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Toxicity concerns send Larimar down

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The company hopes that its novel approach in Friedreich's ataxia could still have legs, but other assets are further ahead.

Despite companies' ongoing efforts there are still no approved therapies for the inherited neuromuscular disorder Friedreich's ataxia. But a look at the pipeline shows that some groups are getting close to big readouts.

Slightly further behind is Larimar, which yesterday reported phase 1 results with its candidate CTI-1601. Although biomarker data looked promising, the group's stock sank 36% yesterday on toxicity concerns in non-human primate studies. The company will need to iron out these issues if its asset is to progress.

Frataxin

Unlike many other projects in development, CTI-1601 takes aim at the root cause of Friedreich's, a decrease in the mitochondrial protein frataxin. This protein is encoded by the *frataxin* gene, which is mutated in the disorder.

CTI-1601 comprises recombinant frataxin fused to a cell-penetrating peptide. More advanced assets, meanwhile, use various mechanisms to try to improve mitochondrial dysfunction and/or reduce oxidative stress.

Notably, Ixchel Pharma says its early-stage project IXC-109 also increases frataxin levels. IXC-109 is a prodrug of monomethyl fumarate, making it similar to Alkermes/Biogen's multiple sclerosis therapy Vumerity.

There are a couple of gene therapies in development designed to deliver a healthy copy of the *frataxin* gene – PTC's GT-FA and Voyager/Neurocrine's VY-FXN01 – but these are still preclinical.

The Friedreich's ataxia clinical pipeline			
Project	**Company**	**Description**	**Trial details**
Phase III			
Omaveloxolone	Reata Pharmaceuticals	Nrf2 stimulant	Moxie trial hit; 2nd pivotal study planned for Q4 2021
RT001	Retrotope	Deuterated polyunsaturated fatty acid	Ph3 completes Nov 2021
Vatiquinone (EPI-743)	PTC Therapeutics	15-lipoxygenase inhibitor	Move-FA completes Jul 2023
Phase II			
Leriglitazone (MIN-102)	Minoryx Therapeutics	PPAR-gamma agonist	Frames reported Dec 2020; primary endpoint "inconclusive"; development continues
Phase I			
CTI-1601	Larimar Therapeutics	Recombinant fusion protein	Ph1 MAD trial reported May 2021
IXC-109	Ixchel Pharma	Monomethyl fumarate prodrug	Not in trial databases
Source: Evaluate Pharma.			

In Larimar's phase 1 trial patients received subcutaneous CTI-1601 at 25mg, 50mg or 100mg daily, or placebo. The primary endpoints concerned safety, but the group also reported a dose-dependent increase in frataxin, to levels near those seen in phenotypically normal heterozygous carriers of *frataxin* mutations.

There were no immediate toxicity concerns, with one of the 27 patients withdrawing with mild-to-moderate nausea and vomiting.

However, investors were apparently spooked by an SEC filing detailing deaths in non-human primates in preclinical trials. One of these was deemed to be due to a bacterial meningitis infection and not related to CTI-1601 but, in a separate study, there were also an undisclosed number of deaths "at the highest dose levels".

Larimar hopes that it can still start its open-label extension study, Jive, and a paediatric multiple-ascending dose trial in the second half of 2021 as planned – but the FDA might have other ideas.

Reata leads

Luckily for patients, the Friedreich's pipeline looks healthier than the last time *Evaluate Vantage* carried out this analysis (*Friedreich's failure highlights thinning pipeline, June 2, 2017*).

Since then, Reata Pharmaceuticals' omaveloxolone has defied odds by producing a win in part two of the Moxie trial. Hopes for a quick filing, though, came to naught; Reata is meeting the FDA this quarter, and no doubt hopes that additional data will be enough for the agency. Still, the group says it plans to start a second pivotal study this year.

Meanwhile, two other phase 3 assets, Retrotope's RT001 and PTC's vatiquinone, are set to yield data in the next year or two.