Evaluate Vantage

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Idorsia’s Fabry flop puts focus on gene therapies

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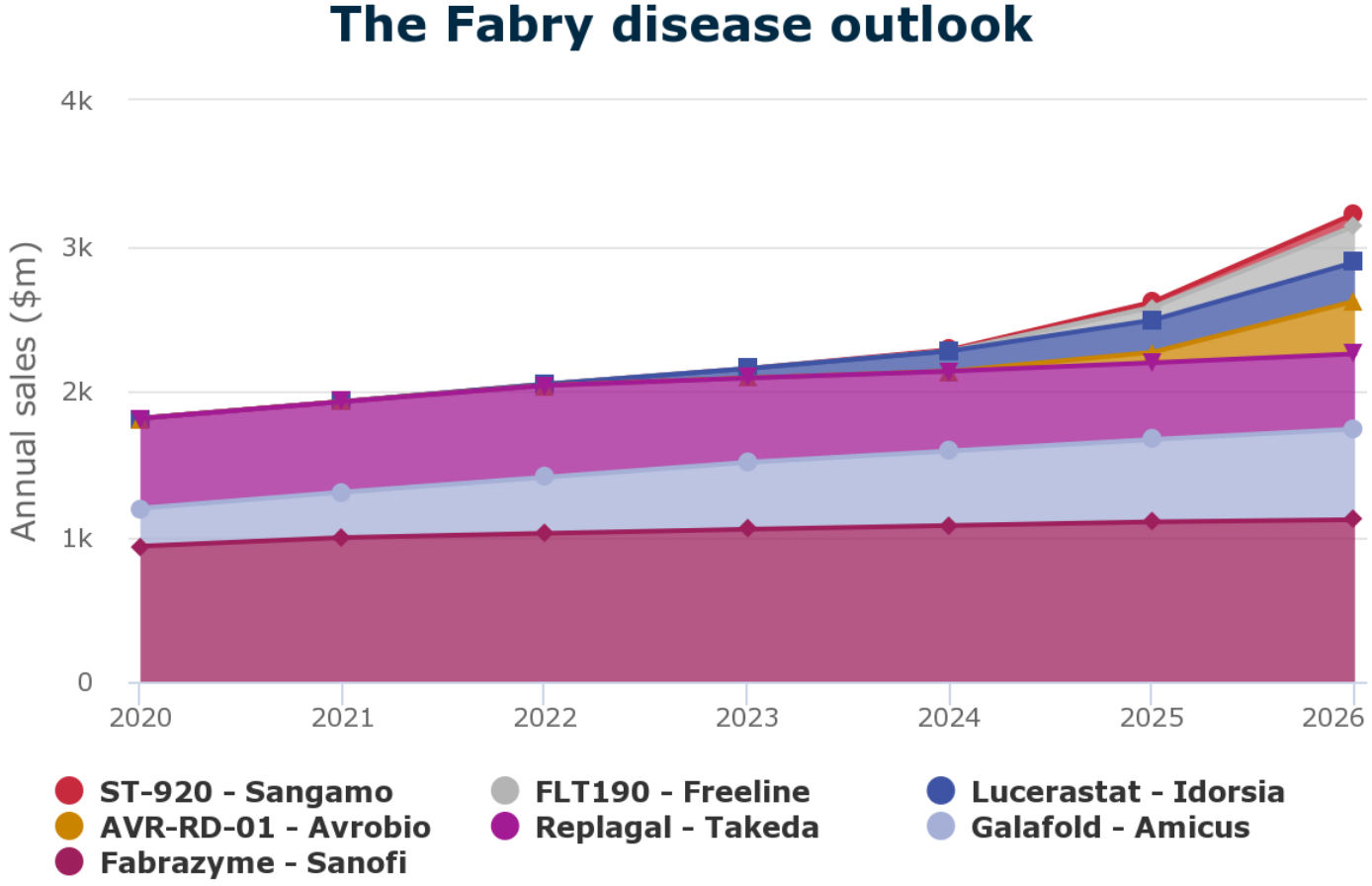
But questions about gene therapy safety could benefit the enzyme-replacement therapy incumbents.

The pivotal failure yesterday of Idorsia’s Fabry disease project lucerastat exposes a dearth of other projects in the late-stage Fabry pipeline, even if it is unlikely to spell the end of the world for the Swiss group.

True, enzyme-replacement therapies are well established, but these do not prevent disease progression and are burdensome, with patients needing infusions every two weeks. Gene therapy is now the main hope for patients seeking an alternative, but recent safety scares in the field could raise doubts about this approach.

