Evaluate Vantage

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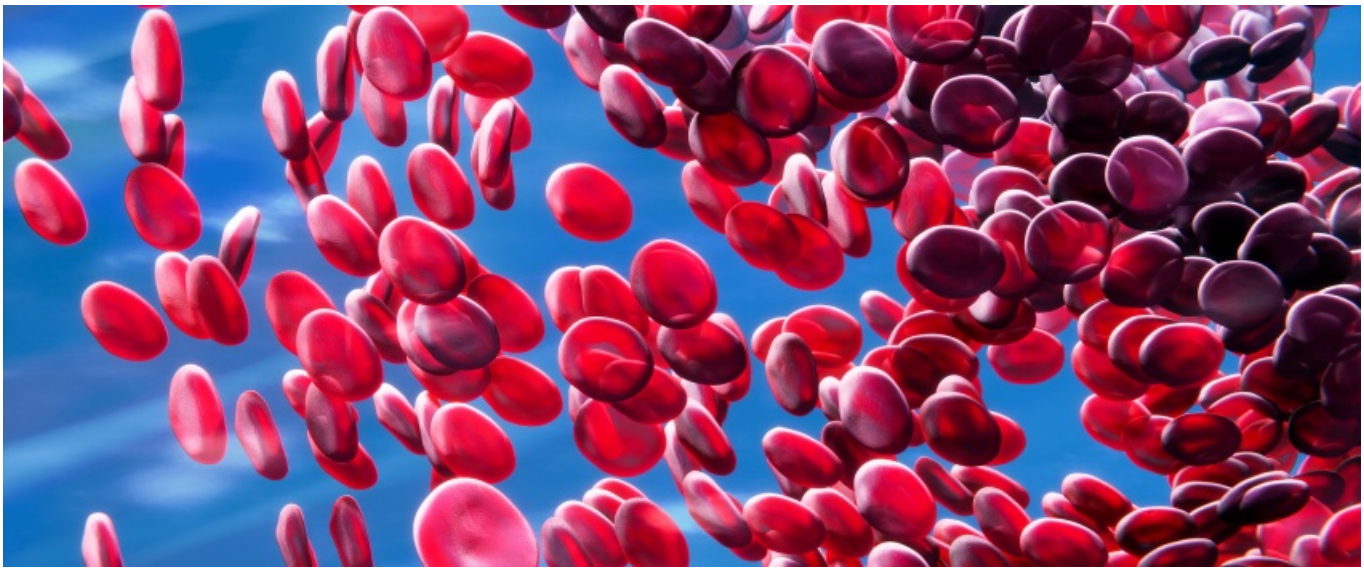
Sigilon hold hurts ahead of key haemophilia meeting

Madeleine Armstrong



After a patient develops inhibitors questions emerge about a new approach to treating haemophilia A.

Sigilon Therapeutics had claimed that its cell therapy SIG-001 could have advantages over gene therapies for haemophilia A. Now the group is contending with a hold on the project's phase 1/2 trial after a patient developed inhibitors.

It is unclear whether SIG-001 caused the issue, and the company suggested that the problem might be patient-specific. Still, the development adds to doubts about uptake of cell and gene therapies for haemophilia, just as the annual meeting of the International Society on Thrombosis and Haemostasis (ISTH) approaches.

Gene therapy data

That meeting, being held on July 17-21, will feature data on various haemophilia A gene therapies, including the current frontrunner, Biomarin's valoctocogene roxaparvovec (valrox), and Roche's SPK-8011, acquired from Spark. There will also be results with a possible wild card, Bayer/Ultragenyx's BAY 2599023, which is designed to be a more durable option.

Questions about durability have hung over haemophilia A gene therapies since Biomarin reported phase 1/2 data with valrox. ISTH will see five-year results with the $6x10^{13}$vg/kg dose, which might make things clearer; at four years the median factor VIII level was 16% of normal.

At the conference there will also be more data from the pivotal Gener8-1 study, for which initial results were released in January. Although mean factor VIII levels were 43% at one year, there were signs that this was beginning to wane over the longer term (*Pivotal valrox data give Biomarin déjà vu, January 11, 2021*).

Nevertheless, on this measure valrox still looks more impressive than SPK-8011. The ISTH abstract for the latter details a mean FVIII level of around 12% in 11 patients followed for over two years. It is unclear how important this metric is, or whether the FDA will be more focused on a reduction in bleeding.

Another question is how much of a priority SPK-8011 is for Roche. The group has been relatively quiet about the project since finalising its purchase of Spark in December 2019; the acquisition was scrutinised by the FTC amid worries that Roche might squash the development of SPK-8011 to benefit its haemophilia blockbuster,

Hemlibra.

A phase 3 study of SPK-8011 is slated to start this year but there is no sign of it yet. A Roche spokesperson told *Evaluate Vantage* that the project "remains a priority", but declined to say when the pivotal trial might begin.

More durable?

