Myonexus becomes the third string to Sarepta’s muscular dystrophy bow

Keenly awaited results from the first trial of MYO-101 broadly beat expectations, leading Sarepta to buy the gene therapy’s originator.

Results from the first three limb-girdle muscular dystrophy type 2E subjects given the MYO-101 gene therapy were a key catalyst for Sarepta. Today investors found out that the data were good enough for the company to acquire Myonexus, the project’s originator, for $165m.

The data themselves, unveiled about an hour after Sarepta announced the takeover this morning, by and large did not disappoint either. The one black mark was liver enzyme elevations in two of three patients, but in terms of gene expression there is now compelling evidence that MYO-101 is doing what it should.

Sarepta therefore now has three strings to its muscular dystrophy bow, the other two being the controversially approved exon-skipping drug Exondys 51 and a microdystrophin gene therapy whose gene expression data had wowed Wall Street last June.

And Myonexus brings with it four additional gene therapies in preclinical development for four other types of limb-girdle muscular dystrophy: 2B, 2C, 2D and 2L. Each seeks to replace the relevant mutated gene, which in the case of type 2E and MYO-101 is SGCB; the mutation leads to insufficient production of the gene’s product, beta-sarcoglycan.

Expression datapoint

Thus the key result investors were looking for today was levels of beta-sarcoglycan in muscle fibres, with expression in 20% of fibres representing the minimum necessary to declare the result robust.

In the event immunohistochemistry testing found that 42-63% of the fibres of the three subjects, each given a $5\times10^{13}$ vg/kg dose, were positive for beta-sarcoglycan, resulting in a mean of 51%. By Western blot analysis the figure was 36% of normal. Sarepta stock opened up 6% today.

A key question, of course, will be whether this translates into an actual benefit for patients. Louise Rodino-Klapac, Sarepta’s vice-president of gene therapy, presented the data on an analyst call today and suggested that she was “seeing early signs of functional improvement”.

However, the company’s chief executive, Doug Ingram, subsequently cautioned that it would be premature to
read too much into such early data in terms of functional benefit. Ms Rodino-Klapac is an inventor of all five Myonexus limb-girdle programmes, and was the group’s acting chief scientific officer.

On the safety front, however, two of the treated subjects had elevated liver enzymes, and one associated increase in bilirubin was designated a serious adverse event. However, the enzyme elevations were seen when the patients were having steroid treatment withdrawn, and were treated with additional steroids.

Such transient adverse events are probably less relevant with a one-time gene therapy than they might be with a chronically dosed treatment, especially as the serious event has resolved, and the subject is now off steroids.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Result</th>
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<tbody>
<tr>
<td>Mean percentage of beta-sarcoglycan +ve fibres</td>
<td>51%</td>
</tr>
<tr>
<td>Mean beta-sarcoglycan expression by Western blot</td>
<td>36% of normal</td>
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<tr>
<td>Mean creatinine kinase reduction</td>
<td>90%</td>
</tr>
<tr>
<td>Liver enzyme elevations</td>
<td>2 of 3 subjects</td>
</tr>
<tr>
<td>Increase in bilirubin (serious AE)</td>
<td>1 of 3 subjects</td>
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Source: Sarepta analyst presentation.

Overall the data signify an excellent result for Myonexus, which had raised just $2.5m in seed funding in December 2017 before Sarepta came in last year with a $60m licensing fee and option to acquire.

The placebo-controlled crossover study aims to enrol nine subjects, and success with 5x10^{13}vg/kg was to inform a decision as to whether to dose the next three subjects at 2x10^{14}vg/kg. A relevant question might be whether there is a need to dose escalate, but Mr Ingram said there was headroom to look at higher doses, the “striking results” notwithstanding.

On today’s call Mr Ingram spelled out a plan for Sarepta to become a major player in gene therapy, the cornerstone of which is MYO-101 and the Duchenne muscular dystrophy asset AAVrh74.MHCK7.micro-dystrophin. Both use the same AAVrh74 vector and MHCK7 promoter, though the former comprises a full-length gene and the latter a truncated version.

He said he now wanted to chart a path forward for all five Myonexus limb-girdle programmes. Three treated subjects is not many, but this is reflected in the takeout price, and paying $165m for Myonexus will not have broken the bank.