Evaluate Vantage

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Imara gets a second shot in sickle cell

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Will upping the dose and changing the primary endpoint pay off?

Imara has been in the doldrums since reporting disappointing phase 2a data with its lead project, tovinontrine, in sickle cell disease a year ago. But it has not given up on the asset, and data due this quarter from the phase 2b Ardent study should indicate whether tovinontrine has a future here.

Ardent tests a higher dose, which could give it a better chance of success, Imara's chief executive officer, Rahul Ballal, believes. The group also recently changed the primary endpoint to focus on vaso-occlusive crises (VOCs), from foetal haemoglobin response previously.

Although Mr Ballal is confident that the tweaks will lead to a positive outcome with the oral PDE9 inhibitor, formerly known as IMR-687, the markets clearly do not agree: Imara's stock is sitting at a five-year low, and the group is trading well below cash.

Project	Tovinontrine (IMR-687)
Company	Imara
Event type	Interim data from phase 2b Ardent trial
Indication	Sickle cell disease
Date	Q1 2022
Trial ID	NCT04474314

Adrent tests tovinontrine at 200-300mg and 300-400mg, depending on a patient's weight, versus placebo over one year. Patients are allowed to receive background hydroxyurea, and the primary endpoint is the annualised rate of VOCs.

The imminent efficacy data will come from an interim analysis comparing the high dose versus placebo in patients who have been treated for at least 24 weeks, encompassing around 80 subjects. The VOC rate will be extrapolated, Mr Ballal explained: "If patients have one VOC at six months, the annualised rate will be two."

"We will be spending alpha, and there will be a p value generated," he added. However, most of the powering is being saved for final readout in the second half, so the statistical bar to be cleared at interim are low, though

the interim results should give a good indication of the outcome of the full trial. A final analysis of all 115 patients over one year, including the low-dose group, is due in the second half.

Dosing higher

However, the earlier phase 2a trial found no meaningful increases in foetal haemoglobin, a surrogate endpoint, with tovinontrine monotherapy (*Imara disappoints in sickle cell disease, January 6, 2021*).

“We didn’t see dramatic changes in foetal haemoglobin,” Mr Ballal admitted. “But we also felt that we were underdosing patients.” The phase 2a trial used starting doses of tovinontrine of 50mg and 100mg, though some patients received a dose as high as 200mg daily.

In any case, foetal haemoglobin is no longer the primary focus of Ardent, though it remains a key secondary outcome. November’s endpoint switch to VOCs was based on advice from the FDA, Imara says, and came before database lock.

The company is taking heart from a post-hoc analysis of the phase 2a showing a 40% reduction in VOCs with tovinontrine versus placebo. 12-month data from an open-label extension trial, presented at last year’s Ash meeting, found a similar 38% reduction in seven patients previously on placebo.

Mr Ballal acknowledged the danger of putting too much faith in post-hoc analyses, but concluded: “We have two datapoints that say the drug can achieve a 40% reduction in the annualised rate of VOCs. And we have exposure response data saying that higher doses should do even better.” The study is 80-85% powered to detect a 30-40% reduction in annualised VOC rate.

Competition

Tovinontrine’s mechanism of inhibiting PDE9 is thought to boost haemoglobin, but its other actions could hit VOCs, including vasodilation and decreasing white blood cell adhesion. Mr Ballal reckons tovinontrine could represent the best of both worlds, reducing VOCs while having an effect on underlying disease.

Notably, the sickle cell market leader, Global Blood’s Oxbryta, has not shown a benefit on VOCs, but instead got accelerated approval based on haemoglobin response. Conversely, Novartis’s Adakveo has been shown to reduce the annual rate of VOCs, by 45%, but does not address the red blood cell component of sickle cell disease; it is also given via intravenous infusion.

The developers of PKR activators, Agios and Forma, are looking at both haemoglobin response and VOCs in their pivotal studies. Other late-stage contenders in sickle cell include Crispr Therapeutics/Vertex's CTX-011, due to be filed later this year, and Bluebird's Lentiglobin, although a planned 2023 filing could be delayed by a recent partial clinical hold.

If Ardent is positive Imara’s base case is that it will need to carry out a “modest” phase 3 to support approval in sickle cell. If negative it would be another nail in the coffin for tovinontrine and Imara.