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A big year for sickle cell

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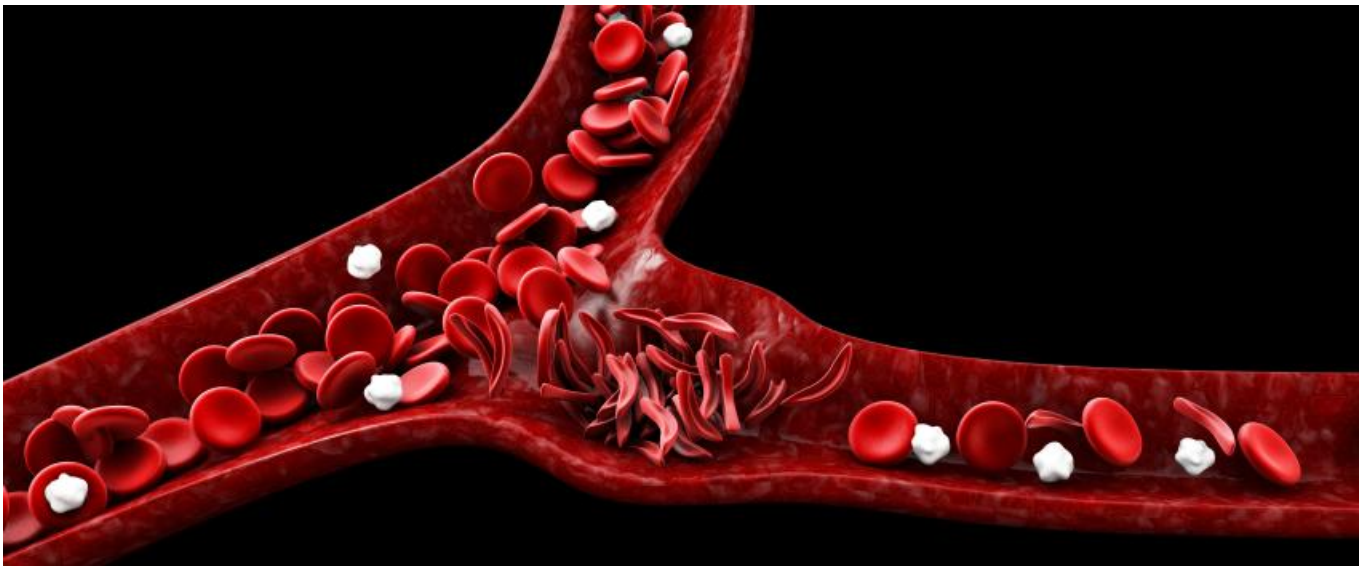

Novel approaches including gene editing are creeping towards approval.

The approval of Agios's mitapivat this month in the rare disease pyruvate kinase deficiency highlighted the tricky pricing decision the group must take should the same compound be approved in the more common condition sickle cell anaemia.

Several other sickle cell agents are also approaching the market: the filing of Crispr Therapeutics' gene-edited CTX001 is imminent, and two more candidates have recently entered late-stage trials. A competitive price could be crucial for Agios – though some industry experts have suggested that the group might simply shelve the project in this indication, despite it having just started a phase 2/3 study here.

The market for sickle cell medicines is currently carved up between Global Blood Therapeutics' Oxbryta and Novartis's Adakveo, which are respectively forecast to sell $333m and $259m this year, according to *Evaluate Pharma*'s sellside consensus.

This duopoly might not exist for long. The phase 2/3 trial of CTX001, a Crispr/Cas9 gene-edited cell therapy targeting BCL11a, is fully enrolled, and Crispr Therapeutics and its partner Vertex are planning submissions in sickle cell and beta thalassaemia this year.

The trial is assessing a single dose of CTX001 in 45 patients aged 12 to 35 with severe disease. It has several primary outcomes, but the rate of severe vaso-occlusive crises (VOCs) is the most important from an efficacy perspective. At the latest update, at the European Hematology Association meeting in June, seven patients receiving CTX001 remained free of VOCs.

Analysts are positive: this project's 2026 sales forecasts of just over $1bn place it second only to Oxbryta.

The sickle cell disease pipeline – late stage			
Project	**Company**	**Mechanism of action**	**Details**
CTX001	Vertex/ Crispr Therapeutics	Crispr/Cas9 gene-edited cell therapy targeting BCL11a	Ph2/3 Climb-121 trial ongoing; filing expected late 2022
Lentiglobin/ Zynteglo	Bluebird Bio	HBB gene therapy	Ph3 and Ph1/2 trials under partial clinical hold; filing expected Q1 2023 but could be delayed
Inclacumab	Global Blood Therapeutics	Anti-P-selectin MAb	Two pivotal trials, 131 and 132, ongoing
Etavopivat	Forma Therapeutics	Pyruvate kinase R activator	Ph2/3 Hibiscus trial began Dec 2021
Mitapivat	Agios Pharmaceuticals	Pyruvate kinase R activator	Ph2/3 Rise Up trial began Jan 2022
Source: Evaluate Pharma, company websites, clinicaltrials.gov.			

