Fulcrum Therapeutics Announces Positive 12-Week Results from the 20 mg Dose Cohort of the Phase 1b PIONEER Trial of Pociredir in Sickle Cell Disease

February 24, 2026 at 7:00 AM EST

— Mean absolute fetal hemoglobin (HbF) increased by 12.2% (from 7.1% to 19.3%) at Week 12 (n=12), representing a rapid, robust, and clinically relevant response, with progression toward pan-cellular HbF induction as F-cells increased from 31% to 63% —

— 7 of 12 patients (58%) achieved absolute HbF levels ≥20%; all patients achieved at least a 6.5% absolute increase in HbF —

— Improvements in markers of hemolysis, improved erythropoiesis, and a >1 g/dL increase in total hemoglobin —

— 7 of 12 patients (58%) reported zero VOCs during the treatment period —

— Pociredir was generally well-tolerated, with no treatment-related serious adverse events (SAEs) —

— Fulcrum plans to initiate a potential registration-enabling trial in the second half of 2026 —

— Conference call and webcast scheduled for 8:00 a.m. ET today —

CAMBRIDGE, Mass., Feb. 24, 2026 (GLOBE NEWSWIRE) -- Fulcrum Therapeutics, Inc.® (Fulcrum) (Nasdaq: FULC), a clinical-stage biopharmaceutical company focused on developing small molecules to improve the lives of patients with genetically defined rare diseases, today reported positive 12-week results from the 20 mg dose cohort of the Phase 1b PIONEER trial of pociredir in sickle cell disease (SCD).

“The 12-week data from the complete 20 mg cohort demonstrated robust and rapid HbF induction and progression toward pan-cellular distribution, accompanied by reductions in markers of hemolysis and associated improvements in anemia,” said Alex C. Sapir, Fulcrum’s President and Chief Executive Officer. “Importantly, the HbF levels achieved are consistent with levels historically associated with reductions in sickling and hemolysis in sickle cell disease. These encouraging results in a severe patient population strengthen our conviction as we prepare for discussions with regulators regarding the design of the next study.”

“The magnitude of HbF induction observed at 20 mg, together with the concomitant increase in F-cells and associated reductions in markers of hemolysis and improvements in anemia, is consistent with what we would expect from a therapy that may be capable of altering the underlying pathophysiology of sickle cell disease,” said Dr. Martin Steinberg, Professor of Medicine, Pediatrics, Pathology and Laboratory Medicine at Boston University Chobanian & Avedisian School of Medicine. “Achieving HbF levels in this range represents an important step toward understanding the potential of pociredir to improve clinical outcomes for patients living with sickle cell disease.”

Trial Design and Data Cut Overview

PIONEER is a Phase 1b open-label dose-escalation clinical trial evaluating the safety and efficacy of pociredir, an oral once-daily HbF inducer, in adult patients with severe SCD. The 20 mg cohort of the clinical trial enrolled adults with severe SCD. As of the December 23, 2025 data cutoff, all 12 evaluable patients in the 20 mg cohort completed the 12-week treatment period and are included in the pharmacodynamic (PD) analysis set. One patient discontinued on Day 1 due to an unrelated Grade 5 serious adverse event and is excluded from the PD analysis set but is included in the safety analysis set. Five patients remained in the 4-week follow-up period as of the data cutoff. Fulcrum plans to report additional data from the 20 mg cohort, including through the 4-week follow-up period, at a future medical conference.

PIONEER Study 20 mg Dose Cohort Data

Results from the 12 week treatment period of the 20 mg dose cohort of the Phase 1b PIONEER trial (n=12) are as follows:

