Evaluate Vantage

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PTC fails phase 3, and looks to a regulatory filing

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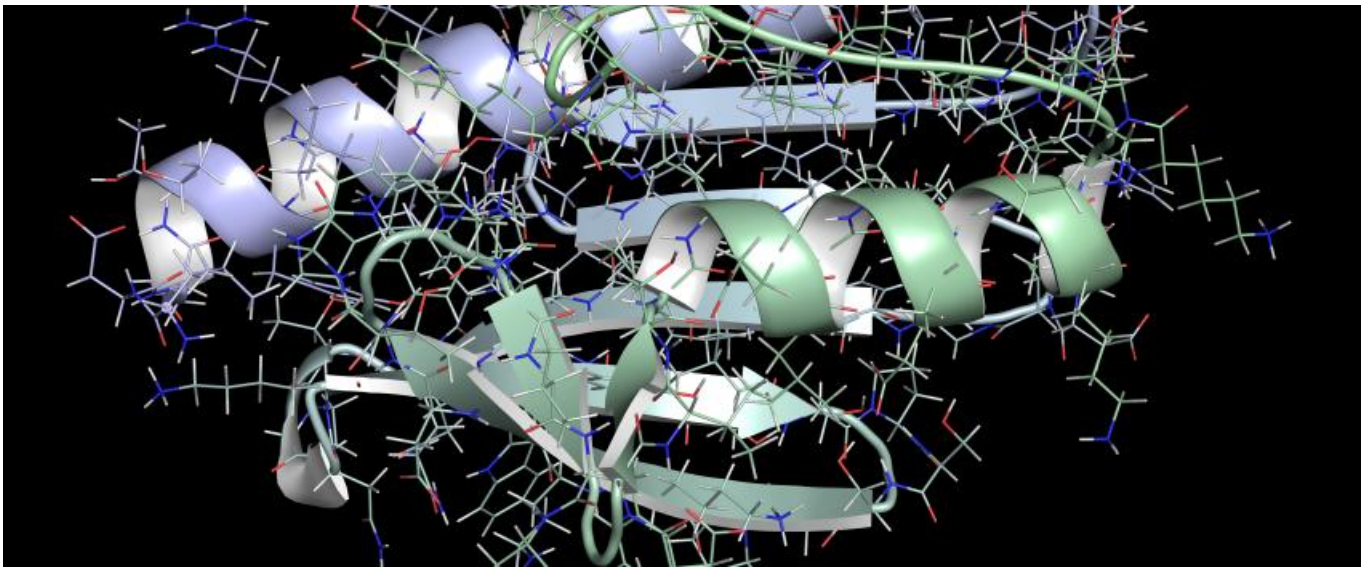

Vatiquinone's pivotal failure in Friedreich's ataxia prompts a data dredge to come up with a regulatory package. And why not?

It is not unusual for failure of a major phase 3 catalyst to prompt cost cutting, but the PTC Therapeutics case is different. Discontinuation of PTC's early gene therapy assets is not part of a focus away from vatiquinone, which blew up in its Move-FA trial yesterday, but rather a doubling down on this Friedreich's ataxia asset.

And who can blame the company? The FDA's neuroscience division has a track record of approving controversial drugs with dubious clinical backing – not least Reata's Friedreich's competitor Skyclarys. Vatiquinone's primary endpoint fail came with glimmers of hope on other metrics, and PTC will now take these on "a potential path to registration with regulatory authorities".

Discussions could centre on the fact that Friedreich's is a relatively unmet need, and that Move-FA took place during the end of the Covid pandemic. The latter resulted in treatment disruption for some patients, and an analysis of trial completers brings vatiquinone closer to a nominal success on Move-FA's primary endpoint, total mFARS score at week 72 versus placebo.

That endpoint had been roundly missed on the trial's prespecified intent-to-treat analysis of 123 patients between the ages of seven and 21, with a 1.22-point decline for vatiquinone versus 2.83 points for placebo yielding a p value of 0.14. Considering only the 96 completers the 2.31-point difference gives a better, but not especially convincing, p=0.054.

PTC also argued that two elements of the total mFARS, bulbar and upright stability scores, were nominally significant in the ITT population, and that there was "meaningful slowing" in measures of disease progression. The company called these signals of clinical benefit, though until the full data are presented or reviewed it will not become apparent whether it has cherrypicked only the most favourable findings.

	Primary Analysis Population Change from Baseline to Week 72			
Analysis	**Placebo**	**Vatiquinone**	**Difference**	**P-value**
mFARS Total*	2.83	1.22	-1.61	0.14
Bulbar	0.22	0.033	-0.18	**0.044**
Upright Stability	2.99	1.73	-1.26	**0.021**
Lower Limb	0.40	-0.11	-0.51	0.23
Upper Limb	-0.51	-0.18	0.32	0.58

*Primary endpoint which did not meet statistical significance

Source: PTC presentation.

In the meantime PTC is discontinuing preclinical gene therapy projects to cut operational expenses by 15%, as well as firing its chief financial officer. PTC says it wants to focus especially on commercialising the ultra rare disease gene therapy Upstaza, and further work with vatiquinone will presumably cost too. The group had $286m of cash in March but made a first-quarter $139m net loss on sales of $188m.

Reata benefits?

However PTC's plan now works out with regulators, the failure of Move-FA can immediately be seen as good news for Reata. That company's Skyclarys was approved in March with a surprisingly broad label, benign toxicity warnings and a priority review voucher, but earlier this month its launch stalled.

This delay, caused by disclosure of a possibly long-standing manufacturing impurity, means that Skyclarys will not be launched in mid-2023 as planned, a fact that had been seen as an advantage for PTC. Now, with vatiquinone at least delayed and at worst a bust, the pressure is off Reata to an extent.

This morning Reata opened up 11% while PTC fell 21%.

Skyclarys is itself controversial, having been approved despite initially being sent back to the drawing board when the FDA in 2020 said existing data were insufficient to back approval. At a pre-NDA meeting the agency appeared to change its tune, and a filing was successful despite no additional clinical study being carried out.

Though Friedreich's is a genetically driven disease Skyclarys and vatiquinone are both small molecules, an Nrf2 activator and 15-lipoxygenase inhibitor respectively, that seek to affect antioxidative pathways.

Stifel analysts, who cover Reata, wrote that Skyclarys's registrational Moxie trial set a high bar, with a placebo-adjusted 2.40-point change in mFARS at week 48; however, this excluded patients with the foot deformity pes cavus.

The FDA agreed that this was good enough, and now PTC will give biotech investors another test of the agency's generosity.

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