

Vascular endothelial growth factor A (VEGF-A) (AZD-8601)

Last program update: May 7, 2020

Modality	Program #	Program Indication	Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
 Localized regenerative therapeutics	AZD8601	VEGF-A <i>Myocardial ischemia</i> 					AZ to pay milestones and royalties

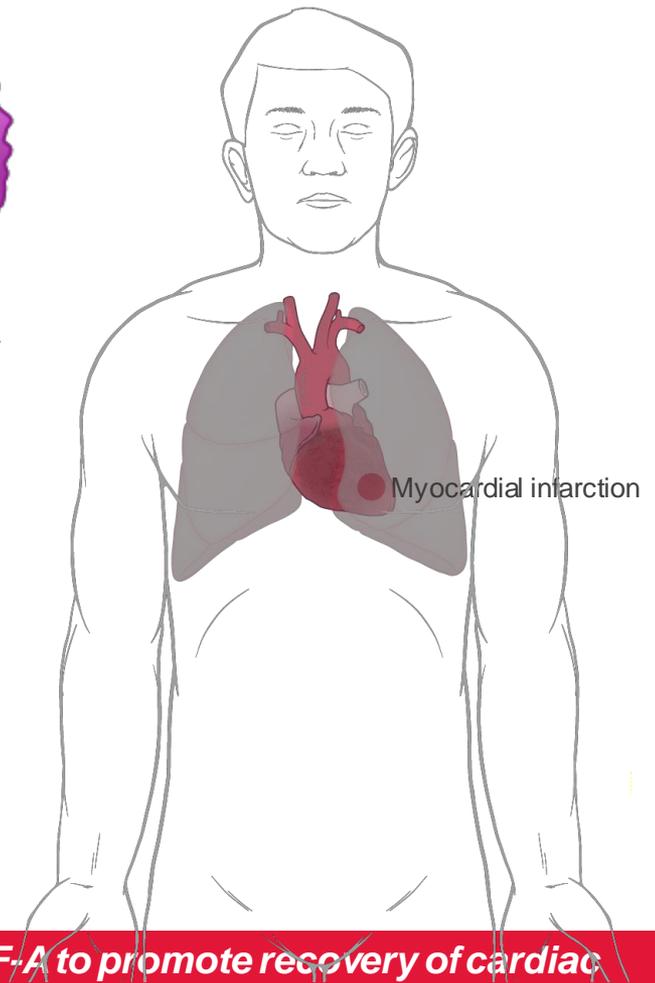
Phase 2a study with patients receiving epicardial injections of VEGF-A mRNA (AZD8601) during coronary artery bypass grafting surgery ongoing

Vascular endothelial growth factor (VEGF-A) overview

- VEGF-A is a potent angiogenic factor that **promotes growth of blood vessels**
- Preclinical data suggests that expression of this growth factor in the ischemic heart could increase blood flow and **partially restore cardiac function**
- Coronary artery disease, the primary cause of ischemic heart failure, affects the arteries providing blood supply to the cardiac muscle
- In 2015, coronary artery disease resulted in 366,000 deaths in the United States, and 8.9 million deaths globally



VEGF-A



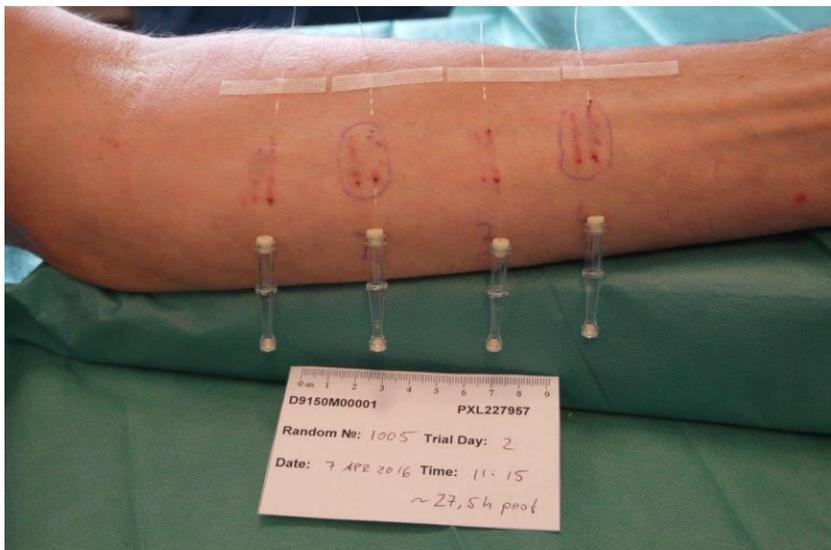
Moderna concept: Locally-administered mRNA encoding VEGF-A to promote recovery of cardiac function through partial tissue regeneration

