Evaluate Vantage

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EHA 2019 – Global Blood faces sickle cell questions

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More data with voxelotor shouldn’t hurt the project’s bid for accelerated approval, but there are still doubts about its effect on a harder patient outcome.

In the space of a year Global Blood Therapeutics’ chances of accelerated approval for its sickle cell candidate voxelotor have gone from slim to high. And full data from the pivotal Hope trial, presented today at the European Hematology Association meeting, will not have dashed expectations for a quick nod.

But Hope has failed to show a benefit with voxelotor on hard outcomes linked with sickle cell disease, notably vaso-occlusive crises, and this could hurt the drug's commercial prospects if it reaches the market. Global Blood’s stock opened down 4% today.

At present voxelotor is forecast to become the biggest-selling sickle cell drug by 2024, according to *EvaluatePharma* sellside consensus. A lack of options in the disease should help Global Blood bag accelerated approval; the FDA agreed to this pathway last December, and Global Blood plans to file in the second half of this year (*Ash 2018 – Global Blood hammers home sickle cell advantage, December 3, 2018*).

The sickle cell landscape				
Project	**Company**	**Mechanism of action**	**Status**	**2024e sales ($m)***
Voxelotor	Global Blood Therapeutics	Sickle haemoglobin polymerisation inhibitor	Filing H2 2019	1,980
Zynteglo/Lentiglobin	Bluebird Bio	Haemoglobin beta gene therapy	Phase III to start end 2019	1,033
Crizanlizumab	Novartis	P-selectin antibody	Filing H1 2019	342
CTX001	Vertex/Crispr Therapeutics	Crispr-associated Cas9 gene therapy	Phase I/II	271
Rivipansel	Pfizer/Glycomimetics	Pan-selectin inhibitor	Phase III	136
**Sickle cell sales only. Source: EvaluatePharma.*				

Voxelotor is vying with Novartis's crizanlizumab to become the first of a new wave of sickle cell projects to reach the market. Novartis has said it will submit its project to regulators in the first half of 2019 based on data from the phase II Sustain trial; a phase III study, Stand, is listed on clinicaltrials.gov but has yet to start recruiting.

The two compounds work differently: voxelotor, which inhibits abnormal sickle haemoglobin polymerisation, is designed to stabilise oxygenated haemoglobin; crizanlizumab is an antibody against P-selectin, and is thought to reduce cell adhesion and inflammation and improve blood flow.

Sustain found that a high dose of crizanlizumab significantly reduced the rate of vaso-occlusive crises.

Global Blood cannot say the same for the 24-week, 274-patient Hope trial, which reported no significant difference between voxelotor and placebo in the rate of vaso-occlusive crises. The annualised incidence rate was 2.77 and 2.76 with voxelotor dosed at 1,500mg and 900mg respectively, versus 3.19 with placebo.

As well as being presented at the EHA meeting in Amsterdam today, the data were published in the *New England Journal of Medicine*.

The study's authors said longer-term follow-up was needed, and added that an analysis at 72 weeks was planned, as well as an open-label extension trial of voxelotor's long-term effects.

Primary endpoint met

On the positive side for Global Blood, the Hope trial met its primary endpoint, the percentage of patients with a haemoglobin response – at least at the 1,500mg voxelotor dose.

Haemoglobin response was defined as an increase of more than 1g/dl at week 24 in the intention-to-treat analysis; 51% of patients in the 1,500mg group met this benchmark versus 7% in the placebo arm, which was statistically significant with a p value less than 0.001. Meanwhile, 33% of patients in the 900mg group had a haemoglobin response.

In the per protocol analysis, the haemoglobin response in the 1,500mg arm was 60%.

These numbers are slightly less impressive than the Hope data presented at last year's Ash meeting, in 150 patients, which found a 65% haemoglobin response in the per protocol analysis of the 1,500mg cohort.

This was technically part A of Hope, although Global Blood scrapped part B last June; this was to have used either patient-reported outcomes or vaso-occlusive crises as a key secondary endpoint (*Global Blood launches bold bid for early sickle cell approval, June 27, 2018*).

This move looked justified when the FDA agreed to the accelerated approval pathway, but it does mean that even if voxelotor gets the go-ahead its true benefit to patients could still be unclear. Even the confirmatory study will only measure a surrogate endpoint, transcranial doppler (TCD) flow velocity – an indicator of a patient's risk of stroke.

Global Blood might well have an approvable drug, but voxelotor could end up being eclipsed if candidates with

stronger data on harder endpoints make it to market.

This story has been updated to clarify that a per protocol analysis was used for the Hope data presented at Ash 2018.