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# Ash 2020 – Forma gets an early edge over Agios in sickle cell disease

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## And both companies' pyruvate kinase R activators could have Global Blood looking over its shoulder, though pain crises sow doubts.

In the battle of the pyruvate kinase R activators in sickle cell disease, Forma Therapeutics has drawn first blood. Early data with the group's FT-4202, presented at Ash today, suggest that the company has blown its rival Agios out of the water in terms of haemoglobin response.

The results have come in just a handful of patients so far, so the situation could still evolve. With decent but slightly less impressive data with Agios's mitapivat also featuring at Ash, the real loser might be Global Blood, which is already having a tough time launching its own oral sickle cell therapy, Oxbryta.

**Haemoglobin and VOCs**

Long-term results from Oxbryta's phase III Hope study were also presented at Ash on Sunday: while haemoglobin levels held up over 72 weeks, there was still no benefit seen on vaso-occlusive crises, the painful episodes that occur when patients' blood vessels are blocked by sickle-shaped red blood cells.

This might not matter much in terms of Oxbryta's accelerated approval. Global Blood gave up on VOCs as an endpoint long ago, saying it planned to use transcranial doppler (TCD) flow velocity – an indicator of a patient's risk of stroke – as the primary endpoint of its confirmatory study (*Ash 2018 – Global Blood hammers home sickle cell advantage, December 3, 2018*).

But Forma and Agios alike believe that their PKR activators could address both sides of the sickle cell coin: raising haemoglobin levels and reducing the occurrence of VOCs. These claims could provide stiff competition for Oxbryta, but whether they hold up is another matter.

On the haemoglobin side the signs are promising. In the phase I trial of Forma's FT-4202, six of seven patients receiving 300mg/day for 14 days had a haemoglobin response; there were no responses in two patients receiving placebo.

Meanwhile, in an NIH-sponsored phase I trial of Agios's mitapivat, six of 11 evaluable patients responded after receiving multiple ascending doses of the project for two weeks per dose, followed by a 12-15-day tapering period designed to prevent withdrawal.

However, the mitapivat analysis left out one patient who was lost to follow-up. Including this subject would

make the responder rate less impressive, but still about in line with what has been seen with Oxbryta, with the usual caveats about cross-trial comparisons.

| Cross-trial comparison of oral sickle cell therapies | | | | |
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| **Project** | **Company** | **Trial** | **% haemoglobin responders** | **Increase from baseline in Hb** |
| FT-4202 | Forma Therapeutics | Ph1 (NCT03815695) | 86% (6/7) | 1.2g/dl (median) |
| Mitapivat | Agios Pharmaceuticals | Ph1 (NCT04000165)* | 55% (6/11) | 1.3g/dl (mean) |
| Oxbryta | Global Blood Therapeutics | Ph3 Hope (NCT03036813) | 51% (46/90)** | 1.1g/dl (mean) |
| *Haemoglobin response defined in all trials as haemoglobin increase of ≥1.0g/dl from baseline. *NIH-sponsored study; **basis for accelerated approval in Nov 2019. Source: Ash 2020, company releases & Oxbryta label.* | | | | |

As for reducing VOCs, things are less clear, and several cases of either VOCs or sickle pain events in both trials raised eyebrows.

The theory is that PKR activators could reduce the incidence of VOCs by decreasing levels of 2,3-DPG, a compound found in red blood cells that regulates oxygen release from haemoglobin. It is thought that lowering 2,3-DPG could help oxygen bind to haemoglobin, reducing red blood cell sickling and preventing VOCs.

And both trials showed decreases in 2,3-DPG levels.

However, there were three sickle pain events in two patients treated with FT-4202. Forma's chief medical officer, Patrick Kelly, stressed that patients managed these events at home, saying there had been no VOCs requiring hospitalisations.

“Two weeks of a therapy is not going to change 43 years of sickle cell disease,” he told *Evaluate Vantage.*

Meanwhile, Agios previously reported a VOC in its trial, during dose taper, that was deemed possibly related to therapy. “We haven’t seen any further [VOCs] since we extended the dose taper by a few days,” the group’s chief medical officer, Chris Bowden, told *Evaluate Vantage*.

There were two more VOCs in the trial, but he said these occurred “long after patients had taken the last dose of drug. They were not deemed related to the drug.”

Still, investors will be sure to look out for any VOCs with either drug in future readouts.

**Side effects?**

As for other potential side effects, investors have been keeping an eye out for signs of cardiac issues since Forma reported cases of palpitations at this year’s EHA meeting with a 700mg dose of FT-4202, and mitapivat’s Ash abstract detailed three cases of heart rate increase.

Both companies dismissed these concerns. Forma’s Mr Kelly put the heart rate increases down to “white coat” syndrome, saying the palpitations reported with FT-4202 were not sustained heart rate elevations that would constitute a true adverse event.

“With the 300mg dose, we’re not reporting any incidences of cardiac arrhythmias,” added the group’s chief executive officer, Frank Lee.

As for Agios, the company has stressed that the heart rate increases were asymptomatic. “We haven’t seen any data from our programmes that indicate we have any kind of cardiac problem,” said Mr Bowden.

**Differentiation**

Aside from potentially better efficacy, the Forma executives highlighted FT-4202’s convenience: it is a once-daily therapy while mitapivat is given twice a day. They also believe that FT-4202 avoids the off-target aromatase inhibition seen with mitapivat, adding that affecting sex hormones could be particularly problematic in children.

Agios’s Mr Bowden responded that the company had years of experience with mitapivat in another indication, pyruvate kinase deficiency, and “we haven’t encountered any component of that side-effect profile that has limited our development at all”.

Both sets of executives were optimistic about the PKR activators' prospects if and when gene and gene editing therapies make it to market. Crispr made waves at Ash on Saturday with promising data on its Vertex-partnered sickle cell project CTX001. Such advanced therapies, although exciting, are "likely going to be limited to a very severe patient population – not only due to cost, but the conditioning regimens are no joke", said Forma's Mr Lee.

Mr Bowden, meanwhile, believes that there is room in SCD for many different therapies, including two PKR activators. "Many patients want to try everything to see what makes them feel the best."

*EvaluatePharma* sellside consensus puts mitapivat's 2026 sales at $591m; there is currently no consensus for FT-4202, but Leerink expects peak sales of $1.5bn, with $1.1bn of this coming in sickle cell disease. Meanwhile, Oxbryta is set to bring in $2.2bn in 2026, according to the sellside.

Both FT-4202 and mitapivat are set to go into pivotal studies in sickle cell disease next year. If the projects' efficacy continues to look good, and VOCs do not prove to be a problem, those Oxbryta figures could be under threat.