Sellside consensus compiled by *Evaluate Pharma* shows enzyme-replacement therapies, as well as Amicus’s Galafold, continuing to dominate this space in 2026 – although this might in part reflect the early-stage nature of the gene therapy projects. As for Idorsia, it has more important upcoming catalysts, and ended yesterday down a relatively modest 4%.



Fabry disease is caused by mutations in the *GLA* gene, which encodes the enzyme alpha-galactosidase A. This enzyme usually breaks down a fatty substance called globotriaosylceramide (Gb3), but in Fabry patients Gb3 builds up, causing symptoms such as pain crises, hearing loss and kidney and heart disease. The disease varies in severity depending on patients' enzyme activity levels.

Replacing the enzyme is a mainstay of care, but the aforementioned issues mean that the search is still on for something better. Amicus's Galafold, an oral drug designed to stabilise alpha-gal A, gained accelerated approved in 2018, but is only indicated for patients with certain GLA mutations.

Idorsia's lucerastat, meanwhile, is an oral glucosylceramide synthase inhibitor designed to reduce Gb3 accumulation. Data from the Modify study suggest it does just that: Idorsia said yesterday that there was a "substantial and consistent reduction of plasma Gb3"; however, the trial did not meet its primary endpoint, reduction in neuropathic pain at six months, measured using the modified brief pain inventory-short form 3 score.

Jefferies analysts previously noted that this was an unusual endpoint, versus the more traditional Fabry outcomes of kidney or heart function, and this could provide a reason for the failure.

Idorsia does not seem to have thrown in the towel on lucerastat just yet. The group said more data, including results from an open-label extension study, would help inform a decision on the project's future. But Jefferies says a path forward looks unlikely.

The Swiss group has other irons in the fire. It is expecting a US approval decision in the first quarter of next year on its insomnia project daridorexant, and data are due this quarter from a phase 2b trial of the sphingosine 1-phosphate receptor modulator cenerimod in systemic lupus erythematosus.

However, daridorexant's pivotal data were mixed, and lupus is a notoriously tough nut to crack.

Gene therapies

If this is the end for lucerastat it will take out a project that had been expected to become the fifth-biggest seller in Fabry by 2026, according to *Evaluate Pharma*.

There is not much else on the near-term horizon. Protalix and Chiesi still hope for approval of PRX-102, which received an FDA complete response letter in April over manufacturing issues. However, this is merely a long-acting enzyme replacement therapy.

Sanofi's venglustat completed a Fabry trial in 2016, but the group has yet to take the project further in the disease, despite still listing it in its pipeline. In any case this works similarly to lucerastat, so hopes cannot now be high.

This leaves a clutch of gene therapies, which all aim to deliver a working copy of the *GLA* gene and provide a once-and-done treatment. It is early days, but several are set to yield phase 1/2 data by the end of this year.

A number of gene therapy scares this year have raised the question about the safety of this approach more broadly – and raise the question of whether Fabry patients will want to go down this route given the availability of enzyme replacement therapies.

Perhaps things will have become clearer by the time the Fabry gene therapy assets have reached later-stage development but, until then, the biggest beneficiaries from lucerastat's failure look like Amicus and the enzyme-replacement players.

Fabry disease pipeline			
Project	**Company**	**Description**	**Note**
Filed			
Pegunigalsidase alfa (PRX-102)	Protalix/Chiesi	Long-acting IV alpha galactosidase regulator	CRL received Apr 2021; resubmission planned
Phase 3			
Lucerastat	Idorsia	Oral glucosylceramide synthase inhibitor	Failed Modify Oct 2021
Phase 2			
Venglustat (GZ402671)	Sanofi	Oral glucosylceramide synthase inhibitor	Ph2 completed 2016; still listed in pipeline
Phase 1/2			
4D-310	4D Molecular	GLA gene therapy (AAV vector)	NCT04519749; initial data due Q4 2021
FLT190	Freeline	GLA gene therapy (AAVS3 vector)	Marvel-1; data from mid-dose cohort due YE 2021
AVR-RD-01	Avrobio	GLA gene therapy (lentiviral vector)	Fab-GT; safety data on 9 pts due Q4 2021, efficacy data due at World Symposium Feb 2022
ST-920	Sangamo	GLA gene therapy (AAV2/6 vector)	Staar; escalating to third dose but initial data no longer expected in Q4 2021
Source: Evaluate Pharma & clinicaltrials.gov.			