- Mean absolute HbF increased by 12.2% at 12 weeks of treatment with pociredir (vs. 8.6% at Week 12 in the 12 mg cohort), increasing from a baseline of 7.1% to 19.3%. Seven of 12 patients (58%) achieved absolute HbF levels ≥20% at Week 12, and all patients demonstrated a clinically relevant HbF increase. HbF levels of 20% are associated with ~90% of patients experiencing zero VOCs per year, based on real-world data that Fulcrum presented at the 20th Annual Sickle Cell & Thalassemia Conference in October 2025.
- The proportion of HbF-containing red blood cells (F-cells) increased from a mean of 31% at baseline to 63% at Week 12 (n=10), indicating progression toward pan-cellular HbF induction (HbF distributed across a substantial proportion of red blood cells (RBCs)). F-cells are more resistant to sickling and hemolysis because of HbF-mediated inhibition of sickle hemoglobin (HbS) polymerization. Higher proportions of F-cells are associated with improved RBC health.
- Mean changes in markers of hemolysis and erythropoiesis improved during the 12-week treatment period:
    - Indirect bilirubin decreased by 40% (vs. 37% at Week 12 in the 12 mg cohort)
    - Lactate dehydrogenase decreased by 34% (vs. 28% at Week 12 in the 12 mg cohort)
    - RBC distribution width decreased by 26% (vs. 27% at Week 12 in the 12 mg cohort)
    - Reticulocyte counts decreased by 42% (vs. 31% at Week 12 in the 12 mg cohort)
- Mean hemoglobin increased by 1.1 g/dL at Week 12 (vs. 0.9 g/dL at Week 12 in the 12 mg cohort), increasing from a baseline of 7.3 g/dL to 8.4 g/dL.

- Based on treating physician-documented medical records from the 6-12 months prior to enrollment, approximately 16 VOCs would have been expected during the 12-week treatment period. During the 12-week treatment period, six VOCs were reported. Seven of 12 patients (58%) reported no VOCs during the treatment period.

Pociredir Safety Update

- As of the December 23, 2025 data cutoff, pociredir has been dosed in 148 adults, including 89 subjects in multiple dose cohorts up to 12 weeks.
    - 103 healthy subjects, including 44 who received pociredir for 10 to 14 days treatment duration
    - 45 SCD patients who received pociredir for up to 12 weeks treatment duration
- The safety profile observed in the 20 mg dose cohort as of the December 23, 2025 data cutoff remained generally consistent with previously reported safety data. Pociredir was generally well-tolerated, with no treatment-related SAEs and no discontinuations due to treatment-related AEs as of the December 23, 2025, data cutoff.

Next Steps

Fulcrum plans to provide additional details regarding the design of its next trial in the second quarter of 2026 following receipt of meeting minutes from its End-of-Phase meeting with the FDA. Pending feedback from the FDA, Fulcrum plans to initiate a potential registration-enabling trial in the second half of 2026. Fulcrum also plans to engage with the European Medicines Agency (EMA) in mid-2026 to obtain protocol assistance and feedback on the design of the next trial. In addition, Fulcrum is activating sites for an open-label extension trial for participants in the PIONEER trial to evaluate the safety and durability of response with pociredir.

Conference Call and Webcast

Fulcrum Therapeutics, Inc. will host a conference call and webcast featuring company leadership and a medical expert today at 8:00 a.m. ET to discuss the results to date from the PIONEER Phase 1b trial. Individuals may register for the conference call by clicking the link here. To register to participate in the conference call, individuals can use the conference call link here. Once registered, participants will receive dial-in details and unique PIN, which will allow them to access the call. The event can be accessed under “Events and Presentations” in the Investor Relations section of Fulcrum’s website (www.fulcrumtx.com), with a recording available following the event.

About Fulcrum Therapeutics

Fulcrum Therapeutics is a clinical-stage biopharmaceutical company focused on developing small molecules to improve the lives of patients with genetically defined rare diseases in areas of high unmet medical need. Fulcrum’s lead clinical program is pociredir, a small molecule designed to increase expression of HbF for the treatment of SCD. Fulcrum uses proprietary technology to identify drug targets that can modulate gene expression to treat the known root cause of gene mis-expression. For more information, visit www.fulcrumtx.com and follow us on X (@FulcrumTx) and LinkedIn.

