Evaluate Vantage

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Upcoming events – Uniqure and Krystal await gene therapy readouts

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Early data are due for Krystal Biotech's epidermolysis bullosa project and Uniqure's haemophilia B candidate.

Welcome to your weekly digest of approaching regulatory and clinical readouts. Krystal Biotech pulled off an upsized flotation just over a year ago to raise $40m, and investors will soon find out whether theirs was money well spent: the company's lead asset, KB103, a gene therapy for the rare childhood disease epidermolysis bullosa (EB), is expected to yield phase I/II data by the end of the year.

EB sufferers have extremely fragile skin that is prone to extensive blistering. There are several types of EB, and Krystal is targeting the dystrophic variety, caused by mutations in the *COL7A1* gene encoding collagen VII; KB103 aims to deliver a functional copy of this gene using a non-replicating HSV-1 vector.

The six-patient study looks at safety as primary endpoint, and presence of collagen VII and wound closure at 12 weeks are secondary measures that should indicate efficacy. The second adult was enrolled in the second quarter, and by the year end Krystal aims to have at least three months' data on three subjects.

There are three competing *COL7A1* gene therapies in the clinic: Abeona's EB-101, Proqr's QRX-313 and Fibrocell's FCX-007. Earlier this year the first of these showed more than 75% wound healing in 71% of grafts and more than 50% wound healing in 90% of grafts at six months in a study involving seven dystrophic EB patients.

William Blair analysts reckon that Krystal will score a hit if its results are in line with these; this is because KB103 is off-the-shelf, while EB-101 is an autologous, *ex vivo* gene therapy.

An advance in EB treatment would be welcome after the phase III blow-up of Amicus's Zorblisa last year. Another company awaiting a key EB readout is Amryt Pharma, though as its asset, AP101, is a topical gel its market differs from than of a curative one-time gene therapy (*Amryt awaits crucial readout as it prepares rare disease push, August 14, 2018*).

Krystal is trading 50% above its IPO price, but with a still undemanding $170m valuation investors will be keen for another uplift.

Early signs

Meanwhile, Uniqure's next-generation haemophilia B gene therapy candidate AMT-061 will soon yield its first

clinical data, which should give investors a clue about whether the company is on the right track.

Data from a three-patient dose-confirmation study of AMT-061 are due by the end of the year, ahead of results from the larger phase III Hope-B trial.

Unusually, these mid-stage data will be the first seen with the project: Uniqure skipped earlier trials, relying instead on phase I/II results with its older candidate, AMT-060.

The compounds are similar, which is why regulators have agreed to this strategy, according to the company. The key difference is the factor IX variant they encode. The older candidate, AMT-060, uses the wild-type variant, while AMT-061 employs the Padua FIX variant that is thought to lead to better efficacy.

The small study could give an early indication of whether this is indeed the case: its primary endpoint is FIX activity six weeks after therapy with AMT-061 dosed at $2x10^{13}$vg/kg. However, it would be dangerous to read too much into a trial in only three subjects.

The bigger test will be the 56-patient Hope-B trial, which uses the same dose and also has a primary endpoint of FIX levels, but at 26 weeks. This has already started enrolling, and the first patient should be dosed early next year, Leerink analysts estimate.

Moving into late-stage trials so quickly could be a risky strategy, and there might also be danger for Uniqure on the intellectual property front. Spark Therapeutics and Pfizer are also developing a haemophilia B gene therapy using the Padua variant, called fidanacogene elaparvovec (previously SPK-9001), which recently went into phase III.

Although Spark had worked on this project well before Uniqure started trials with AMT-061, the latter believes that it has the relevant patents. Meanwhile, Spark has told *Vantage* that the IP situation is “somewhat confused” (*WFH 2018 – Spark keeps its haemophilia B gene therapy edge, for now, 22 May 2018*).

This could become a problem for Spark. But first AMT-061 has to deliver in the clinic.

Project	Company	Details	Trial ID
KB103	Krystal Biotech	PhI/II trial	NCT03536143
AMT-061	Uniqure	PhII dose-confirmation trial	NCT03489291
AMT-061	Uniqure	PhIII Hope-B trial	NCT03569891