Evaluate Vantage

May 18, 2016

EHA preview – First blood for Spark

Jacob Plieth

The beleaguered but slowly awakening gene therapy field got another boost yesterday with the revelation that Spark Therapeutics' haemophilia B project SPK-FIX managed to generate high levels of factor IX activity, setting a new bar for competitors.

The initial findings were disclosed among the abstracts for next month's European Hematology Association congress, and were probably the last thing Uniqure investors wanted to hear. Stung by the commercial failure of Glybera, Uniqure is reliant on its own haemophilia B gene therapy, AMT-060, but now risks being outclassed before getting off the ground.

AMT-060 features in its own EHA abstract, though the data offer little of note, and the focus remains on results of higher dosing, due in the second half. While Spark stock climbed 14% yesterday Uniqure was off 5% (*Spark stumbles into gene therapy landmark, October 6, 2015*).

Padua vs wild type

An important difference between the rival gene therapies is the type of factor IX – the missing blood-clotting factor in haemophilia B patients – that they seek to express.

Uniqure's encodes normal, or wild-type, factor IX, whereas Spark focuses on a mutated protein called factor IX Padua. The latter variant, caused by a single amino acid alteration in the protein structure, results in affected individuals generating a factor IX with over eightfold higher specific activity, presumably leading to a commensurate increase in ability to generate thrombin.

So far, in two of the first five patients treated with low-dose AMT-060, Uniqure's gene therapy has shown about 5% expression of factor IX, and the EHA presentation will include data on all five patients. Spark's SPK-FIX, meanwhile, is seen generating factor IX activity levels of 16% to 30% in the first three patients treated, the EHA abstract says.

True, these are extremely small patient numbers, and comparisons across studies should be treated carefully, but the initial signs are that Spark has taken an important lead. A key point is that factor IX activity of only 5-10% is sufficient for a therapeutic effect, suggesting the viability of lower SPK-FIX dosing that could avoid the risk of liver enzyme elevations and other side effects.

For Uniqure the problems include not only a relatively lower level of activity but also growing competition in haemophilia B. In addition to Spark, Baxalta also has a gene therapy programme coding for factor IX Padua, though this has yet to enter phase III – perhaps a sign of its originator stagnating during its pending acquisition by Shire.

Haemophilia B gene therapy projects

Company	Project	Mechanism	Note
Baxalta (Shire)	BAX 335	AAV8-Padua FIX	Phase III to start 2016
Uniqure/Chiesi	AMT-060	AAV5-wild-type FIX	Low-dose update at EHA; high-dose data H2 2016
Spark Therapeutics/Pfizer	SPK-FIX	Bio-engineered AAV-Padua FIX	Initial data at EHA
Dimension Therapeutics	DTX101	AAVrh10-wild-type FIX	Initial data H2 2016
Sangamo Biosciences	SB-FIX	*In vivo* protein replacement using zinc finger nucleases	Initial data 2016

Still, earlier phase I data from Baxalta's BAX 335 were mixed, with only one of seven patients reaching therapeutically relevant factor IX activity.

Of course safety is being watched closely; Leerink analysts pointed to a suspected ankle bleed among one of the SPK-FIX patients, but said no other bleeds were seen while noting the need for longer-term follow-up.

Evercore ISI's Mark Schoenebaum went further, suggesting a theoretical possibility that Spark's haemophilia A project SPK-FVIII could show similar benefits. Similar levels of active factor VIII – the missing factor in haemophilia A – might be achievable with much lower doses versus competitors, he speculated.

Haemophilia A is about four times as common as haemophilia B, and what is more, while SPK-FIX is partnered with Pfizer, SPK-VIII is still wholly owned by Spark. This presents the possibility of another lucrative transaction as the profile of Spark's assets rises and more data emerge.

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobPlieth on Twitter