



Vascular endothelial growth factor A (VEGF-A) (AZD8601)

Last updated: December 6, 2018

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

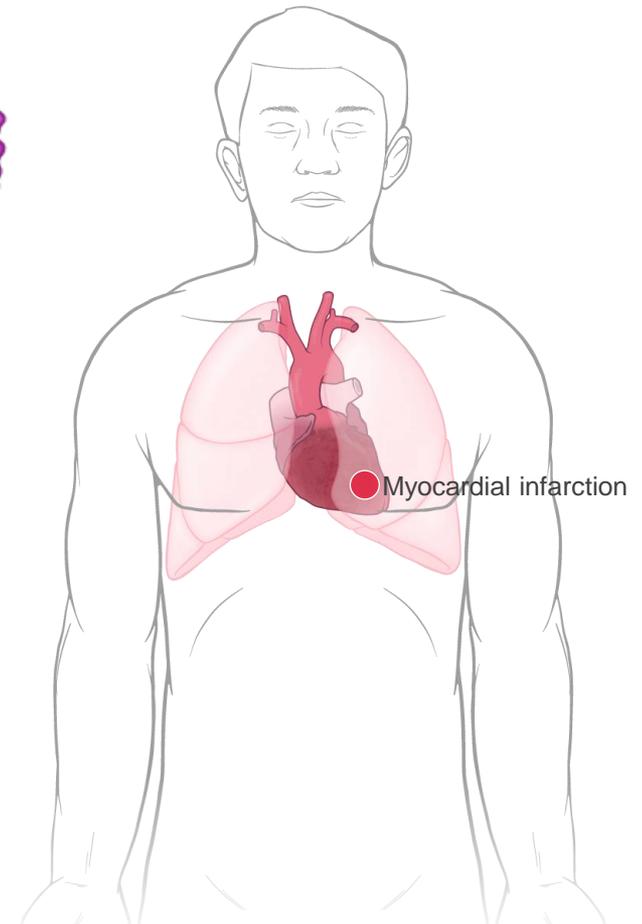
AZD8601 is currently dosing in a Phase 2a clinical trial in Europe

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

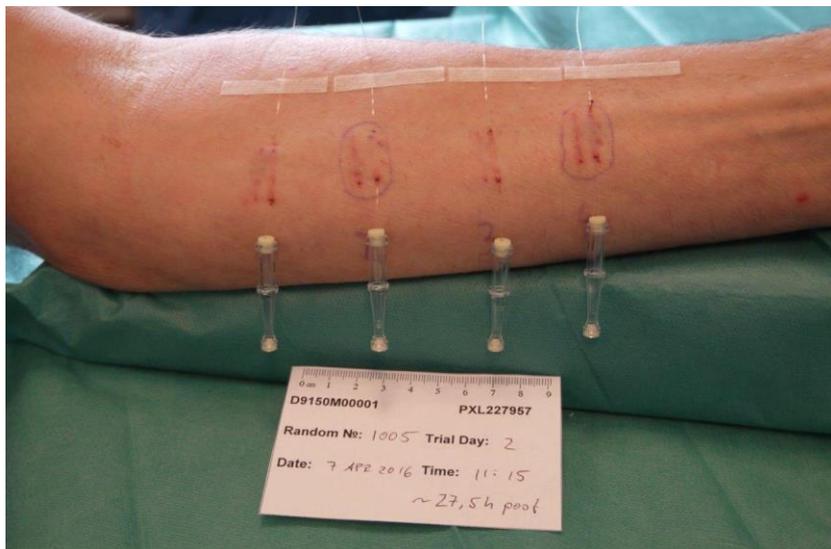


Moderna concept: Locally-administered mRNA encoding VEGF-A to promote recovery of cardiac function through partial tissue regeneration

VEGF-A (AZD8601) clinical summary – Phase 1 successful, Phase 2 underway

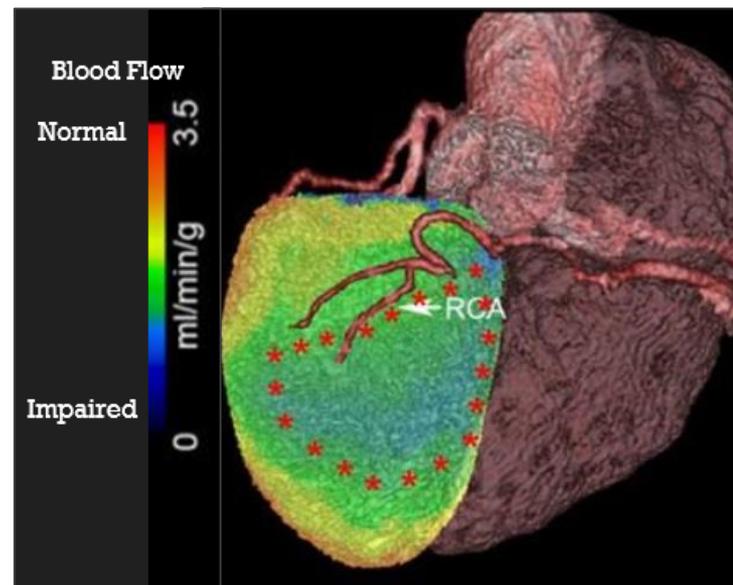
Phase 1

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.

