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Novartis nears gene therapy confirmation

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After buying Avexis for $8.7bn to access a potentially transformative treatment for spinal muscular atrophy, data approaches from Novartis.

Novartis's swiftly executed takeover of Avexis earlier this year was pitched as a way for the Swiss pharma giant to gain a gene therapy pipeline and manufacturing capabilities. In reality the $8.7bn price tag was mostly attached to one product: AVXS-101, for spinal muscular atrophy.

An impending update from an ongoing phase III study of the project will help determine whether this was money well spent. But it is not only Novartis and its investors that will be scrutinising the data with interest. The results have a bearing on SMA assets from Biogen and Roche, which will be keen to see exactly how transformative AVXS-101 might become.

Early data suggest that the therapy could herald a huge leap forward for infants born with the genetic condition, which causes progressive muscle atrophy and respiratory failure. Those with the most severe form, SMA type 1, rarely live beyond two years.

Biogen’s Spinraza, an oligonucleotide injected into the spine once a month, already represents something of a revolution for this field. However, there remains much room for improvement.

At the final analysis of Spinraza’s pivotal study in SMA type 1, which enrolled 121 infants under the age of one, 61% of the treated group remained alive and could breathe without help, against 32% of the control group. The children were tracked for around a year. And 71% of the Spinraza group managed an increase of at least four points on a composite measure of various motor functions, called the Chop-Intend scale, versus only 3% of the placebo arm.

Another leap

A phase I study of AVXS-101 raised hopes that the gene therapy could bestow an even bigger benefit.

Of the 15 babies recruited, all were alive and able to breathe without assistance at 20 months of age; historical data point to a survival rate of only 8% at this age. In the 12 patients given the highest dose of the gene therapy the infants showed an average increase of 9.8 points at one month and 15.4 points at three months on the Chop-Intend scale.

At the World Muscle Society meeting on October 3 Novartis will present an update from the ongoing pivotal Str1ve study, which will hopefully confirm these signals.

A first glimpse of data was released back in April from six treated patients, who had received the gene therapy at least one month previously: all were alive and event-free. An event is defined as either death or the need for near-permanent breathing support, and event-free survival is one of the co-primary endpoints of Str1ve.

Even more impressively, Chop-Intend scores had increased by an average of 7.8 points at one month after gene transfer in six of the infants, and 17.3 points at three months after gene transfer in three of the babies. 15 infants have been recruited into Str1ve, and Novartis expects to file for US approval by the end of September.

The update in October is likely to include survival and event rates and other motor measures, while investors will be keen to see evidence of durability. Any safety update will also be crucial, which given the strength of existing efficacy data is probably the biggest risk to this project. Liver safety signals have been seen in some patients treated with AVXS-101 – something that has been associated with AAV vector gene therapies – but nothing significant enough to raise huge concerns.

The sellside has been sufficiently convinced to project sales of $1.4bn in 2024. The final price tag of this project remains another issue entirely.

The SMA landscape – selected clinical-stage projects						
			Annual sales ($m)			
Product	**Company**	**Mechanism**	**2018**	**2019**	**2022**	**2024**
Spinraza	Biogen	SMN 2 antisense	1,692	1,931	2,098	2,060
AVXS-101	Novartis	SMN gene therapy	-	189	1,159	1,339
Reldesemtiv*	Astellas	Troponin activator	-	-	171	189
Risdiplam	Roche	SMN 2 gene splicing modifier	-	-	33	82
LMI070	Novartis	SMN 2 gene splicing modifier	-	-	-	-
ALG-801	Biogen	Myostatin inhibitor	-	-	-	-
**Also in trials for ALS and COPD. Source: EvaluatePharma.*						

Having spent so much money on this asset Novartis will naturally be very keen to deliver another strong set of data. But the biggest impact of a knockout result is more likely to be felt by Biogen.

One of this company's main defences of Spinraza is that this can be used on top of gene therapy. Biogen has claimed that several patients in the phase I AVXS-101 study have subsequently gone on to Spinraza and, while the durability of the gene therapy remains unknown, a combination of mechanisms remains a possibility.

But if Novartis's update reveals across-the-board improvements in motor function, to near normal levels, this argument will start to lose water. It is perhaps telling that Biogen has been stressing the potential for Spinraza in adults with the less severe type 3 disease, patients who would be unlikely to qualify for an expensive gene therapy.

Perhaps surprisingly, the advance of AVXS-101 has not deterred Biogen from further work in this space. Earlier this year the US biotech bought from Alivegen two programmes targeting the myostatin pathway – a muscle building approach with potential beyond SMA – and it also has its own gene therapy, though this has yet to enter the clinic.

And Roche also must see mileage here. The company unveiled some very impressive data on its RNA-targeting splicing modulator risdiplam over the summer, though again the asset looks more threatening to Biogen than Novartis.

The gene therapy revolution has barely begun, so it is not surprising that drug developers see no need to turn their attention away from diseases like SMA just yet. But, if Novartis lays out another very strong set of data next month, the economic case for such investments could start to weaken.

Results from Biogen and Roche in type 1 SMA patients		
	Spinraza (Endear trial final analysis; n=73)	**Risdiplam (Firefish trial part 1, n=11)**
Chop-Intend improvement from baseline; at least 4 points, at 6 months	71%	91%
Source: Company press releases, NEJM.		