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Xylocor sees enough to press on with angina gene therapy

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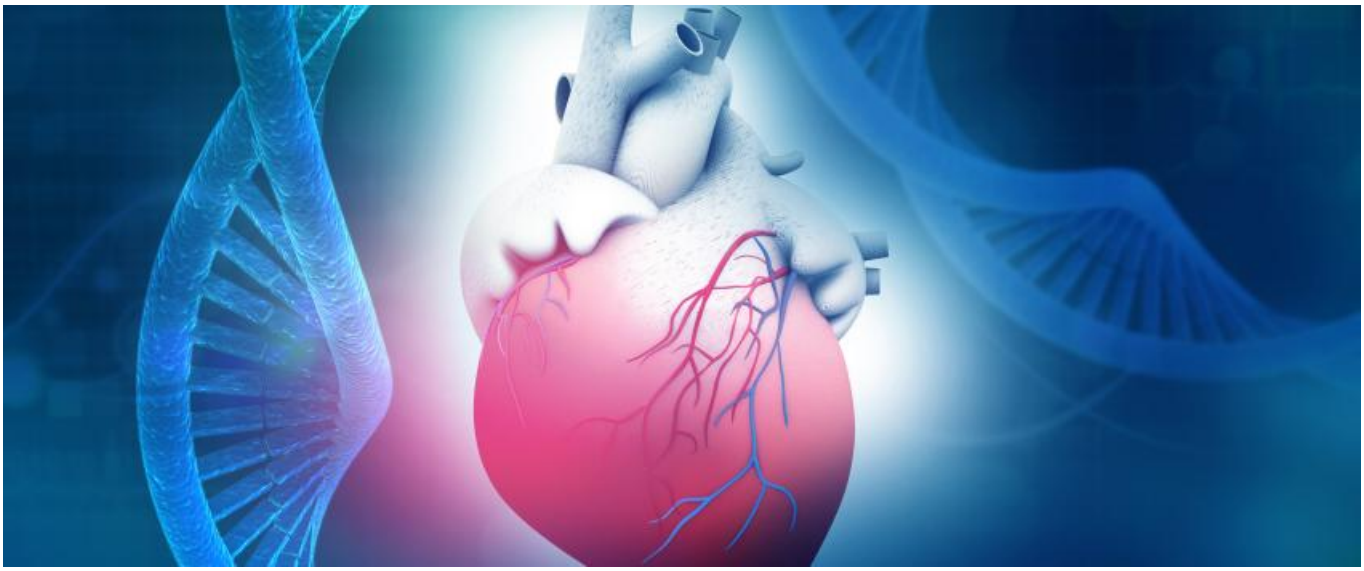

A pivotal trial is in the works, but can the group succeed where other VEGF gene therapies have failed?

Angina might be an unusual use for gene therapy, but Xylocor Therapeutics today released topline phase 2 data that it believes justify pushing into pivotal development.

Not many details are available, so it is tricky to gauge the chances of success for the group's project, XC001. The therapy is designed to spur transient production of VEGF by the patient's cardiac cells, leading to the formation of new blood vessels.

This is something that researchers have been working on for years with little success. And another group taking a similar approach seems to have stalled: Moderna has reported what it deemed positive phase 2 results with AZD8601, an mRNA project encoding VEGF, in patients undergoing coronary artery bypass grafting (CABG) surgery. However, its erstwhile partner Astrazeneca returned rights last year, leaving the future of this asset unclear.

Meanwhile, Gene Biotherapeutics has a rival gene therapy project for angina, Generx, but a phase 3 trial is yet to start recruiting.

Transient

Unlike XC001, Generx encodes the FGF-4 gene, but the principle seems similar: to promote new blood vessel growth. Another similarity is that both projects use an adenoviral vector – specifically, serotype 5 – that is transiently expressed.

According to Xylocor's chief executive, Albert Gianchetti, this is desirable in a disease like angina. "We wouldn't want chronic expression of VEGF in the heart, because you would overproduce blood vessels," he told *Evaluate Vantage* ahead of the phase 2 readout.

The transient nature of the vector could also address the theoretical concerns about insertional oncogenesis with gene therapies, he added.

Still, an adenovirus type 5 vector was implicated in the death of Jesse Gelsinger, which has been blamed on an immune response to the vector. Xylocor's study excluded patients with certain levels of pre-existing anti-Ad5 neutralising antibodies.

And in general Mr Gianchetti contended that, because XC001 is injected directly into the heart via a mini-thoracotomy rather than given systemically, this means lower doses, which could reduce the potential for toxicity. The highest dose in the phase 1/2 Exact trial, presented today, was $1x10^{11}$ viral particles. This was used in the phase 2 portion.

When asked whether patients might baulk at an invasive operation, Mr Gianchetti replied that the injection itself only took 10-15 minutes and was carried out by surgeons "very familiar with these procedures". And it is designed to be a one-off therapy – although the effect on VEGF levels is transient, the new blood vessels are expected to be durable.

As for why Xylocor might succeed where others have failed, Mr Gianchetti pointed to the fact that XC001 encodes several isoforms of VEGF, while earlier approaches have used just one.

All this still needs to be proven. The private group today reported six-month results from 28 patients in the phase 2 portion of Exact. All Xylocor is saying is that there were no serious treatment-related adverse events, and that there were improvements in exercise capacity and reductions in chest pain – without putting out any actual numbers. These are being reserved for publication or presentation at a medical meeting.

While gene therapies have largely been limited to rare diseases, the chief exec pointed to the lack of options for refractory angina patients, the population Xylocor is targeting. This is still a sizeable niche, with over a million patients apiece in the US and Europe, the company estimates.

A pivotal study now beckons. Mr Gianchetti previously said a likely endpoint could be total exercise duration, but presumably this would need to be hammered out with regulators.

Xylocor also has plans to evaluate XC001 as an adjunct to CABG.

Advanced therapies in clinical development for cardiovascular uses

Project	Company	Description	Indication	Trial details
Phase 3				
Generx (Ad5FGF-4)	Gene Biotherapeutics	Adenoviral vector (serotype 5)-based FGF-4 gene therapy	Refractory angina	Affirm not yet recruiting
Phase 2				
XC001 (encoberminogene rezmadenovec)	Xylocor Therapeutics	Adenoviral vector (serotype 5)-based VEGF gene therapy	Refractory angina	Ph1/2 Exact; ph2 data reported Jan 2023
AZD8601	Moderna	VEGF-A mRNA	Coronary artery bypass grafting	Data from Epiccure presented at AHA 2021; Astrazeneca returned rights 2022
NAN-101	Bayer (Askbio)	AAV-based phosphatase inhibitor 1 gene therapy	Heart failure & non-ischaemic cardiomyopathy	GenePHIT completes Dec 2029
Phase 1				
VERVE-101	Verve Therapeutics	In vivo base-editing project targeting PCSK9	Familial hypercholesterolaemia	Ph1 Heart-1 enrolling in NZ & UK; US IND put on clinical hold in Dec 2022

Note: list not exhaustive; Source: Evaluate Pharma & clinicaltrials.gov.

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