Evaluate Vantage

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Jury still out on Sarepta’s next generation

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The group’s lead next-gen exon skipper beats a low bar set by Exondys, but adverse events loom large.

Sarepta, still bruised from the failure of its Duchenne muscular dystrophy gene therapy SRP-9001 in January, needs something to get investors excited again. Data released yesterday on its lead next-generation exon skipper, SRP-5051, suggests that this project might not be it.

First the good news for Sarepta: on dystrophin expression SRP-5051 outperformed the group’s approved DMD therapy Exondys 51. However, this had set a low bar to beat. And three serious adverse events raised alarm bells; how much better SRP-5051 needs to be than Exondys to gain approval is now an open question.

Sarepta’s stock climbed 9% yesterday on the data, which came from four patients receiving 30mg/kg per month of SRP-5051 in part A of the phase 2 Momentum study. But the group is still worth less than half of what it was in January, just before the mid-stage flop with SRP-9001 (*Gene therapy trial fails to rectify Sarepta’s sorry record, January 8, 2021*).

Leerink, which had hoped to see up to tenfold greater exon skipping with the 30mg/kg versus the 20mg/kg dose, described the latest SRP-5051 data as “good but not great”. At least SRP-5051 did much better than Exondys, which controversially gained accelerated approval in 2016 and only started its confirmatory trial last year.

Cross-trial comparison of Exondys and SRP-5051		
Therapy	**Mean % exon skipping**	**Mean % dystrophin expression**
Exondys 51	0.59	0.82
SRP-5051 20mg/kg	2.57	3.06
SRP-5051 30mg/kg	10.79	6.55
Note: Exondys data at 24 weeks in Promovi study; SRP-5051 at 12 weeks in Momentum study. Source: company presentation.		

An improved performance is the bare minimum, however, and indeed this is the whole point of Sarepta’s next-gen assets, which it calls PPMOs. The idea is that by adding a peptide to the phosphorodiamidate morpholino

oligomer (PMO) technology on which the group's existing products are based, cell penetration and uptake – and therefore efficacy – should be increased.

Balancing efficacy and safety was always going to be tricky, Leerink predicted back in 2018. And toxicity worries have already reared their head with SRP-5051. The three serious treatment-related side effects included two cases of hypomagnesemia, which Sarepta said resolved when patients were given supplements.

Sarepta added that there was no link between hypomagnesemia and markers of kidney toxicity; it had discontinued a previous PPMO, AVI-5038, after seeing kidney toxicity in animal studies.

This is no doubt something regulators will be keeping an eye on as more patients are treated with SRP-5051.

These side effects could explain why Sarepta has chosen not to test a 40mg/kg dose of SRP-5051, as previously planned, and instead will push the 30mg/kg dose into part B of Momentum, which the group hopes will act as the project's US pivotal trial.

Analysts do not appear convinced by Sarepta's PPMOs: the sellside does not ascribe any value to SRP-5051, according to *Evaluate Pharma*. Sarepta also has five more PPMOs in preclinical development.

Surprisingly, the group's most valuable pipeline project is still SRP-9001, suggesting that not everyone has written this off. Data are due this quarter from Endeavor, a study of commercial-grade SRP-9001, and a pivotal trial is slated to begin mid-year.

Sarepta's marketed products & clinical-stage pipeline

Project	Description	Indication(s)	Status	2026e sales ($m)
Exondys 51	PMO antisense oligonucleotide (exon 51 skipping)	DMD	Marketed	442
Vyondys 53	PMO antisense oligonucleotide (exon 53 skipping)	DMD	Marketed	243
Amondys 45	PMO antisense oligonucleotide (exon 45 skipping)	DMD	Marketed	202
SRP-9001*	Micro-dystrophin gene therapy	DMD	Ph2 Endeavor study of commercial-grade therapy, data due Q2'21	805
SRP-9003	Beta-sarcoglycan gene therapy	LGMD type 2E	Ph1/2 trial, data reported Mar 2021	287
LYS-SAF302**	SGSH gene therapy	MPS IIIA	Ph2/3 trial completes Mar 2022	16
SRP-5051	PPMO antisense oligonucleotide (exon 51 skipping)	DMD	Ph2 Momentum trial, part A reported	-
GALGT2	GALGT2 gene therapy	DMD	Ph1/2 trial completed Nov 2020	-

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