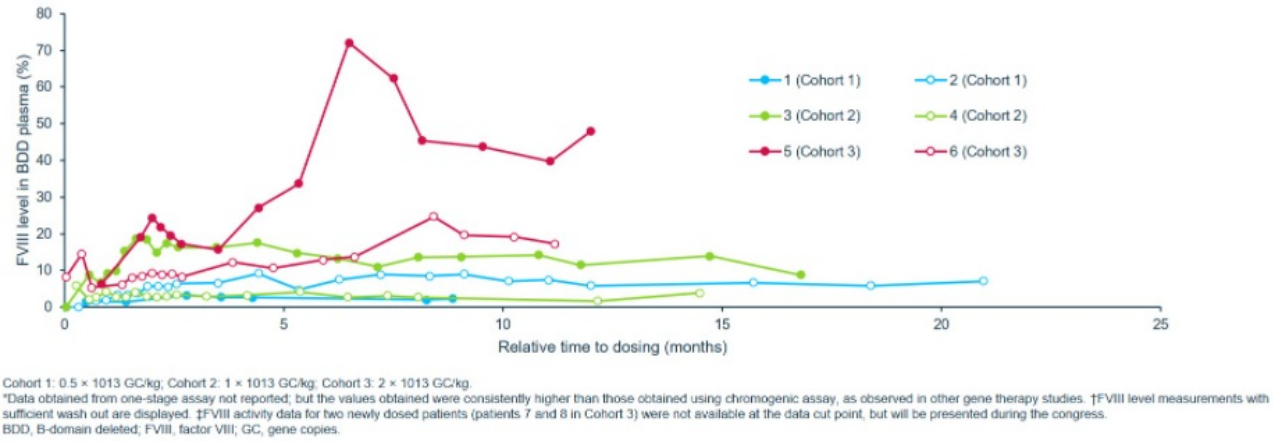
Questions over durability – which have also hit Pfizer/Sangamo's giroctocogene fitelparvovec – could make haemophilia A patients wary about gene therapy, particularly as these therapies cannot be redosed, and patients already have other options.

Step forward Bayer, which believes that it has a longer-lasting candidate in BAY 2599023. Initial data on the project from six patients, presented at last year's Ash meeting, suggested a dose response, although FVIII levels remained relatively low, apart from in one patient.

However, Bayer's head of rare disease, Francesca Ferrante, previously stressed to *Evaluate Vantage* that this is was dose-finding study and that any efficacy would be a bonus.

ISTH will feature data on eight patients, including two new patients receiving a $2x10^{13}$vg/kg dose of BAY 2599023 plus prophylactic steroids. Bayer also has the option to increase the dose to $4x10^{13}$vg/kg.

Figure 2. FVIII levels (chromogenic* [BDD plasma]) by patient over time† in Cohorts 1, 2 and 3 (n=6‡)



Cohort 1: 0.5 × 1013 GC/kg; Cohort 2: 1 × 1013 GC/kg; Cohort 3: 2 × 1013 GC/kg.
*Data obtained from one-stage assay not reported; but the values obtained were consistently higher than those obtained using chromogenic assay, as observed in other gene therapy studies. †FVIII level measurements with sufficient wash out are displayed. ‡FVIII activity data for two newly dosed patients (patients 7 and 8 in Cohort 3) were not available at the data cut point, but will be presented during the congress.
BDD, B-domain deleted; FVIII, factor VIII; GC, gene copies.

> *Figure 2. FVIII levels (chromogenic* [BDD plasma]) by patient over time† in Cohorts 1, 2 and 3 (n=6‡)*

Source: ISTH abstract

As for Sigilon, that group might take heart that other studies of haemophilia A therapies have been put on hold and then restarted again relatively quickly: Novo Nordisk's concizumab and Alnylam/Sanofi's fitusiran both managed to overcome non-fatal thrombotic events and get pivotal trials going again last year.

It is also worth noting that inhibitors are a common complication of FVIII therapy, a current mainstay of haemophilia A treatment.

Still, Sigilon's stock sank 25% on Friday and, with a market cap of $218m, the group is trading not far off cash levels. Gaining an edge in a crowded market was always going to be tricky, and things have just got trickier for the company.

This story has been updated to include comments from Roche.

Selected novel projects in development for haemophilia A			
Project	**Company**	**Description**	**Trial details**
Phase 3			
Valoctocogene roxaparvovec	Biomarin Pharmaceutical	Factor VIII gene therapy	Gener8-1, initial data reported Jan 2021
Giroctocogene fitelparvovec (SB-525)	Pfizer/Sangamo	Factor VIII gene therapy	Affine
Efanesoctocog alfa (BIVV001)	Sanofi/Sobi (ex Bioverativ)	Once-weekly factor VIII replacement therapy	Xtend-1; Xtend-Kids
Concizumab	Novo Nordisk	Tissue factor pathway inhibitor antibody	Explorer 7; Explorer 8*
Marstacimab (PF-06741086)	Pfizer	Tissue factor pathway inhibitor antibody	Basis
Fitusiran	Alnylam/Sanofi	Anti-thrombin-targeting RNAi therapeutic	Atlas A/B; Atlas-PPX*
Phase 1/2			
SIG-001	Sigilon Therapeutics	Encapsulated allogeneic factor VIII cell therapy	Ph1/2 on hold – pt developed inhibitors
SPK-8011 (RG6357)	Roche (ex Spark)	Factor VIII gene therapy	Ph1/2
SPK-8016 (RG6358)	Roche (ex Spark)	Factor VIII gene therapy	Ph1/2 in inhibitor pts
BAY 2599023/DTX201	Bayer/Ultragenyx (ex Dimension)	Factor VIII gene therapy	Ph1/2
ASC-618	ASC Therapeutics	Factor VIII gene therapy	Ph1/2
CD68-ET3-LV	Expression Therapeutics	Haematopoietic stem cell transplantation gene therapy	Ph1
**Previously paused but restarted; Source: Evaluate Pharma & clinicaltrials.gov.*			