VEGF-A (AZD8601)

Phase 1 successful, Phase 2 ongoing

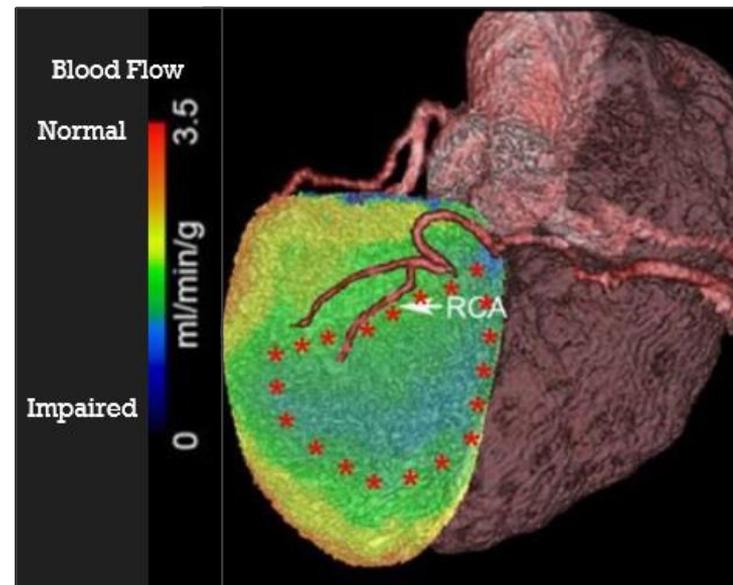
Phase 1

Intradermal injection, mRNA vs. placebo, in diabetic patients



Phase 2

Intracardiac injection, mRNA vs. placebo, in patients undergoing CABG



VEGF-A (AZD8601)

Phase 1 first-in-human study demonstrated safety and tolerability

Safety and tolerability monitoring procedure:

- Adverse events were monitored from screening and during the 6-month follow-up period.
- Vital signs (pulse and blood pressure), electrocardiography, physical examinations, and laboratory assessments (hematology, blood biochemistry, coagulation, urinalysis, viral serology, and urine drug and alcohol tests).
- Local reactions at injection sites: redness, bruising, swelling, itching and pain.

Safety results and conclusions:

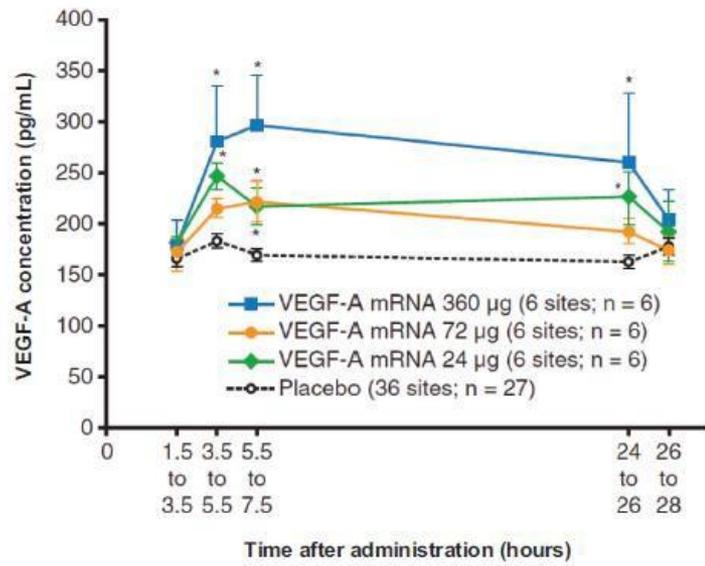
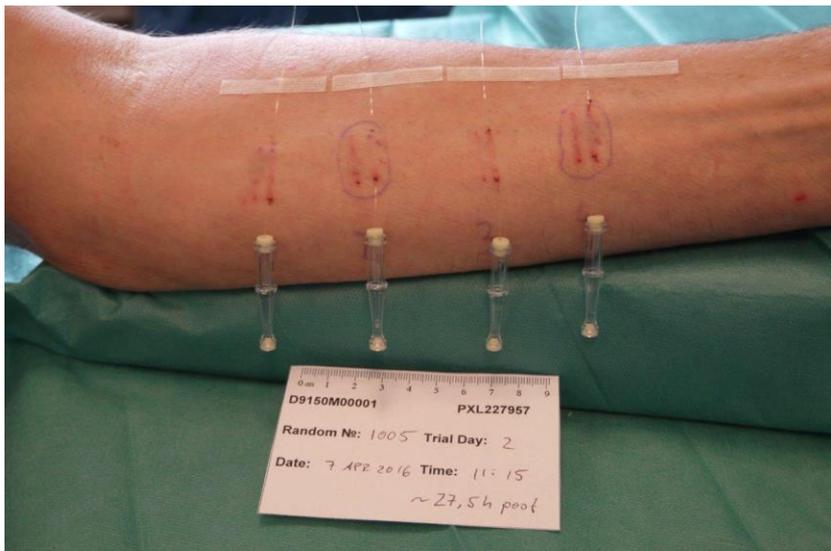
- **No adverse events leading to discontinuation occurred.**
- The only causally treatment-related adverse events were injection-site reactions (all mild), occurring in all but one participant receiving VEGF-A mRNA. These local reactions were attributable to VEGF-A-mediated vasodilation, **supporting further clinical investigation of VEGF-A mRNA as an angiogenic therapy.**
- Minor changes from baseline in laboratory parameters or vital signs were noted but **none of these was considered clinically relevant.**

