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Adverum halt raises more gene therapy questions

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A serious adverse event puts ADVM-022's future in doubt, and it could hurt other eye disease gene therapy players too.

Developing gene therapies for eye disorders like wet age-related macular degeneration was always going to be tough. But a toxicity scare with Adverum's ADVM-022 yesterday raises the question of why patients would take the risk of gene therapy when they could instead opt for effective, albeit unpleasant, regular ocular injections.

Adverum lost more than half of its value this morning, and it is hard to see a path forward for ADVM-022, on which the group is heavily reliant. But the news could have a knock-on effect on Adverum's main rival, Regenxbio, if it makes AMD patients wary about gene therapies.

It should be stressed that no similar issues have been seen with Regenxbio's lead project, RGX-314, which is in a pivotal study in wet AMD. However, the image of gene therapy has not been helped by several recent toxicity alerts. Perhaps, in diseases with no other options, patients will still be willing to try gene therapies, but in disorders with alternative therapies they could become a hard sell.

Several other projects are in development for both the wet and dry forms of AMD, although most are at a much earlier stage than Adverum's.

Selected gene therapies in development for AMD			
Project	**Company**	**Description**	**Trial(s)**
RGX-314 Subretinal	Regenxbio	Subretinal AAV8 anti-VEGF gene therapy	Pivotal Atmosphere in wet AMD completes Mar '23; 2nd pivotal study to start H2'21
RGX-314 Suprachoroidal	Regenxbio	Suprachoroidal AAV8 anti-VEGF gene therapy	Ph2 Aaviate in wet AMD completed Feb '21; ph2 Altitude in diabetic retinopathy completes May '21
ADVM-022	Adverum Biotechnologies	Intravitreal AAV.7m8 anti-VEGF gene therapy	Ph1 Optic in wet AMD; ph2 Infinity in DME unblinded after serious adverse event
GT005	Gyroscope Therapeutics	Subretinal AAV2 complement factor I gene therapy	Ph1/2 Focus, Explore & Horizon trials in dry AMD & geographic atrophy
4D-150	4D Molecular Therapeutics	Intravitreal R100 vector (AAV) anti-VEGF/PlGF gene therapy	Ph1/2 trial in wet AMD to start in H2'21
OXB-103	Oxford Biomedica	Retinal lentiviral vector anti-VEGF gene therapy	Preclinical
Dry AMD project	Applied Genetic Technologies Corporation	AAV complement factor H gene therapy	Preclinical
GS030	Gensight Biologics	AAV2.7m8 channelrhodopsin gene therapy & biomimetic goggles	Preclinical (dry AMD)
Wet AMD project	Generation Bio	Intravitreal lipid nanoparticle anti-VEGF gene therapy	Preclinical
A006	Meiragtx	AAV anti-VEGFR2 gene therapy	Preclinical (wet AMD)
Source: Evaluate Pharma & clinicaltrials.gov.			

As for ADVM-022 and Adverum – which has already had one reinvention after failing as Avalanche – the future looks bleak.

The company has unmasked the phase 2 Infinity study of ADVM-022 in diabetic macular oedema after a serious adverse reaction in a patient receiving a high dose, $6x10^{11}$vg/eye. The subject developed decreased ocular pressure, inflammation and loss of vision in the treated eye.

Diabetic macular oedema is not the main prize for Adverum. The company is also developing ADVM-022 in wet AMD, where *Evaluate Pharma* sellside consensus puts 2026 sales at $165m; forecasts for diabetic macular oedema the same year are just $13m.

Still, ADVM-022's chances in AMD have also now taken a blow. The company had hoped to take the project into pivotal trials here in the fourth quarter, testing a one-off dose of $1x10^{11}$vg/eye or $3x10^{11}$vg/eye of the gene therapy versus Regeneron/Bayer's Eylea given every eight weeks.

Leerink analysts now see “meaningful delays”, but maybe the bigger question is whether these trials will – or should – start at all.

There had already been worries about inflammation seen with the $6x10^{11}$vg/eye ADVM-022 dose in the phase 1 Optic trial in AMD; the study also found worsening in patients’ vision. Adverum had hoped to tackle the inflammation with steroid eye drops, but these have problems of their own, including glaucoma risk. The group is presenting more data from Optic at this weekend's Arvo meeting, and investors will no doubt keep an eye out for inflammation.

Proponents of gene therapies for AMD contend that, in real-life, drugs like Eylea are given less frequently than recommended, which can lead to vision deterioration. There probably is a need for longer-term options, but the

jury is still out on whether gene therapies will provide the answer.

The table in this story has been updated to include Meiragtx's A006.