While a gene-edited agent like CTX001 would certainly be differentiated from the marketed products, the perils of novel technologies were illustrated by the partial clinical hold the FDA slapped on Bluebird's Lentiglobin gene therapy last year. Global Blood's second shot at the indication, inclacumab, is arguably on safer ground, sharing a mechanism with Adakveo.

The clutch of late-stage projects is rounded out by the pyruvate kinase R activators. Forma's etavopivat appeared to have a slight edge over Agios's mitapivat in phase 1, and the company cherishes hopes of accelerated approval (*Agios and Forma take different paths in sickle cell disease, December 11, 2021*). The respective phase 2/3 trials have similar efficacy endpoints, focusing on a combination of haemoglobin response and VOCs.

Analysts from Leerink favour Forma's PKR activator, to the point where they believe Agios might pull the plug on mitapivat. They believe the latter's twice-daily dosing is not competitive in sickle cell versus the once-daily etavopivat, and now consider Agios's sickle cell programme to be spearheaded by the phase 1-stage AG-946.

The sickle cell disease pipeline – mid-stage			
Project	**Company**	**Mechanism of action**	**Details**
Tovinontrine (IMR-687)	Imara	PDE9 inhibitor	Ph2b Ardent trial ongoing; data due Q1 2022
RG6107	Roche	Anti-complement factor C5 MAb	Ph2 Crosswalk-C trial ongoing
Vamifeport	Vifor Pharma	Ferroportin inhibitor	Ph2a SCD-202 trial ongoing; data due 2022
SAR445136	Sangamo	Zinc finger nuclease gene-edited cell therapy targeting BCL11a	Ph1/2 Precizn trial ongoing
EDIT-301	Editas Medicine	Crispr/Cas12a gene-edited cell therapy targeting beta-globin to increase foetal haemoglobin	Ph1/2 Ruby trial ongoing; data due 2022
GPH101	Graphite Bio	Homology-directed repair gene-edited cell therapy targeting underlying beta-globin mutation	Ph1/2 Cedar trial ongoing
OTQ923 & HIX763	Intellia Therapeutics/ Novartis	Crispr/Cas9 gene-edited cell therapy targeting BCL11a	Ph1/2 trial ongoing
ARU-1801	Aruvant Sciences	Foetal haemoglobin gene therapy	Ph1/2 Momentum trial ongoing
Source: Evaluate Pharma, company websites, clinicaltrials.gov.			

The phase 3 pipeline could soon swell: a slew of data is due this year from early and mid-stage trials. First up will be Imara's tovinontrine; the company has already said that despite the Ardent trial being phase 2b, even if it is positive a phase 3 trial, albeit a "modest" one, will still be necessary (*Imara gets a second shot in sickle cell, February 1, 2022*).

Another Crispr candidate, Editas's EDIT-301, is poised to take a step forward. The first patient in the Ruby trial has not yet been dosed; nevertheless Editas confirmed on its fourth-quarter call last week that initial data would be reported this year.

Two other gene-editing approaches are in phase 2. In January, Sanofi handed rights to the zinc finger-based SAR445136 back to Sangamo, prompting Stifel analysts to downgrade its probability of success from 66% to 10%, despite the project yielding decent data at last year's Ash meeting.

Meanwhile Novartis's phase 1/2 study is evaluating OTQ923 and HIX763, its two genome-edited, autologous cell products, both separately and in combination.

As for phase 1 data, the next company to report is likely to be Fulcrum Therapeutics. FTX-6058 is an oral inhibitor of embryonic ectoderm development that has been demonstrated to induce expression of foetal haemoglobin in mouse models of sickle cell, and has also yielded data in healthy volunteers. The small phase 1b trial is focused on safety and plasma concentrations of the drug, but foetal haemoglobin levels, as well as other sickle cell biomarkers, are secondary outcomes.

The coming months could see data validating a range of mechanisms and technologies. Alternatively, a few more sickle cell projects could join the many that have disappointed in the past.

The sickle cell disease pipeline – early stage

Project	Company	Mechanism of action	Details
FTX-6058	Fulcrum Therapeutics	Embryonic ectoderm development inhibitor	Ph1b trial ongoing; data due Q2 2022
GBT021601	Global Blood Therapeutics	Sickle haemoglobin polymerisation inhibitor	Ph1 data at Ash; Ph2 to start 2022
TAK-755	Takeda/Meiji Holdings	ADAMTS13 enzyme replacement therapy	Ph1 Raise Up trial began Dec 2021
ASP8731	Astellas Pharma	Bach1 inhibitor	Ph1 trial ongoing
CSL889	CSL	Haemoglobin regulator	Ph1 trial ongoing
HBI-002	Hillhurst Biopharmaceuticals	Heme oxygenase stimulant	Ph1 trial ongoing
PF-07209326	Pfizer	E-selectin antagonist	Ph1 trial ongoing
Rifaximin EIR	Bausch Health Companies	Bacterial DNA-directed RNA polymerase inhibitor	Ph1 trial ongoing
AG-946	Agios Pharmaceuticals	Next-gen pyruvate kinase R activator	Ph1 trial ongoing

Source: Evaluate Pharma, company websites & clinicaltrials.gov.