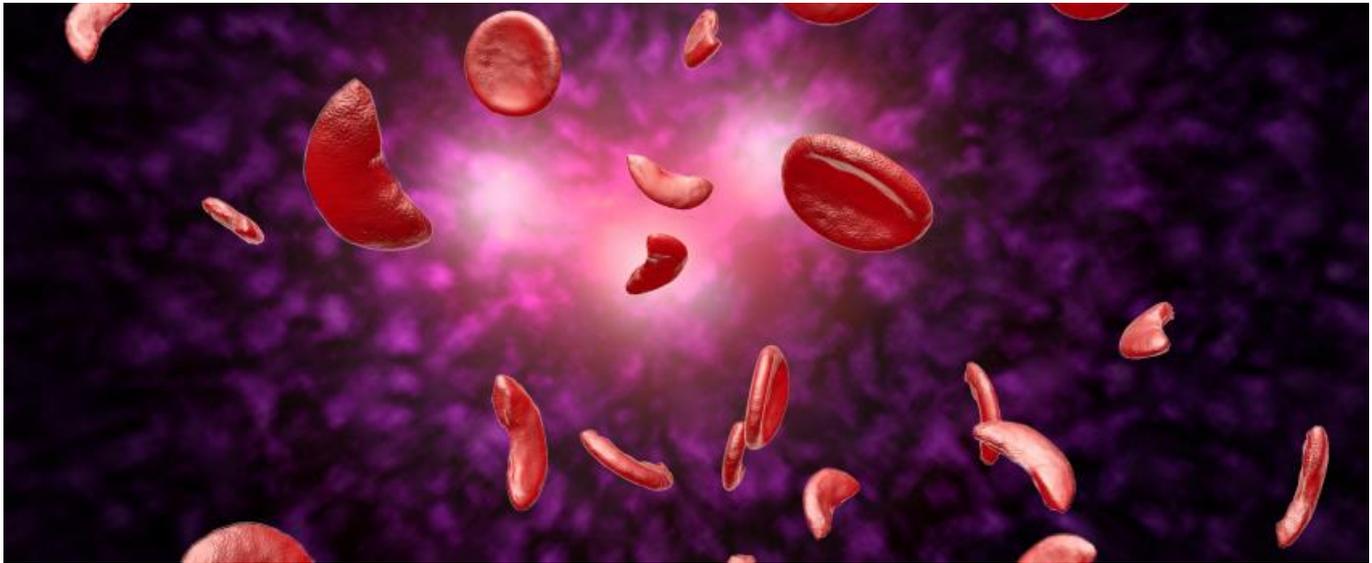


Global Blood takes on gene therapy



[Madeleine Armstrong](#)



Proof-of-concept data at Ash should give clues about whether GBT021601 could be an oral functional cure for sickle cell disease.

Global Blood Therapeutics already has a marketed sickle cell therapy, Oxbritya, but admits that there is room for improvement. To this end it is developing the next-generation asset GBT021601, designed to be much more potent than its predecessor.

Indeed, the group believes that '601, a once-daily pill, could rival gene therapies in terms of efficacy. There will soon be an indication of whether Global Blood is on target here, with phase 1 data expected to be unveiled in an Ash abstract next week.

Plus points

If '601 can achieve this goal the benefits are obvious. Ex vivo gene therapies in development for sickle cell disease, such as Bluebird's Lentiglobin and Crispr Therapeutics and Vertex's CTX001, both require chemotherapy preconditioning to clear the patient's bone marrow of cells. This is not necessary with oral drugs.

[Price has also proved to be a stumbling block for gene therapies](#), and this issue is particularly pertinent in sickle cell disease, which is most commonly seen in Africa, as well as in people of African descent.

"'601 could be made widely available very easily, because there's no hospital admission and no huge up-front cost," Global Blood's chief executive, Ted Love, tells *Evaluate Vantage*. "We could even make it available in poor countries where obviously doing the kind of complicated medical procedures [involved in gene therapy] is not going to be realistic."

Finally, the safety scares that have hit gene therapies – [including Lentiglobin](#) – could also work to Global Blood's advantage.

30%+ haemoglobin modification

First, though, '601 has to live up to the hype. The project, like Oxbritya, is a sickle haemoglobin (HbS) polymerisation inhibitor, which binds to haemoglobin and stabilises its oxygenated state. Two phase 1 studies are ongoing, one [in 124 healthy volunteers](#) and the other [in six sickle cell patients](#); data from both are expected at Ash in December.

The trials measure various parameters, but a key one will be the amount of haemoglobin modification. Here,

Global Blood hopes to see levels of 30-40%, which would be enough to convert a sickle cell patient to one with sickle trait; people with sickle trait carry only one copy of the altered haemoglobin gene, and rarely have symptoms. Importantly, as well as addressing symptoms this level of activity would be enough to stop long-term organ damage.

Jefferies analysts also expect a 3-4g/dl increase in total haemoglobin from baseline with '601. By contrast, [Oxbryta has shown haemoglobin modification of around 26%](#), and a mean increase in haemoglobin of [1.1g/dl at six months](#).

If '601 hits this target it will not be far off what has been seen with Lentiglobin and CTX001, which also aim to modify haemoglobin, though in different ways. Lentiglobin spurs the production of an anti-sickling haemoglobin, HbAT87Q, while CTX001 is designed to boost levels of foetal haemoglobin.

Lentiglobin therapy [has been shown to lead to a contribution from HbAT87Q of around 45%](#), albeit in just 16 patients; while in seven CTX001-treated subjects, foetal haemoglobin accounted for 40-50% of total haemoglobin, [this year's EHA meeting heard](#).

Global Blood's Mr Love questions whether pushing above 35% haemoglobin modification will lead to better efficacy. This might become clearer when larger trials with harder outcomes read out.

Catch up

If the early studies of '601 show promise, though, Global Blood could have the likes of Bluebird and Crispr looking over their shoulders.

The former [had once planned a US filing for Lentiglobin in sickle cell disease this year](#), but timelines have slipped, not helped by this year's [clinical hold](#), which was lifted in June. Bluebird has promised an update on its sickle cell regulatory plans by the end of 2021.

And Crispr is under increased pressure to make CTX001 a success – and justify its \$7bn valuation – after recent data called the viability of its Car-T pipeline into question ([Crispr's reminder about allogeneic Car-T redosing, October 13, 2021](#)).

Mr Love seems undaunted about the prospect of going up against gene therapy. "Some people get really infatuated by the high tech. I call it the shiny, glistening toy," he says. "But if the simple approach solves a problem, why would you go to a more complicated, risky approach?"

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