Evaluate Vantage

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Avexis buy endorses gene therapy and gives Biogen a headache

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After Solid Biosciences' clinical hold dealt gene therapy a body blow Novartis has ridden to the technology's rescue. The Swiss firm's $8.7bn takeover of Solid's peer Avexis will be seen as a strong endorsement of gene therapy, especially given the premium – nearly double Avexis's closing price on Friday.

Indeed, Solid's problems, with a Duchenne muscular dystrophy project, had been seen as having a direct readthrough to Avexis's work in spinal muscular atrophy – both gene therapies use the AAV9 vector. Investors will no doubt take comfort in the boldness of the takeover, the first big move by Novartis's recently appointed chief executive, Vas Narasimhan.

Overall, the acquisition is in line with Mr Narasimhan's aim of taking Novartis into approaches using ever more advanced technologies. Bernstein analysts today pointed out that a recent meeting with the group's chief financial officer, Harry Kirsch, highlighted gene therapy as an area of interest.

It will also not go unnoticed that Avexis is studying its lead, AVXS-101, in spinal muscular atrophy (SMA), which has in recent years seen significant industry involvement. No doubt interest has been piqued by Biogen/Ionis's Spinraza, an antisense therapy that in 2016 became the first disease-modifying SMA treatment, and is expected to generate 2022 sales of $2.2bn, according to *EvaluatePharma* consensus.

And Novartis itself has shown interest in SMA: it has two mid-stage assets, BVS857 and LMI070/branaplam, though at present only the latter seems to be in active development. Today Jefferies speculated that Biogen might have been interested in Avexis to bolster its SMA offering, though the analysts thought Roche was more likely to have come up with a takeover.

Knockout bid

Avexis is curious in that it had received interest from Roche before the Swiss group's local rival, Novartis, tabled today's knockout bid.

Roche had employed a multi-pronged SMA approach: in 2011 it struck a deal with PTC Therapeutics covering gene splicing modifiers, before buying the private group Trophos for its lead asset, olesoxime, in 2015; Roche also participated in Avexis's series D financing, and had an option over AVXS-101, then known as chariSMA.

Though olesoxime had shown significant promise initially, it is at present only in one actively enrolling trial, Oleos; RG7916, one of its two PTC-derived assets, is presently Roche's main focus in SMA.

Key projects for spinal muscular atrophy (SMA)

Product	Company	Mechanism of action	2022e sales ($m)	Status
Spinraza	Biogen	SMN2 antisense	2,223	Marketed
AVXS-101	Avexis (Novartis)	SMN1 gene therapy	1,376	Phase III
RG6083/olesoxime	Roche (formerly Trophos)	Mitochondrial pore modulator	9	Phase II
RG7916	Roche/PTC	SMN2 splicing modifier	6	Phase II
LMI070	Novartis	SMN2 splicing modifier	5	Phase II
CK-2127107	Astellas/Cytokinetics	Troponin activator	-	Phase II

Source: EvaluatePharma.

For Novartis, of course, AVXS-101 is Avexis's key attraction. The project is intended as a one-time treatment to restore production of the SMN protein, whose deficiency, primarily owing to mutations in the *SMN1* gene, is the main cause of SMA. Pivotal trials are still ongoing, but in the meantime a pre-BLA meeting is due to take place with the US regulator.

Novartis today said it was targeting a 2019 filing in the US, a delay versus Avexis's second-half 2018 expectation. AVXS-101's clinical programme comprises various studies in different types of SMA, while the key supporting data generated so far concern the 15 type 1 patients enrolled into the CL-101 trial, 100% of whom were alive and event-free at 20 months' follow-up.

While the only available comparison versus Spinraza is across studies, this favours Avexis; the Endear trial showed Spinraza beating placebo in a broadly similar subject population to that studied in CL-101, but one-year event-free survival, a secondary endpoint, was around 60% in the active group.

Across-study or not, many analysts now see AVXS-101 as a major threat to Spinraza. Bernstein today wrote that Novartis's takeover ratcheted up the pressure on Biogen, putting the main competing SMA programme in the hands of a "well-funded, payer-competent, global-reaching company".

The analysts said they had for some time been concerned that sellside consensus was underestimating the Avexis threat. Given where Spinraza's 2022 revenue consensus stands the scope for this to be trimmed is considerable.

Selected studies of AVXS-101

Study	SMA type	Disease characteristics	Design	Trial ID
CL-101	Type 1	2 SMA2 gene copies; 90% death by age 2	15 pts, open-label (100% 20mth event-free survival)	NCT02122952
Str1ve	Type 1	2 SMA2 gene copies; 90% death by age 2	15 pts, single-arm	NCT03306277
Strong	Type 2	3 SMA2 gene copies; 32% death by age 25	27 pts, open label	NCT03381729
Spr1nt	Presymptomatic	–	44 pts, single-arm	Planned Q2 2018
Reach	Types 1, 2 & 3	Type 3 have 3 or 4 SMA2 copies; normal survival	50 pts, single-arm	Planned Q1 2019

Source: Avexis/Novartis.

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