Evaluate Vantage

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The Sarepta fairy tale takes a worrying turn

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A complete response letter for Sarepta's follow-on Duchenne therapy is a big blow for the company, but in hindsight was the FDA's decision actually that surprising?

Strike three for Sarepta, which last night announced that the FDA had declined to approve Vyondys 53, the company's next-to-market Duchenne muscular dystrophy therapy. Coming in the wake of news of a substantial delay to its gene therapy project, SRP-9001, which was then hit by a safety scare a couple of days later, it is little wonder that August has proved a torrid time for the group's stock.

Shares fell 13% in early trade today, meaning that so far this month Sarepta has seen almost a third of its value erased. This is a substantial decline but it could also be argued that the company has actually got off pretty lightly. An assumption that the Vyondys 53 complete response letter represents a delay rather than anything more serious presumably sheltered the stock from a more severe slump today.

Notes from supportive sellside analysts this morning will have helped contain the situation. These variously described how the Vyondys 53 application had already progressed to labelling and press release discussions, and emphasised Sarepta executives' surprise at the decision. A staunch shareholder support base will also have limited the damage, and many seem to be holding out for a launch some time next year.

Still, Sarepta is one of the most polarising biotech names, with a band of detractors that are as vocal as its supporters. Many critics believed that this outcome was possible after the agency garnered so much criticism for the controversial approval of Sarepta's first DMD drug, Exondys 51, three years ago.

Vyondys 53, generically known as golodirsen, had also been filed on surrogate endpoints, in the absence of firm evidence that it improves muscle function in children with DMD. A confirmatory study called Essence is at least under way for Vyondys 53 and another follow-on project, casimersen; all three exon-skipping therapies address different, genetically defined DMD subsets.

Pay back?

Sarepta's failure to start the confirmatory Exondys 51 trial in the three years that the drug has been on the market only adds to the controversies around this company. Many believe this foot-dragging could have contributed to the FDA's reluctance to approve the company's second therapy.

According to the company, the reasons cited by the FDA in the Vyondys 53 CRL had never previously been raised. Specifically, they were the risk of infection at intravenous infusion ports and kidney toxicity, which had been seen in preclinical studies. With scant evidence of efficacy it was perhaps inevitable that the agency

would need squeaky clean safety to grant accelerated approval.

Whatever one's stance on Sarepta, it is hard to see this decision as anything but a determination that the company needs to generate more clinical evidence before more patients are exposed to its therapies. If this is indeed the consensus view within the agency, it is hard to see any of Sarepta's exon-skipping products reaching the market before placebo-controlled data are available.

Essence is unlikely to yield data until 2022, so a delay of several years cannot be ruled out.

Slow lane

Whether this shows that the regulator is taking a firmer line more generally with experimental therapies filed under accelerated pathways, rather than slapping down Sarepta individually, is another question.

But a wider read across is hard to argue against here: FDA data show that approvals based on surrogate endpoints have exploded in the last couple of years (*The Gottlieb legacy: a surge in unproven treatments?, March 6, 2019*).

As such, it is hard to escape the notion that the FDA has actively moved Sarepta's exon-skipping therapies into the slow lane. To believers in the company's gene therapy potential this should not matter much – except that this project too has moved down a gear.

Earlier this month Sarepta said it would substantially upsize the pivotal trial of SRP-9001 – from 24 to 40 subjects – and pushed back the start of a trial using a commercial supply to 2020. If all goes well, this means data at the back end of 2020 from the pivotal study, according to the company's expectations..

Even after the past month's declines, Sarepta's market cap stands at almost $8bn; hopes for the gene therapy project account for a big chunk of this figure. But unless some best-case scenarios start to emerge in the coming months, this valuation will become increasingly hard to justify.

This article has been amended to reflect the company's expectations of data from the pivotal gene therapy study.