Fulcrum Therapeutics Announces Positive Initial Results from the 20 mg Dose Cohort of the Phase 1b PIONEER Trial of Pociredir in Sickle Cell Disease at the 67th American Society of Hematology Annual Meeting

December 6, 2025 at 5:30 PM EST

— Clear dose-response observed, with a robust and clinically meaningful fetal hemoglobin (HbF) induction at the Week 6 timepoint (n=12): mean absolute HbF in the 20 mg cohort increased by 9.9% at Week 6 (vs. 5.6% at Week 6 in the 12 mg cohort); 7 of 12 patients in the 20 mg cohort (58%) achieved absolute HbF levels ≥20% —

— >3.75-fold mean induction of HbF at Week 12 in the 20 mg cohort among patients who reached the Week 12 visit as of November 11, 2025 data cutoff (n=6), compared to a 2.4-fold induction at Week 12 in the 12 mg cohort —

— Consistent early evidence of pan-cellular HbF induction, improvements in markers of hemolysis and anemia, and encouraging trends in vaso-occlusive crisis (VOC) reduction —

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

— Fulcrum to host investor event at 7:00 a.m. ET December 7, 2025 —

CAMBRIDGE, Mass., Dec. 06, 2025 (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 initial results from the ongoing 20 mg dose cohort of the Phase 1b PIONEER trial of pociredir in sickle cell disease (SCD).

“We are highly encouraged by these initial data from the 20 mg cohort, which show clear evidence of a dose-response and build on the strong profile established with the 12 mg cohort,” said Alex C. Sapir, Fulcrum’s President and Chief Executive Officer. “At just six weeks of treatment, we have observed robust and clinically meaningful increases in fetal hemoglobin with the majority of patients achieving absolute HbF levels ≥20%. These results reinforce pociredir’s potential as a best-in-class, once-daily oral HbF inducer. Importantly, pociredir continues to demonstrate a favorable safety profile with no treatment-related SAEs reported.”

“These data reinforce that induction of fetal hemoglobin remains one of the most scientifically grounded strategies for treating SCD,” said Dr. Martin Steinberg, Professor of Medicine, Pediatrics, Pathology and Laboratory Medicine at Boston University Chobanian & Avedisian School of Medicine. “The clear dose-response observed with the 20 mg cohort, including robust early increases in HbF and evidence suggesting pan-cellular induction, is consistent with the mechanistic understanding that higher and more uniformly expressed HbF can inhibit polymerization of sickle hemoglobin, the root cause of SCD. These results represent an important step in evaluating the therapeutic potential of pociredir.”

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 Phase 1b PIONEER trial includes 12 adults with severe SCD. At the November 11, 2025 data cutoff, all 12 patients completed the Week 6 visit and are included in the Week 6 analyses. Six patients (50%) who enrolled earlier in the cohort reached the Week 12 visit at the time of data cutoff and are included in the Week 12 analyses. Week 6 results therefore reflect all 12 patients, while Week 12 results reflect the first 6 patients to complete the full treatment period. All 12 patients are expected to complete the full 12-week treatment period, and Fulcrum plans to report updated results in Q1 2026.

PIONEER Study 20 mg Dose Cohort Initial Efficacy Data

Initial results from the 20 mg dose cohort of the Phase 1b PIONEER trial (n=12) are as follows:

- Mean absolute HbF increased by 9.9% at 6 weeks of treatment with pociredir (vs. 5.6% at Week 6 and 8.6% at Week 12 in the 12 mg cohort), increasing from a baseline of 7.1% to 16.9%. As of the November 11, 2025 data cutoff, 7 of 12 patients (58%) achieved absolute HbF levels ≥20% at Week 6, and all patients demonstrated a robust HbF increase. HbF levels of 20% are associated with ~90% of patients experiencing zero VOCs per year, based on real-world data presented by Fulcrum at the 20th Annual Sickle Cell & Thalassemia Conference (ASCAT) in October 2025.
- A clear dose-response was observed, with a >3.75-fold mean induction of HbF at Week 12 among patients who reached the Week 12 visit as of the November 11, 2025 data cutoff (n=6), compared to a 2.4-fold mean induction at Week 12 in the 12 mg cohort. The average baseline for these six patients is 5.0% as compared to 7.1% for the full cohort. Fold induction accounts for differences in baseline HbF levels and enables a normalized comparison of dose-response.
- The proportion of F-cells (HbF-containing red blood cells) increased from a mean of 31% at baseline to 58% at Week 6 (n=9), indicating early progression toward pan-cellular HbF induction (evenly distributed across red blood cells). F-cells are resistant to sickling and hemolysis because of HbF-mediated inhibition of sickle hemoglobin (HbS) polymerization. Consequently, higher proportions of F-cells are associated with improved red blood cell health.
- Markers of hemolysis and erythropoiesis improved at Week 6:
    - Indirect bilirubin decreased by 37% (vs. 37% at Week 12 in the 12 mg cohort)
    - Lactate dehydrogenase (LDH) decreased by 37% (vs. 28% at Week 12 in the 12 mg cohort)
    - Red cell distribution width decreased by 22% (vs. 27% at Week 12 in the 12 mg cohort)

- Reticulocyte counts decreased by 33% (vs. 31% at Week 12 in the 12 mg cohort), indicating healthier bone marrow function

- Mean hemoglobin increased by 0.8 g/dL at Week 6 (vs. 0.9 g/dL at Week 12 in the 12 mg cohort), increasing from a baseline of 7.3 g/dL to 8.1 g/dL. Combined with reductions in reticulocyte counts, these findings indicate decreased red blood cell destruction and improvements in anemia.
- A trend of reduced VOC frequency was observed relative to patients' documented VOC frequency during the 6–12 months prior to enrollment. As of November 11, 2025 data cut off, eight of 12 patients (67%) reported no VOCs during the treatment period.

Pociredir Safety Update

- As of the November 11, 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 November 11, 2025 data cutoff, together with follow-up data from the 12 mg dose cohort, remained 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 November 11, 2025, data cutoff.

ASH Investor Event Information

Fulcrum Therapeutics, Inc. will host a live and webcast investor event featuring company leadership and medical experts on Sunday, December 7, 2025 at 7:00 a.m. ET in Orlando to discuss the results to date from the PIONEER Phase 1b trial. The event will be webcast live and 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. Individuals may register to participate in the webcast using the conference link here.

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 fetal hemoglobin (HbF) for the treatment of sickle cell disease (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 Twitter/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 fetal hemoglobin (HbF). Pociredir is being developed for the treatment of SCD. Initial data in SCD in the PIONEER Phase 1b clinical trial showed proof-of-concept and achieved absolute levels of HbF increases associated with potential overall patient benefit. Through the completion of the 12 mg dose cohort, pociredir was demonstrated to be generally well-tolerated in people with SCD with up to three months of exposure, with no treatment-related serious adverse events reported. Pociredir has been granted FDA Fast Track designation and Orphan Drug Designation 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). Initial 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, of which 50% (n=6) reached 12 weeks of the November 11, 2025 data cut, and 100% (n=12) reached at least 6 weeks as of the data cut. 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 initial 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 early HbF and hemolysis improvements; and VOCs during the 12-week treatment period, 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 completing the 20mg cohort in the PIONEER clinical trial; achieving the same results in the full cohort as observed in a limited number of patients after six weeks; Fulcrum’s ability to continue to advance pociredir and its other product candidates in clinical trials, including enrollment and completion; estimating the potential patient population and/or market for Fulcrum's product candidates; interpreting initial clinical data, including the risk that early data (such as week 6 data from the 20 mg cohort) may not be predictive of full cohort results, 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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