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Ash – Spark strengthens case for haemophilia gene therapy

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Spark Therapeutics has cemented its position as the haemophilia gene therapy company to beat with an update on its early stage trial showing “disease altering” levels of clotting factor activity after 12 weeks of treatment.

The emergence of an immune response to the adeno-associated virus capsid used to deliver the therapy in two patients is worth watching, although the company said a short course of corticosteroids was counteracting this. Spark will need to show success in neutralising immune reactions to address regulators’ and payers’ caution about the risk of gene therapy.

News of the immune response caused shares of the Pennsylvania-based group to tumble 10% on Thursday. However, at Ash, Katherine High, Spark’s president and chief medical officer, described the immune reaction as a greater concern for efficacy than safety. “The patient may lose the donated gene,” she said at a press conference at the Ash meeting in San Diego.

Thus Spark is now looking at protocols to identify quickly those haemophilia B patients who are having an immune response, with early signs being a fall in factor IX levels or a rise in liver enzymes. “If you catch it quickly it looks like you can arrest the decline,” Ms High said.

This will be equally important to payers looking at a therapy that will almost certainly fall in the $1m range. Pfizer’s Benefix cost $336,000 per patient in 2015 in the US, according to *EvaluatePharma*, so a once-and-done treatment could plausibly argue for a seven-figure price-tag.

However, payers have argued for money-back guarantees in the case of GlaxoSmithKline’s gene therapy Strimvelis, so Spark and its partner Pfizer should be keen to show that they have developed a protocol for preventing gene loss.

The data are from nine patients in the phase I/II trial, who showed average factor IX activity of 28% or greater after 12 weeks of therapy; subjects had to have activity levels of 2% or less to enrol.

None of the patients experienced a bleeding episode or needed a regular clotting factor infusion as of November 30, a data cut that included 1,650 patient days. At the historical bleeding rate before participants’ entry into the trial, 41 episodes would have been expected, the company reported.

Rivals falling away

Spark remains slightly behind Uniqure in terms of clinical development of a haemophilia B gene therapy as it is preparing a pivotal trial (*New data Spark haemophilia B gene therapy battle, June 17, 2016*). With its comparatively modest single-digit factor IX response from an initial dose, first-mover advantage will be important for Uniqure as Spark seeks to make up ground – if, indeed, Uniqure can claim that advantage.

At Ash, Uniqure presented updated data from a higher-dose cohort of its phase I/II trial showing 6.9% average factor IX activity following infusion of AMT-060. One spontaneous bleed was recorded.

The difference could be down to Spark’s use of the FIX-Padua gene versus Uniqure’s wild-type factor IX. The former is a mutant identified in an Italian man with excessive thrombosis and has eight to 12 times the clotting potency of wild type.

Spark’s way has also been cleared by Shire’s decision to discontinue the BAX 335 project it inherited in the takeout of Baxalta. Other projects include Dimension Therepeutics’s DTX101, another wild-type gene therapy project, and Sangamo’s SB-FIX. Both of these are behind Spark, with Dimension’s phase I/II data due in January 2017, and Sangamo having started phase I/II in October.

Spark has set a very high bar, and has been helped along by stumbles from its competitors. Payers and regulators remain wary of the costs and safety profile of gene therapies, however. It will need to continue to show that the immune response can be managed safely without limiting the efficacy of this expensive

treatment approach.

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