Evaluate Vantage

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Novartis and Biogen face spinal muscular atrophy reckoning

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The upcoming American Academy of Neurology meeting could provide clues on how the market will shake out.

A strong first quarter helped Novartis recoup the losses it suffered last week after reporting two deaths with its big pipeline hope, the spinal muscular atrophy gene therapy Zolgensma.

But the project's safety profile is clearly on investors' minds as an FDA approval decision looms next month. Questions about this, as well as Zolgensma's price and labelling, dominated Novartis's earnings call yesterday as analysts tried to shed light on how the SMA market might split between Zolgensma, Biogen's approved therapy Spinraza, and another new contender from Roche, risdiplam.

Spinraza maturing?

Biogen also reported its quarterly results yesterday and Spinraza sales beat expectations, although there were worrying signs about the project's future. Growth was driven by sales outside the US, while the number of new patient starts in the US slowed to 160 in the first quarter, from 230 in the last three months of 2018.

This slowdown, coming before competition from Zolgensma hits, is puzzling. Biogen brushed off a suggestion that patients and their parents might be holding on for the Novartis gene therapy, instead putting the decrease down to seasonal issues: apparently, patients are less compliant in the winter.

In any case, such a warehousing effect for Zolgensma seems unlikely for a life-threatening disease like SMA – the most seriously affected patients, those with type 1 disease, usually die within a few years.

Spinraza is approved by the US FDA for any subtype of SMA, including the less severe type 2 and 3 patients, but there are questions about whether Zolgensma will get a similarly broad label.

Zolgensma label

The gene therapy has been filed for type 1 only, although analysts obviously hope that the FDA might be more generous, with yesterday's call hearing several questions about Zolgensma's approvability beyond type 1 disease.

Novartis's chief executive, Vas Narasimhan, would not speculate on this; when asked he pointed to positive data in the Start and Strive trials, both in type 1 disease.

At the American Academy of Neurology meeting in Philadelphia in May Novartis will present more data from both studies, but investors will be keen to see results from the Strong trial using an intrathecal formulation of Zolgensma in type 2 disease; in previous trials the gene therapy has been given intravenously.

Biogen and Roche will also present at AAN; more data from the latter's Firefish and Sunfish trials of risdiplam could help investors gauge just how big a threat the oral SMN2 splicing modifier might pose. Risdiplam, which has yet to be filed with regulators, looks particularly worrying for Biogen, based on data seen so far (*Roche and Novartis confirm dual threat to Biogen's biggest growth driver, October 4, 2018*).

AAN presentations to watch in SMA

Project	Company	Trial	Setting	Details
Zolgensma	Novartis	Strive, NCT03306277	Phase III trial in type 1	Poster, May 5
		Strong, NCT03381729	Type 2, intrathecal delivery	Poster, May 5
		Sprint, NCT03505099	Presymptomatic, types 1, 2, 3*	Poster, May 5
		Start, NCT03421977	Long-term extension, type 1	Presentation, May 7
Spinraza	Biogen	Shine, NCT02594124	Long-term extension	Poster, May 5
		Nurture, NCT02386553	Presymptomatic, types 1, 2, 3	Presentation, May 7
Risdiplam	Roche	Firefish, NCT02913482	Type 1	Presentation, May 7
		Sunfish, NCT02908685	Type 2 & 3	Presentation, May 7

**As per Novartis slide, company subsequently told Vantage that Sprint is in patients with 2-3 copies of SMN2, which most closely aligns to Types 1 & 2 disease.*
Source: Evercore ISI AAN planner.

However, a new oral option might not help Novartis's efforts to penetrate the type 2 and 3 SMA populations. This quest took a blow last week with the news of two deaths in trials of Zolgensma. One, in the Strive study, has already been deemed unrelated to therapy; the second, in Strive-EU, is still being investigated.

Mr Narasimhan brushed off any toxicity concerns with Zolgensma, highlighting the life-threatening nature of SMA and the fact that deaths had also occurred in trials of other therapies. He added that the second patient who died had already had signs of lung infection before receiving therapy.

Any lingering worries here are unlikely to hold Zolgensma back in type 1 SMA, which only has a 50% survival rate at 10 months, but could provide a reason to be cautious about its chances in less severe patients.

Another big question surrounding Zolgensma is its eventual price. Here, Mr Narasimhan said Novartis was looking at a range of $1.5-5m (*Icer sets Novartis a gene therapy pricing challenge, December 21, 2018*).

Many expect Zolgensma to become the world's most expensive drug, but Novartis seems unlikely to charge the $4-5m figure that has previously been mooted. Mr Narasimhan concluded: "Icer [the US cost watchdog] recommend we should price lower than $4-5m. We take that as useful information."

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