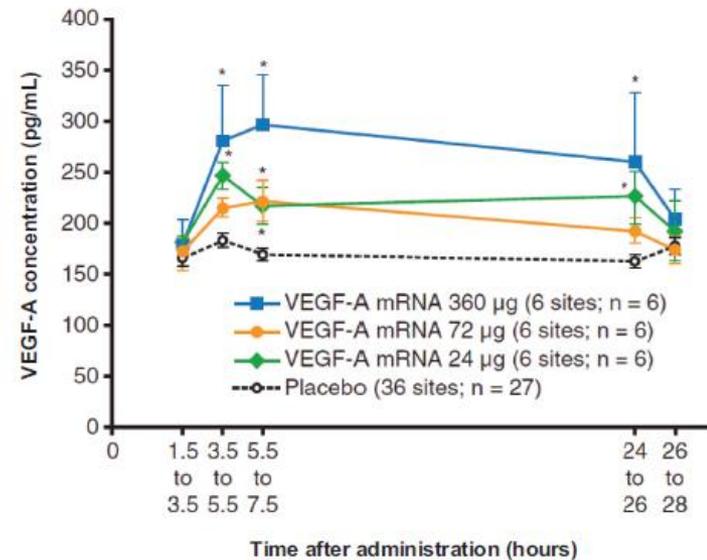
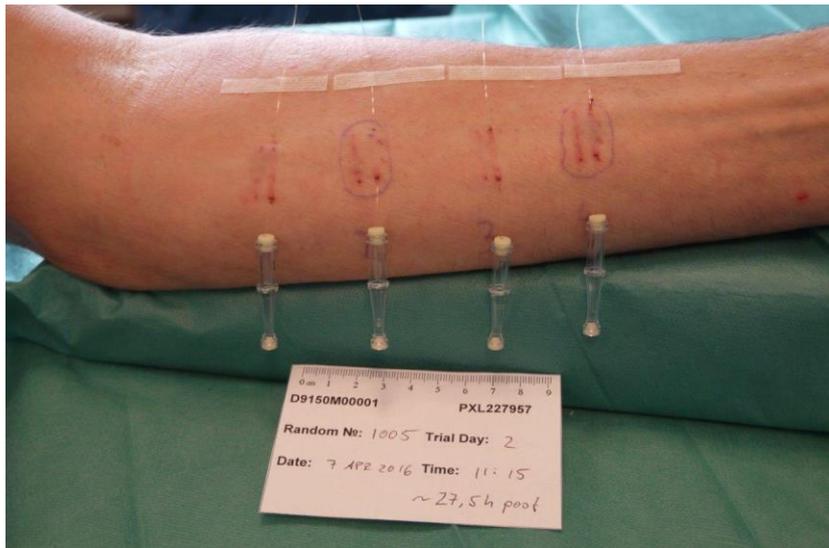
Safety results and conclusions:

- **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.**

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

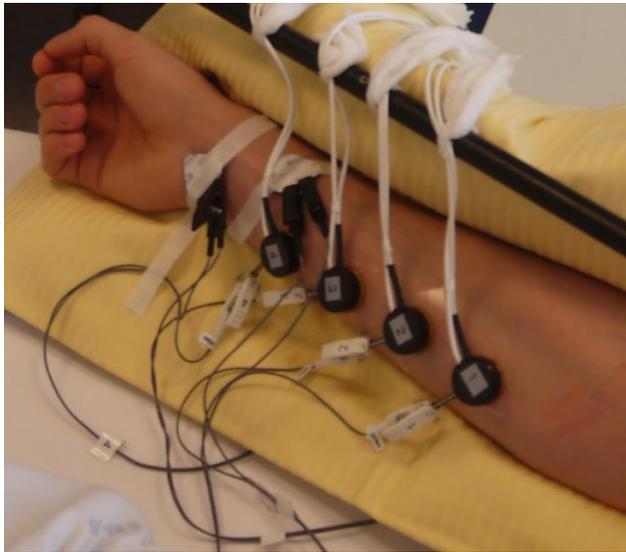
Proof of mechanism fulfilled following a single intradermal injection of AZD8601



