BIOPHARMADIVE

Fulcrum rejoins sickle cell drug race as FDA lifts study hold

The regulator had flagged a cancer risk in drugs like Fulcrum's, leading the biotech to focus further testing in patients with more severe disease.

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The Food and Drug Administration has cleared Fulcrum Therapeutics to resume testing an experimental medicine for sickle cell disease, ending a six-month hiatus that began when regulators flagged a potential cancer risk observed in studies of other, similar medicines.

In a statement Tuesday, Fulcrum said it plans to restart patient enrollment in a Phase 1b trial of the drug, known as FTX-6058 and one of two medicines the Cambridge, Massachusetts-based biotechnology company has in human testing. It didn't specify when the study might begin again.

Still, future testing will be geared towards sicker patients. To qualify, patients have to have experienced at least four vaso-occlusive crises — the painful episodes associated with the disease — within a year of screening, or at least two within the last six months. Study participants must also have previously received one or possibly two other sickle cell medicines.

The more targeted focus could mean a far smaller market opportunity for Fulcrum, which is already facing a large group of

more advanced competitors. Fulcrum has estimated about 7,500 to 10,000 patients in the U.S. fit the new study criteria, a fraction of the roughly 100,000 in the country believed to have the disease.

While the actual opportunity for FTX-6058 will "remain a point of interest," the lifting of the clinical hold "marks an important 'win' for the new management team" and instills confidence "they can right [a] ship that has undergone a series of mishaps/adversities," wrote Stifel analyst Dae Gon Ha, in a note to investors on Tuesday.

Fulcrum shares surged about 50% in pre-market trading Tuesday.

The company started up in 2016 and was originally run by Robert Gould, the former CEO of the biotech Epizyme. Like Epizyme, Fulcrum formed with a plan to develop epigenetic drugs, which are meant to control molecular switches that turn genes on or off. But whereas Epizyme — now owned by Ipsen — developed cancer medicines, Fulcrum targets rare genetic diseases. Its lead program is for a muscle disorder called facioscapulohumeral muscular dystrophy, or FSHD.

Fulcrum raised about $140 million in private funding from Third Rock Ventures and others, and followed with a $72 million initial public offering in 2019. Yet at about $6 apiece, shares are worth less than half their $16 debut price, and far below their peak of about $31 in September 2021.

Data supporting the company's lead program, currently in Phase 3 testing, have been mixed. The company has changed leaders multiple times, with Gould stepping down in 2021, returning as CEO in early 2023 and then giving way to new head Alex Sapir in July. And its sickle cell program has been held up since February, sending shares to record lows.

The FDA was concerned with the drug's mechanism. An oral medication, FTX-6058 is meant to spur production of "fetal"

hemoglobin, a form of the oxygen-carrying protein the body stops making shortly after birth. Boosting levels of fetal hemoglobin is associated with a reduction in the "sickling" of red blood cells. Genetic medicines from Bluebird Bio and Vertex Pharmaceuticals have shown that doing so can, in turn, lower the rate of vaso-occlusive crises.

Yet Fulcrum's drug, while having the convenience of a pill, boosts fetal hemoglobin in a different way: by blocking a component of an assembly of proteins collectively known as PRC2. Inhibiting PRC2 has been associated with a risk of developing blood cancer, an issue U.S. regulators flagged when stopping testing of FTX-6058 in February. The FDA asked Fulcrum to narrow testing to a group where the potential benefits outweighed the risks, leading to the study design the company will carry forward.

The new target population is much smaller than Fulcrum previously envisioned. But some analysts expressed optimism in the drug's prospects. "[W]e believe there could be a need, especially among those with severe disease that could benefit from reduced recurring events and/or a functional cure," wrote Leerink Partners analyst Joseph Schwartz, in a note to investors Tuesday.