VEGF-A (AZD8601) Phase 1a data

Intradermal AZD8601 gives rise to dose-dependent production of VEGF-A protein

Phase 1a microdialysis sampling of VEGF-A protein in diabetic patients

Proof of mechanism fulfilled following a single intradermal injection of AZD8601



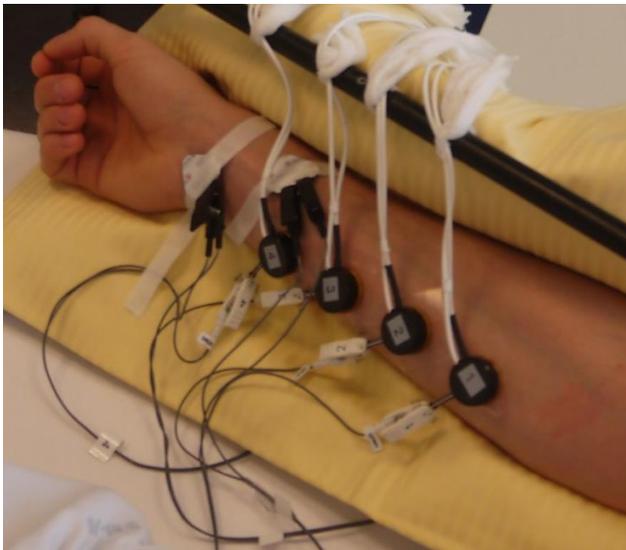
Intradermal delivery of modified mRNA encoding VEGF-A in patients with type 2 diabetes

Li-Ming Gan^{1,2,3}, Maria Lagerström-Fermér¹, Leif G. Carlsson⁴, Cecilia Arfvidsson¹, Ann-Charlotte Egnell¹, Anna Rudvik¹, Magnus Kjaer¹, Anna Collén⁴, James D. Thompson⁵, John Joyal⁵, Ligia Chialda⁶, Thomas Koernicke⁶, Rainard Fuhr⁶, Kenneth R. Chien^{7,8} & Regina Fritsche-Danielson⁴