About Pociredir

Pociredir is an investigational oral small-molecule inhibitor of Embryonic Ectoderm Development (EED) that was discovered using Fulcrum’s proprietary discovery technology. Inhibition of EED leads to potent downregulation of key fetal globin repressors, including BCL11A, thereby causing an increase in HbF. Pociredir is being developed for the treatment of SCD. In the PIONEER Phase 1b clinical trial in people with SCD, pociredir has demonstrated dose-dependent increases in HbF, pan-cellular HbF induction, and improvements in markers of hemolysis and anemia. Across the 12 mg and 20 mg dose cohorts, pociredir has been generally well-tolerated with up to three months of exposure, with no treatment-related serious adverse events reported. Pociredir has been granted Fast Track and Orphan Drug Designation from the FDA for the treatment of SCD. To learn more about clinical trials of pociredir please visit ClinicalTrials.gov.

About Sickle Cell Disease

SCD is a genetic disorder of the red blood cells caused by a mutation in the HBB gene. This gene encodes a protein that is a key component of hemoglobin, a protein complex whose function is to transport oxygen in the body. The result of the mutation is less efficient oxygen transport and the formation of red blood cells that have a sickle shape. These sickle shaped cells are much less flexible than healthy cells and can block blood vessels or rupture cells. People with SCD typically suffer from serious clinical consequences, which may include anemia, pain, infections, stroke, heart disease, pulmonary hypertension, kidney failure, liver disease, and reduced life expectancy.

About PIONEER

PIONEER (NCT05169580) is a Phase 1b open-label dose-escalation clinical trial evaluating the safety and efficacy of pociredir, an oral once-daily HbF inducer, in adult patients with severe SCD. Secondary endpoints include HbF induction, hemolysis, and anemia. Exploratory endpoints include globin gene expression, % F-cells and incidence of VOCs. Fulcrum has previously completed cohort 1 (6 mg, n=10), cohort 2 (2 mg, n=2), cohort 3a (12 mg, n=4), and cohort 3b (12 mg, n=16). Updated results of cohort 4 (20 mg, n=12) are reported today. A total of 13 patients enrolled, but there was one discontinuation due to death, which was determined by the investigator to be unrelated to treatment following complications from VOC reported on Day 1 of the study. The pharmacodynamic (PD) analysis data for cohort 4 includes 12 patients. The safety analysis set for 20mg includes all 13 patients who enrolled.

Forward-Looking Statements

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including express or implied statements regarding the significance of results from the 20 mg cohort; Fulcrum’s goals for pociredir; pociredir’s best-in-class potential for the treatment of SCD; pociredir’s ability to induce HbF; the durability or clinical relevance of HbF, hemolysis improvements, and VOCs during the 12-week treatment period; plans to engage with FDA and EMA and receipt of feedback on trial design; initiation of a registration-enabling trial; and conducting an open-label extension trial of pociredir; among others. All statements, other than statements of historical facts, contained in this press release are forward-looking statements, including express or implied statements regarding Fulcrum’s strategy, future operations, future financial position, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,”

“would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, risks associated with Fulcrum’s ability to continue to advance pociredir and its other product candidates in clinical trials, including feedback on trial design with regulators, as well as enrollment and completion; estimating the potential patient population and/or market for Fulcrum’s product candidates; interpreting initial clinical data, including the risk that 12-week data may not be predictive of longer-term outcomes, later timepoints, or future studies; replicating in clinical trials positive results found in preclinical studies and/or earlier-stage clinical trials of pociredir and any other product candidates; obtaining, maintaining or protecting intellectual property rights related to its product candidates; managing expenses; and managing risks associated therewith; and raising the substantial additional capital needed to achieve its business objectives; among others. For a discussion of other risks and uncertainties, and other important factors, any of which could cause Fulcrum’s actual results to differ from those contained in the forward-looking statements, see the “Risk Factors” section, as well as discussions of potential risks, uncertainties, and other important factors, in Fulcrum’s most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent Fulcrum’s views as of the date hereof and should not be relied upon as representing Fulcrum’s views as of any date subsequent to the date hereof. Fulcrum anticipates that subsequent events and developments will cause Fulcrum’s views to change. However, while Fulcrum may elect to update these forward-looking statements at some point in the future, Fulcrum specifically disclaims any obligation to do so.

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