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Ash 2017 – Biomarin breaks away in haemophilia A gene therapy chase

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Biomarin stuck a nose out in front of the pack of DNA therapeutics seeking to treat haemophilia A with long-term phase II data suggesting that, not only could the gene therapy valoctocogene roxaparvovec eliminate bleeding episodes, it could also restore clotting factor to normal levels.

This could be upended later in the haematology meeting with Spark Therapeutics scheduled to present on its dosing trial of SPK-8011, although the abstract suggests that it could struggle to leap the high bar set by Biomarin. Bigger patient numbers in phase III and longer follow-up will almost certainly take the shine off these initial valoctocogene roxaparvovec results, but nevertheless Saturday's data show gene therapy inching closer to the market.

Not just better, but normal

Biomarin revealed data from a dose-escalation trial of valrox, previously known as BMN 270, with follow-up out to 78 weeks for severe patients infused with the highest dose, 6×10e13vg/kg. While the researchers had hoped to achieve clotting factor VIII levels of 5 international units per deciliter (IU/dl), above which spontaneous bleeding is rare, in fact all seven patients achieved normal levels of above 50IU/dl.

Annualised bleeding rates among the six patients on prophylactic factor VIII therapy at baseline dropped to zero, as did factor VIII infusions. This remained true of a later patient cohort that received a lower dose of 4×10e13vg/kg, even though the mean factor VIII expression in this group had just managed to reach that 50IU/dl threshold at week 44, rather than at week 12.

"This is way more than we wanted to achieve," Dr John Pasi, director of the Royal London Hospital Haemophilia Centre and a professor at Queen Mary University of London, said at an Ash press conference. "Bleeding rates have essentially collapsed. All the patients have come off prophylaxis. That's going from 140 to 150 plus injections a year to essentially zero."

Consequently, patient quality of life as measured by the Haem-QoL-A instrument created by Bayer for rating its haemostasis products had increased by 16.6 points over baseline, above that achieved by patients taking Kogenate.

An apparent falloff of factor VIII expression at 78 weeks with the gene therapy is worth watching as these data mature and as Biomarin moves the doses into two separate single-arm phase III trials – especially as gene therapy is intended as a once-and-done treatment for which the California-based group might command as much as $1m per patient.

"Durability, that is a huge question for any gene therapy approach," Dr Pasi said, adding that haemophilia B patients treated with gene therapies were expressing factor IX years later, and that looking at the valrox data as they stand meant "you could argue that we've reached a steady state".

"I think there will be some steadying out," he said.

The gene therapy crowd

Among the non-factor infusion approaches to haemophilia A valrox trails only Roche's recently approved Hemlibra, and that antibody currently only has the go-ahead in patients who have developed inhibitors to factor VIII.

Alnylam's RNA interference project fitusiran, which has struggled with safety issues – the US FDA recently lifted a clinical hold thanks to risk-mitigation efforts – is also in late phase II. In any case, fitusiran seeks to prevent bleeding by targeting thrombin, and is not necessarily a direct mechanistic competitor.

But, given the genetic expression of haemophilia and scientific advances, there are a number of potential gene therapy competitors queueing behind Biomarin. Spark is among them – its Ash abstract mentioned three patients dosed with SPK-8011 at a maximum of 23 weeks, and presumably there will be an update when

investigators present on Monday. That abstract shows a best steady-state factor VIII level of 14%, which if unchanged on Monday will come as a disappointment.

The Pfizer-partnered Sangamo project SB-525, which now carries the Pfizer code PF-07055480, was dosed in its first patient in August, and a second one was announced in November. Shire, meanwhile, had hoped to begin dosing SHP654 by the end of 2017 and Ultragenyx's DTX201, acquired with Dimension Therapeutics, is expected to follow SHP654 into the clinic in early 2018.

Surprisingly, there are bigger expectations for Spark's project than for Biomarin's – *EvaluatePharma*'s consensus of sellside analysts puts sales at $338m and $223m respectively. That should change should Biomarin's apparent efficacy edge hold.

And it will be a tough pace for Sangamo, Shire and Ultragenyx to match.

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