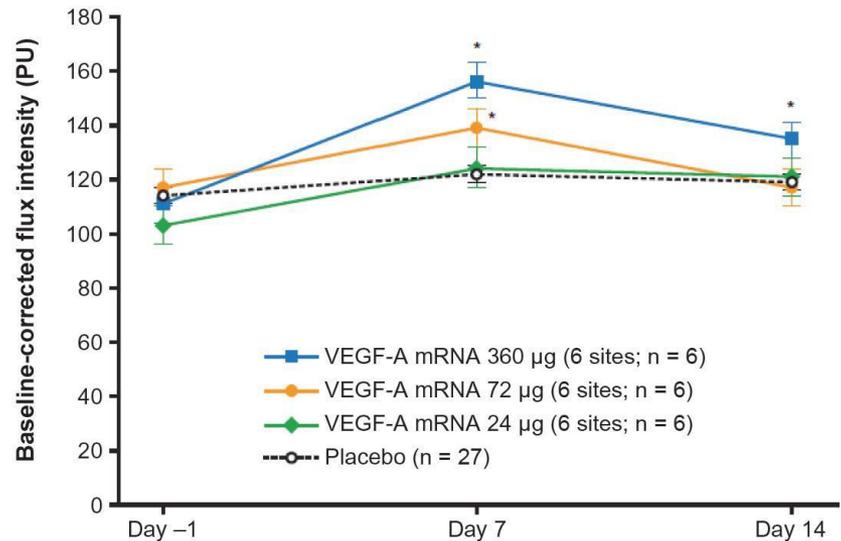
VEGF-A (AZD8601) Phase 1b data

Single dose of intradermal VEGF-A mRNA acutely restored baseline skin blood flow

Phase 1b laser scanning microscopy of injection sites in diabetic patients



Acute improvement in skin blood flow

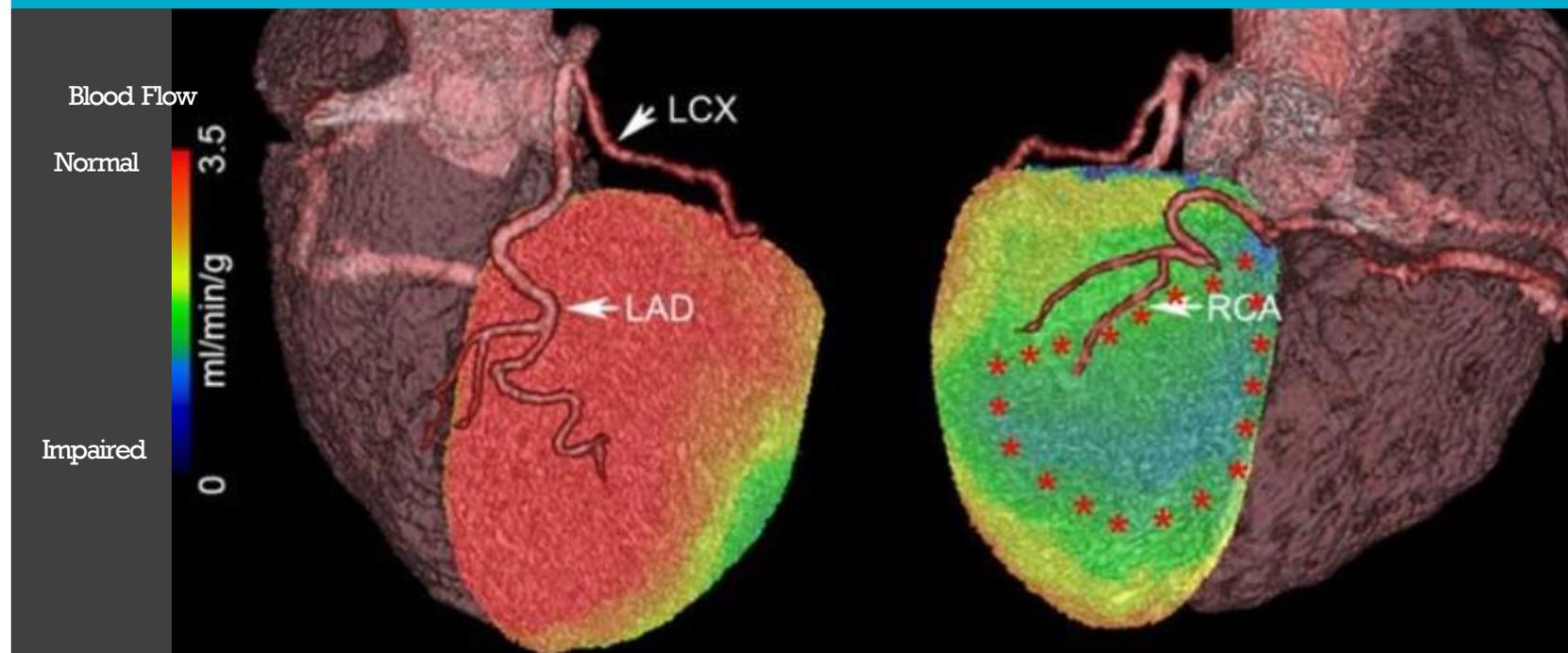


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VEGF-A (AZD8601) Phase 2a to evaluate safety and activity on blood flow in a heterogeneous CABG population

O^{15} -PET imaging is used to create tailored injection maps in patients



★ Injection sites in areas with impaired blood flow

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