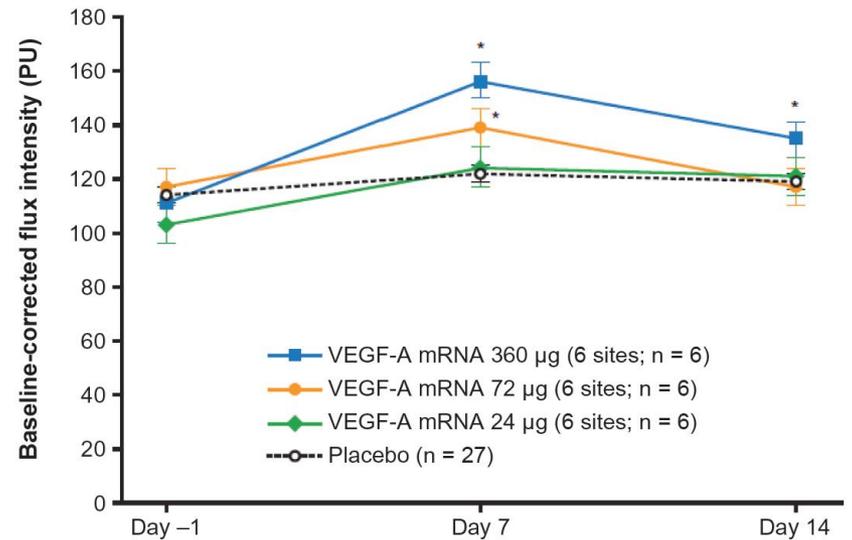
Gan, Fermer, and Fritsche-Danielson, Safety, tolerability, protein expression profile and physiological function of modified mRNA encoding for VEGF-A following intradermal administration to male patients with type II diabetes – results from a Phase 1, randomized, placebo controlled study

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



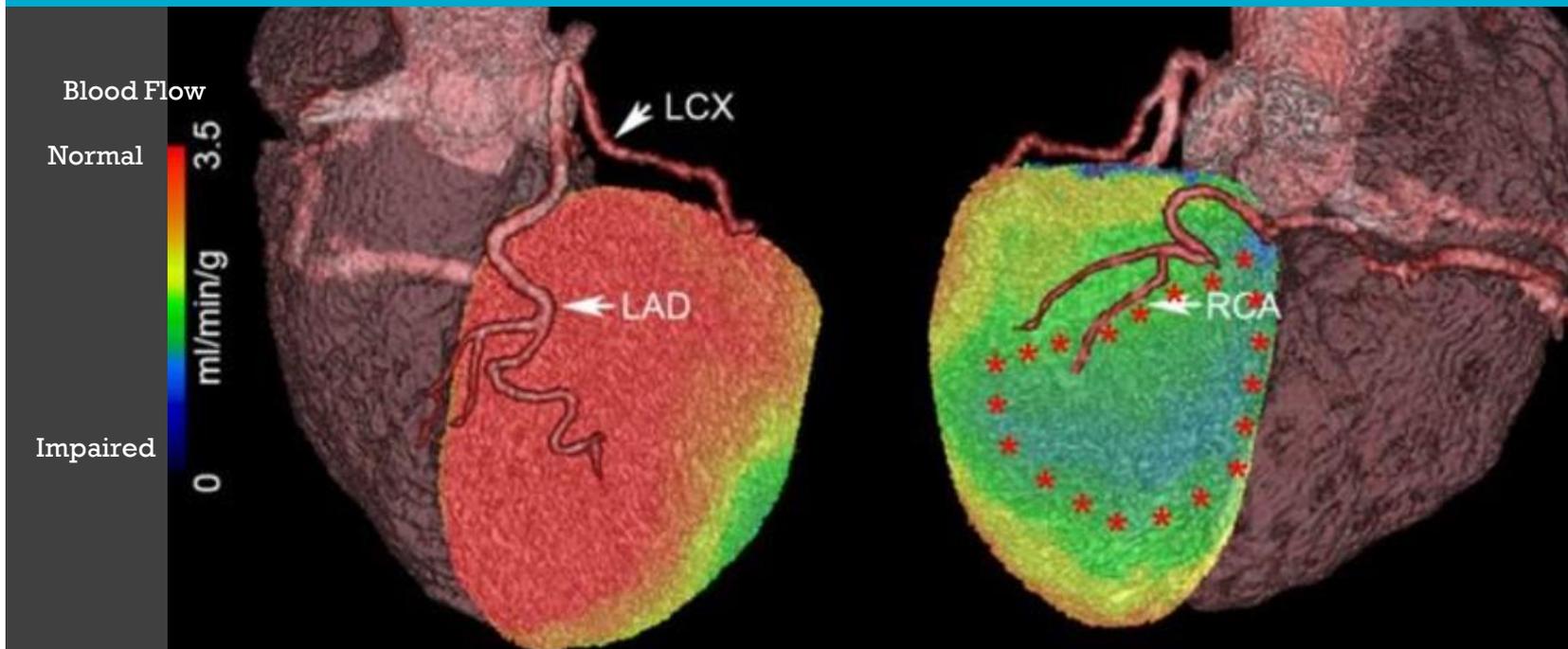
Acute improvement in skin blood flow



Gan, Fermer, and Fritsche-Danielson, Safety, tolerability, protein expression profile and physiological function of modified mRNA encoding for VEGF-A following intradermal administration to male patients with type II diabetes – results from a Phase 1, randomized, placebo controlled study

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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