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A Spark for gene therapy in the US

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The US FDA capped off a fairly stellar year for drug approvals by giving the green light to Spark Therapeutics's inherited blindness treatment, 24 days before the decision deadline. Luxturna will become the first bona fide gene therapy to be launched in America.

Developer Spark Therapeutics will be thankful for some good news after disappointing data on its highly touted haemophilia A project, SPK-8011, caused shares to fall. This month's stock price collapse has taken the shine off 2017 but a recovery could build next year if more mature data emerge to put SPK-8011 in a better light.

One small step for man

Luxturna treats vision loss caused by biallelic RPE65 mutation-associated retinal dystrophy, a rare condition. Using an adeno-associated viral vector, Luxturna delivers a functioning version of the gene that codes for retinal pigment epithelium protein, without which photoreceptor cells die and patients to go blind.

The experts convened by an FDA advisory committee were comfortable with the novel endpoint used by Spark, which involved patients navigating a course in various degrees of darkness to detect improvement, as measured by the ability to improve by two levels of darkness (*US gene therapy on track to arrive with positive Luxturna vote, October 13, 2017*). Eleven of 21 patients were able to do so.

Still, the fact that nearly half were not raises the question of cost-effectiveness, an issue beyond the remit of the regulator. As a gene therapy, Luxturna would be expected to represent a permanent cure and therefore could command a price suggested to be in the $1m range. Payers may only want to pay for responders and, should the effectiveness fade, be reluctant to pay for retreatment.

A draft report from the Institute for Clinical and Economic Review (ICER) suggested that at a $1m pricetag Luxturna's cost would be $741,000 per additional quality adjusted life year (QALY) gained for patients treated at age 15 and $299,600 per additional QALY in patients treated at age 3, assuming its effects fade after 10 years.

ICER will convene an expert panel in January to consider the cost-effectiveness evidence it has gathered.

This controversy has not prevented the sellside from attaching ambitious targets. *EvaluatePharma*'s consensus of analyst forecasts suggests sales of $364m in 2022 - consensus sits at $76m next year.

One giant leap of faith

Luxturna's relative value to Spark depends largely on the fate of SPK-8011. On the positive side this gene therapy eliminated bleeding and the need for infusion in the first four patients dosed, but also showed a variable dose response and some hints of immunogenicity *(Ash 2017 – Spark extinguished by Biomarin haemophilia data, December 11, 2017*).

Expression of factor VIII, the clotting protein that is deficient in haemophilia A patients, rose to 35% of normal in the best-performing patient. But in a separate trial also presented at Ash, patients taking Biomarin's valoctocogene roxaparvovec at the highest dose achieved 100% of normal factor VIII expression, making Spark's data look weak (*Ash 2017 – Biomarin breaks away in haemophilia A gene therapy chase, December 9, 2017*).

But Spark is not out in haemophilia yet. Its relatively cautious approach to dosing – it has so far delivered 20 to 30 times fewer vector genomes as the highest dose of valrox – could mean that adding a higher dose group to its phase I/II trial of SPK-8011 could lead to better responses.

In addition, more mature data to be presented at medical meetings next spring and summer could reveal that the first four patients dosed manage to achieve steady-state factor VIII at 15% of normal, a level above which spontaneous bleeds do not typically occur, with no signs of immune response.

Hitting that level might make SPK-8011 a more attractive proposition, given that many of the valrox patients achieved a level of factor VIII expression that could put them at risk of thrombosis.

In Spark’s pipeline, SPK-8011 figures as a much bigger product than Luxturna in terms of net present value – $1.8bn vs $621m – though that is based on sales forecasts made before the disappointing Ash data emerged. Signs that SPK-8011 can be a safer alternative in haemophilia gene therapy could help rebuild confidence.

A return to pre-Ash levels will probably not happen until Spark can steady investors’ nerves with more data. But in the meantime the Luxturna decision should at least help recover lost ground.

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