Evaluate Vantage

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Bluebird split looks premature

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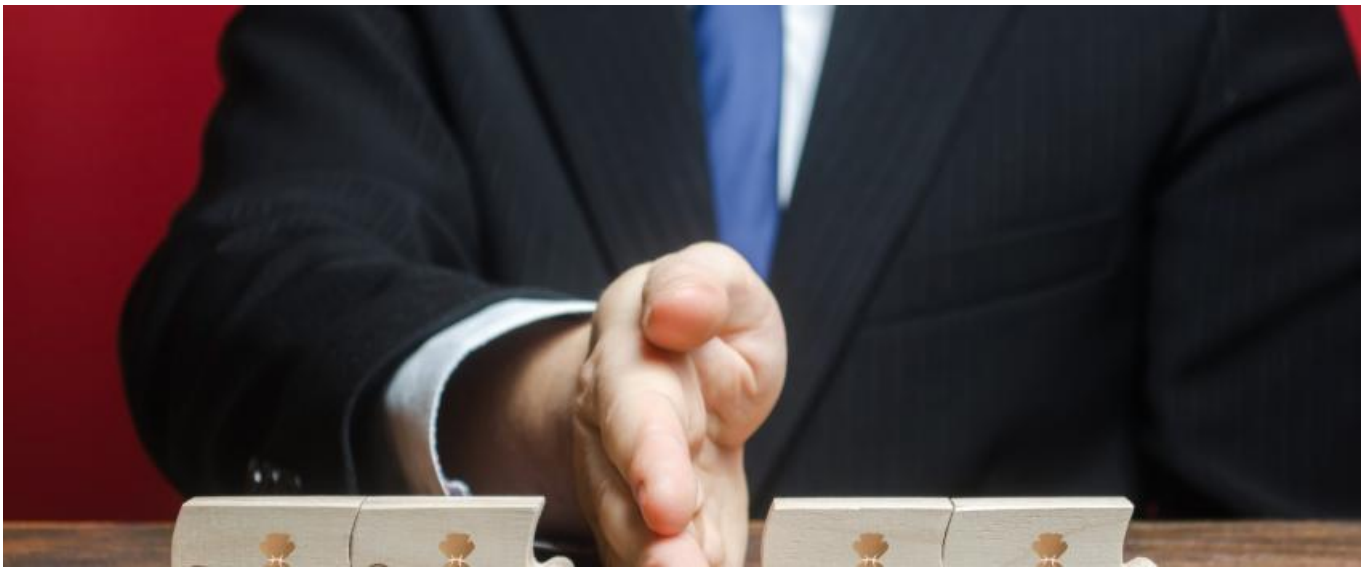

Today’s safety scare with Lentiglobin calls into question the logic behind Bluebird’s planned business separation.

Bluebird's self-styled “chief bluebird”, Nick Leschly, insisted today that his company’s split into separate gene therapy and oncology businesses was still on track, but a safety scare with the lead asset, Lentiglobin, suggests that a rethink might be needed.

Assuming a worst-case scenario, without Lentiglobin the remaining gene therapy entity is left with little to attract investors' attention. The question has to be asked whether it is a wise move to press ahead now with the oncology spin-out, however attractive that tax-free plan might seem to those hoping for an acquisition.

Of course, Bluebird might still be able to avoid that worst-case scenario. A causal link has not yet been proven between Lentiglobin and the two cases of cancer – acute myeloid leukaemia and myelodysplastic syndrome – that were revealed today. Both occurred in the HGB-206 phase I/II trial in sickle cell disease, and Bluebird has now halted this trial, as well as its phase III sickle cell study, HGB-210.

The group has also suspended sales of Lentiglobin for beta-thalassaemia in Europe, where the therapy is branded Zynteglo, although Mr Leschly stressed that no cases of AML or MDS had been reported in this population.

Bluebird lost about $1bn in market cap this morning.

It probably does not help that the company has been here before. In December 2018 a separate case of MDS was reported in the HGB-206 trial; at the time Bluebird blamed the busulfan preconditioning regimen used before therapy to damp down patients’ immune systems.

Insertional mutagenesis?

The big worry with the new cases is that Lentiglobin, an *ex vivo* gene therapy that employs a lentiviral vector, has led to insertional mutagenesis, namely that the vector-delivered gene has tampered with a target cell's chromosomal arrangement and in effect triggered a cancerous phenotype.

Regarding the case of AML, which occurred more than five years after dosing with Lentiglobin, there is a worrying sign: during a conference call today Mr Leschly said vector had been detected in the patient’s tumour cells. However, it is still unclear whether the vector is merely a “passenger” here or if it helped drive the oncogenic mutations.

To figure this out Bluebird will now investigate whether the vector was inserted near to genes involved in oncogenesis or genome stability and, if so, whether there was any upregulation of those genes.

For the case of MDS, the company has not yet ascertained whether the tumour cells are carrying the vector. However, the signs here are more promising from Bluebird's perspective: this patient had a genetic abnormality, trisomy 8, seen in 10-15% of MDS cases, suggesting that underlying risk factors might have contributed. And the timeframe looks better for the company, with the diagnosis being made around six months after Lentiglobin dosing.

Mr Leschly stressed that sickle cell disease itself could cause blood cancers, given the stress that it puts on patients' bone marrow.

Bluebird also said busulfan could be to blame for the latest cancer cases. But the group's chief scientific officer, Philip Gregory, conceded that it would be hard to unpick whether preconditioning was the cause versus an underlying mutation.

The company's investigation should take weeks, rather than months, Mr Leschly said. If the vector is indeed at fault this would be bad news for the bulk of Bluebird's genetic disease pipeline, including Lenti-D, as well as for other gene therapy players evaluating lentivirus-based approaches.

For now Bluebird has its oncology pipeline to fall back on. Unless the worst case for Lentiglobin can be ruled out conclusively Bluebird needs to hold on to this business.

Splitting the difference: Bluebird's planned separation

Project	Description	Status
Oncology newco…		
Ide-cel (bb2121)	Anti-BCMA Car-T therapy for multiple myeloma	Filed (delayed Mar 27, 2021 Pdufa date)
bb21217	Anti-BCMA Car-T therapy for multiple myeloma	Ph1/2
MCC1 TCR	Anti-MCC1 engineered TCR for Merkel cell carcinoma	Ph1/2
bbT369	Anti-CD79a & CD20 dual Car-T therapy for NHL	Preclinical
DARIC33	Rapamycin-regulated anti-CD33 Car-T therapy for AML	Preclinical
Mage-A4 TCR	Anti-Mage A4 engineered TCR for solid tumours	Preclinical
…and what Bluebird is left with		
Beti-cel (Lentiglobin)	Lentiviral β-globin gene therapy for beta-thalassaemia & sickle cell disease	Approved in EU for beta-thal as Zynteglo; ph3 for SCD
Eli-cel (Lenti-D)	Lentiviral ABCD1 gene therapy for cerebral adrenoleukodystrophy	Ph3
BCL11A shRNA	Short-hairpin microRNA for sickle cell disease	Ph1

Source: company filings.