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

July 29, 2025 at 6:45 AM EDT

— Robust and clinically meaningful absolute mean fetal hemoglobin (HbF) induction of 8.6% from baseline at 12 weeks of treatment; 7 of 16 patients achieved absolute HbF levels greater than 20% —

— Evidence of pan-cellular induction of HbF based on an increase in F-cells (red blood cells containing HbF) from a mean of 34% at baseline to 67% at 12 weeks of treatment —

— Meaningful improvements in key markers of hemolysis coupled with a 0.9 g/dL mean increase in total hemoglobin (Hb) —

— Encouraging trends in vaso-occlusive crisis (VOC) reduction compared to baseline —

— Pociredir continued to be generally well-tolerated with no treatment-related serious adverse events (SAEs); all treatment-related adverse events (AEs) were Grade 1 —

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

CAMBRIDGE, Mass., July 29, 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 results from the 12 mg dose cohort of the Phase 1b PIONEER trial of pociredir in sickle cell disease (SCD).

“We are highly encouraged by these data from the 12 mg cohort of the PIONEER trial and believe they represent an important milestone in our mission to transform the treatment of sickle cell disease.” said Alex C. Sapir, Fulcrum’s President and Chief Executive Officer. “We believe that with the level of HbF induction observed coupled with improvements in key markers of hemolysis and anemia, evidence of pan-cellular induction of HbF, and an encouraging trend in VOC reduction, pociredir, as a once-daily oral therapy, has the potential to treat SCD patients around the world who continue to battle with their disease. Importantly, pociredir continued to be generally well-tolerated, with no treatment-related SAEs reported and all treatment-related AEs limited to Grade 1.”

“Patients with sickle cell disease continue to face a significantly shortened life expectancy and a lifelong burden of frequent and debilitating pain crises,” said Wally Smith, M.D., Director, VCU Adult Sickle Cell Program and Professor, VCU School of Internal Medicine. “These data, showing clinically-meaningful increases in HbF levels, reductions in pain crises, and improvements in markers of hemolysis, are both impressive and encouraging. Pociredir’s ability to induce HbF is a promising approach for treating SCD, as HbF directly interferes with the polymerization of sickle hemoglobin, the root cause of sickle cell disease. Sickle cell patients with hereditary persistence of HbF are largely protected from the clinical manifestations of the disease, and these data suggest that pociredir may replicate that protective biology. A once daily oral therapy that can meaningfully reduce hemolysis and pain crises, while maintaining a favorable safety profile, has the potential to represent a paradigm shift for sickle cell patients. I look forward to longer-term data as pociredir continues through clinical development.”

PIONEER Study 12 mg Dose Cohort Efficacy Data

Results from the 12 mg dose cohort of the Phase 1b PIONEER trial, following conclusion of the 12-week treatment period, in 16 patients are as follows:

- Mean absolute HbF increased by 8.6% at 12 weeks of treatment with pociredir, representing an increase from a baseline of 7.6% to 16.2%. Seven of 16 patients achieved absolute HbF levels greater than 20% after 12 weeks of treatment with pociredir. HbF levels of 20% are associated with approximately 90% of individual patients experiencing zero VOCs per year, based on a recent analysis of real-world data conducted by Fulcrum, which has been accepted for publication at the 20th Annual Sickle Cell & Thalassaemia Conference (ASCAT), to be held in London, United Kingdom, October 1-4, 2025.
- Proportion of F-cells (HbF-containing red blood cells) increased from a mean of 34% at baseline to 67% at 12 weeks of treatment (n=8), consistent with pan-cellular HbF induction (evenly distributed across red blood cells). F-cells are resistant to red blood cell sickling and hemolysis because of HbF-mediated inhibition of sickle hemoglobin (HbS) polymerization. Consequently, a higher proportion of F-cells is associated with improved red blood cell health.
- Markers of hemolysis and erythropoiesis improved with pociredir treatment at 12 weeks:
    - Decreased indirect bilirubin (mean decrease of 37%)
    - Decreased lactate dehydrogenase (LDH) (mean decrease of 28%)
    - Decreased red cell distribution width (mean decrease of 27%), indicating a more uniform red blood cell population
    - Decreased reticulocyte counts (mean decrease of 30%), indicating healthier bone marrow function
- Mean hemoglobin concentration increased by 0.9 g/dL at 12 weeks of treatment with pociredir, from a baseline of 7.8 g/dL to 8.7 g/dL. Together with the observed decrease in reticulocyte counts, the increase in total hemoglobin indicates that pociredir decreased red blood cell destruction and showed reductions in anemia.
- A trend of reduced VOC rates was observed during the study period (as assessed by VOCs reported as AEs), compared to cohort patients’ VOC frequency over the 6–12 months prior to enrollment. Eight of 16 patients (50%) reported no VOCs

during the treatment period (12 weeks); 3 VOCs occurred during the follow-up period as of the June 26, 2025 data cut-off date.

Pociredir Safety Update

- Through the completion of the 12 mg dose cohort, pociredir has been dosed in 135 adults, including 76 subjects in multiple dose cohorts up to 12 weeks.
    - 103 healthy subjects, including 44 who received pociredir from 10 to 14 days treatment duration
    - 32 SCD patients who received pociredir up to 12 weeks treatment duration
- The safety profile for pociredir observed in the 12 mg dose cohort was consistent with previously reported safety data. Pociredir was generally well-tolerated, with no drug-related SAEs and no discontinuations due to treatment-emergent AEs through the completion of the 12 mg dose cohort. In addition, all treatment-related AEs were Grade 1.
- Additional observations after completion of the 4-week follow-up period for 12 mg dose cohort (ongoing) will be shared at a future medical meeting.

The 12 mg data (n=16) discussed in this press release relates to cohort 3b (incomplete prior 12 mg cohort (3a) conducted prior to study hold not included in this analysis).

Conference Call and Webcast

Fulcrum Therapeutics, Inc. will host a conference call and webcast 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. An audio webcast will be accessible through the Investor Relations section of the company's website at www.fulcrumtx.com or by clicking here. Following the live webcast, an archived replay will also be available for 90 days.

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.

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. All statements, other than statements of historical facts, contained in this press release are forward-looking statements, including express or implied statements regarding pociredir's potential to transform the treatment of SCD; pociredir's ability to replicate protective biology through HbF induction; continued clinical development of pociredir; Fulcrum's Phase 1b PIONEER clinical trial of pociredir; Fulcrum's ability to progress its early stage development programs and planned IND filings related thereto; among others. 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 its product candidates in clinical trials; initiating and enrolling clinical trials on the timeline expected or at all; obtaining and maintaining necessary approvals from the FDA and other regulatory authorities; replicating in clinical trials positive results found in preclinical studies and/or earlier-stage clinical trials; obtaining, maintaining or protecting intellectual property rights related to its product candidates; managing expenses; realize the anticipated benefits of the workforce reduction and strategic realignment 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.

Contact:

Kevin Gardner
LifeSci Advisors, LLC
kgardner@lifesciadvisors.com
617-283-2856