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Vertex and Crispr up the ante in gene therapy chase

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The first sickle cell and beta thalassaemia patients have been enrolled into a Crispr/Cas9 trial, heating up a race with Bluebird, Sanofi, Sangamo and Editas.

Another gene therapy race is on thanks to Vertex and Crispr Therapeutics's initiation of clinical trials in beta thalassaemia and sickle cell disease. Their candidate, CTX001, is a Crispr/Cas9 gene-edited stem cell therapy that has been dosed in beta thalassaemia and could soon be in sickle cell disease.

Still, the companies are still some way behind the most advanced gene therapy candidate for the diseases, Bluebird Bio's Lentiglobin, which uses a lentiviral approach. Crispr and Vertex believe Crispr gene editing will win out because of its precision and durability, although that will obviously need to be proven in the clinic.

Thanks to these new studies, beta thalassaemia and sickle cell join Duchenne muscular dystrophy, haemophilia and choroideremia as hotly contested targets for gene therapy developers. This explosion in interest could encourage investors and big pharma business development teams looking for the next big thing – particularly with gene therapy buoyed by Roche's takeout of Spark yesterday (*Roche buy-in is another vote of confidence in gene therapy, February 25, 2019*).

Careful approach

CTX001 is an *ex vivo* therapy that entails extraction of haematopoietic stem cells from blood cells, gene editing and re-infusion as part of a stem cell transplant. Vertex's science chief, David Altshuler, described the procedure as a bone marrow transplant in which "we're introducing a new part".

That is what made the two haemoglobinopathies attractive as a starting point for Crispr/Cas9, he told *Vantage*, minimising the number of cells exposed to the new technology and allowing researchers to learn how it works in human cells. Both are important considerations given how few patients have been exposed to Crispr/Cas9. Indeed, the US FDA has acted cautiously around Crispr/Cas9 in humans, putting a hold on the IND for four months last year while it sought new information from Vertex and Crispr Therapeutics.

The partners say their trials mark the first company-sponsored use of Crispr/Cas9 in the clinic, a claim that is not quite correct. After a long delay occasioned by FDA questions Tmunity last year started a phase I trial of NY-ESO-1-redirected Crispr-edited T cells, though its clinicaltrials.gov entry cites the academic centre, the University of Pennsylvania, as primary sponsor.

Vertex and Crispr Therapeutics are running a separate study in each disorder. The first two patients in each will be dosed sequentially, and if these procedures are successful each trial will be cleared to dose 12 more concurrently; assuming all is well from that stage, a total of 45 can receive treatment in each.

As an *ex vivo* procedure, CTX001 is similar to Bluebird's Lentiglobin, something that should not put it at a competitive disadvantage. However, Lentiglobin is awaiting an EU approval decision in beta thalassaemia and could get the go-ahead by the end of 2019, which will give it clear first-mover advantage.

Gene therapies in beta thalassaemia and sickle cell disease

Project	Company	Pharmacology class	Indication	2024e sales ($m)	Status
Lentiglobin	Bluebird Bio	Beta-globin gene therapy	Thalassaemia/sickle cell disease	1,758	Filed
CTX001	Vertex/Crispr Therapeutics	Anti-Bcl 11A gene therapy	Thalassaemia/sickle cell disease	315	Phase I
BIVV003/ST-400	Sanofi/Sangamo	Anti-Bcl 11A gene therapy	Thalassaemia/sickle cell disease	45	Phase II
Hematologic Diseases Project	Editas Medicine	EPO gene therapy	Thalassaemia	5	Preclinical

Source: EvaluatePharma.

As with Lentiglobin, CTX001 will be studied in transfusion-dependent non-β0/β0 beta thalassaemia subjects – the less severe subtype. In sickle cell disease Mr Altshuler described enrollees as the most serious patients experiencing repeated pain crises, although he would not say what the threshold for enrolment was.

Lentiglobin's trial in sickle cell disease specified that patients had to have been hospitalised for a vaso-occlusive episode at least four times in the two years before entry, so the CTX001 criteria will probably be similar.

While the competition looks intense, Mr Altshuler says this is good news for patients: "We've known about these diseases for 70 or more years. The fact that we're on the cusp of functional cures is very exciting."