-operative atrial fibrillation
• No severe clinically significant arrhythmias in any group up to 6 months after therapy
• Two out of four patients in the placebo group had pleural effusion
• No infections occurred
• All leucocyte counts, including monocytes, returned to normal levels after surgery
Results

Stress Myocardial Blood Flow

- No difference in treatment area stress myocardial blood flow between AZD8601 and placebo

In all patients (N = 11):
- 0.85 mL/g/min (69%) increase from baseline to day 30 ($p < 0.01$)
- 0.42 mL/g/min (37%) increase from baseline to day 90 ($p < 0.01$)

Comparison with placebo

<table>
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<tr>
<th>LS mean difference</th>
<th>95% CI</th>
<th>p-value</th>
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<td>0.0272</td>
<td>(−0.5912, 0.6456)</td>
<td>0.923</td>
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Myocardial blood flow during stress in treated area

CI, confidence interval; LS, least squares
Results

Left Ventricular Ejection Fraction

Month 6

Mean (95% CI) change from baseline LVEF (%)

AZD8601 3 mg

Placebo

CI, confidence interval; LS, least squares
Results

Biomarker: NT-proBNP

All AZD8601-treated patients versus 1 of 4 placebo-treated patients had NT-proBNP levels below heart failure limit at 6 months.

Individual patient data

NT-proBNP (pmol/L) vs Month

AZD8601 3 mg
Placebo

NT-proBNP, N-terminal pro–B-type natriuretic peptide
Results

Patient Reported Outcomes

KCCQ-OSS

- AZD8601 3 mg
- Placebo

Data are mean (90% CI)

Month

SAQ-TSS

Points

Data are mean (90% CI)

Month

KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Symptom Score; SAQ-TSS, Seattle Angina Questionnaire Total Symptom Score
Summary

• Seven patients treated with VEGF-A mRNA, AZD8601, compared with four placebo-treated patients

• The EPICCURE study met the primary endpoint of safety and tolerability for the 3 mg dose

• No statistically significant changes in exploratory endpoints, but encouraging trends in the 3 main heart failure domains, LVEF, NT-proBNP, and patient related outcomes

• Results support further investigation of AZD8601 in future larger clinical studies
Acknowledgements

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