Evaluate Vantage

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Therapy focus – Spinal muscular atrophy pipeline awaits nusinersen news

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Nusinersen's quick transition from clinical stage to regulatory review highlights much-needed progress in treating spinal muscular atrophy. For other pipeline assets behind it, however, its presence on the market could complicate clinical development.

If the antisense therapy from Biogen and Ionis Pharmaceuticals reaches the market early next year with a broad label, as many expect, the prospect of running placebo-controlled studies becomes much more problematic ethically. Phase III strategies of the likes of Avexis, Roche and Novartis are surely up in the air until regulators pass judgement on nusinersen (see table below).

Showdown in Granada

The World Muscle Society meeting in Spain at the weekend was the scene for competing encouraging data presentations in this rare condition, which results from a defect in the SMN1 gene, leading to spinal motor neurone degeneration and muscle wasting.

Type 1, also called Werdnig-Hoffmann disease, is the most severe, emerging within the first six months of life; type 2 patients cannot walk; type 3s can, but often become non-ambulant later in life; the relatively infrequent type 4 is the least severe, occurring in adulthood.

At the congress Biogen and Ionis presented incremental but encouraging new safety information from the recently stopped phase III Endear trial in type 1 patients. This recruited babies of up to seven months of age with two copies of the SMN2 gene. A full efficacy analysis of the study remains keenly awaited.

The companies also released a first look at data from the Nurture trial. This recruited pre-symptomatic patients diagnosed with type 1 SMA, who receive their first dose before they are six weeks old. The results showed nusinersen-treated babies achieving motor milestones at their expected ages – an encouraging sign in this degenerative disease.

Key clinical SMA projects				
	Project	**Pharma class**	**Company (partner)**	**Forecast 2022 sales ($m)**
Phase III	Nusinersen	Muscular atrophy antisense	Biogen (Ionis)	934
Phase II	Olesoxime	Mitochondrial pore modulator	Roche (Trophos)	65
	CK-2127107	Troponin activator	Astellas Pharma (Cytokinetics)	22
	BVS857	Other musculoskeletal agent	Novartis	-
	LMI070	Other musculoskeletal agent	Novartis	-
Phase I	RG7800 (suspended)	SMN2 gene splicing modifier	Roche (PTC)	-
	RG7916	SMN2 gene splicing modifier	Roche (PTC)	-
	RG3039	DcpS inhibitor	Repligen	-
	AVXS-101	SMN gene therapy	AveXis (Regenxbio)	-

Finally, updated analyses from a phase II trial in later-onset type 2 and 3 patients showed continuing improvements in motor function and the six-minute walk test for up to three years. The phase III Cherish trial looks at this cohort more rigorously; results from this are expected mid-2017.

Biogen completed the filing for approval in the US at the end of September and a decision is expected by March or April; an EU filing is expected imminently. It has submitted data from the Endear trial and other ongoing open label studies and is hoping for a broad label covering all types of the disease. Data presented over the weekend will have done little to dissuade those hoping for this to be awarded.

Avexis good, but what is its outlook?

Biogen's completion of its filing does complicate the outlook for Avexis, which has one of the most closely-watched earlier stage SMA assets in the gene therapy AVXS-101. The group has sought a meeting with the FDA to discuss pivotal trial design, and until it has seen the report from that meeting it is declining to publicly discuss endpoints, comparative arms and follow-up time.

Its phase I/II results so far have given investors some hope, with a 5% share rise sparked yesterday by presentation of data from the second cohort of patients in its phase I/II trial of AVXS-101. This group of 12 patients had type 1 disease, and were exposed to the company's proposed therapeutic dose, which is delivered with a single intravenous infusion.

The cohort achieved an improvement in motor skills as measured by a mean increase of 24.8 points on the Children's Hospital of Philadelphia infant test of neuromuscular disorders.

Of the 12 patients, 11 scored more than 40 and three scored more than 60, a range that the company says is considered to be normal. The one that did not reach 40 was the oldest one dosed in the cohort, and like the older three babies in the lower-dose cohort 1 stabilised but did not improve motor functions.

The company was keen to emphasise that eight of the 12 in the second cohort are sitting unassisted, which can subsequently lead to the strength improvements that can result in other motor function milestones.

Avexis does not expect to initiate a pivotal trial until sometime in the first six months of 2017. In the meantime, it plans on initiating a phase I dosing trial in type 2 patients, which will receive the gene therapy intrathecally.

The Swiss guard

While Avexis gets much attention in this space – no doubt thanks to its retail investor following – Roche is actually a much bigger player. It bought its lead candidate olesoxime from Trophos last year and since then it has started a new 171-patient phase II study that looks unlikely to generate data until 2020 (*Roche muscles*

into the lead in rare wasting disease, January 16, 2015).

Key SMA trials				
Project	**Enrolment**	**Trial ID**	**Acronym**	**Details**
Phase III				
Nusinersen	274	NCT02594124	Shine	Endear open-label extension study
Nusinersen	111	NCT02193074	Endear	Early onset – up to 7 months
Nusinersen	117	NCT02292537	Cherish	Later onset – 2 to 12 years
Phase II				
Nusinersen	25	NCT02386553	Nurture	Pre-symptomatic – up to six weeks old
Olesoxime	171	NCT02628743	-	Type 2 or 3
CK-2127107	72	NCT02644668	-	Types 2-4
RG7916	186	NCT02908685	Sunfish	Types 2 and 3
RG7916	48	NCT02913482 (not yet recruiting)	Firefish	Type 1
Phase I/Phase II				
LMI070 (Novartis)	42	NCT02268552	-	Type 1
Phase I				
AVXS-101 (AveXis)	15	NCT02122952	-	-

It is not clear which types of patient this trial is targeting – type 2 and 3 looks likely – and these are the subject of a second major trial it started this month, with RG7916. This is a 186-patient trial in types 2 and 3, called Sunfish, and again results are not due for some time.

RG7916 is a SMN2 gene-splicing modifier gained from a collaboration with PTC; a former candidate, RG7800, has been placed on clinical hold pending safety investigations.

Crosstown rival Novartis also has a stake in this space although its work appears to be more muted. It has two agents in phase I/II testing, LM1070 and BVS857, neither of which appear to be in active clinical trials or have generated data worthy of Novartis publishing.

Moving forwards

Should nusinersen receive approval in all SMA subtypes, Avexis will not be the only one left wondering how to amend future clinical plans. Even if initial approval is only given in type 1, Biogen and Ionis's broad clinical programme could easily see nusinersen win wider approval later next year. So the drug's presence on the market, representing a new standard of care, would change the game significantly for all involved.

As an independent small cap drug developer, Avexis is most exposed to this medical advance. At the end of August, before Biogen had completed its FDA filing for nusinersen, BMO analyst Ian Somaiya said he believed that there was a 50/50 chance of a single-arm design for AVXS-101 in phase III.

This has to be a best-case scenario for the small drug developer. Demands for a study in combination with nusinersen, against nusinersen alone, would be much more onerous – and ought to be considered by the investment community to represent a huge risk.

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