UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 OR 15(d) of The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 08, 2025

Fulcrum Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**001-38978**	**47-4839948**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**
26 Landsdowne Street Cambridge, Massachusetts		**02139**
(Address of principal executive offices)		**(Zip Code)**

Registrant's telephone number, including area code: (617) 651-8851

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common stock, par value $0.001 per share	FULC	Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure

On December 6, 2025, Fulcrum Therapeutics, Inc., or Fulcrum, issued a press release announcing initial results of the 20 mg dose cohort of the Phase 1b PIONEER trial of pociredir in sickle cell disease, or SCD, in connection with a presentation at the 67th American Society of Hematology Annual Meeting.

A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K.

The information furnished in this Item 7.01, including Exhibit 99.1, shall not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities of that section or Sections 11 and 12(a)(2) of the Securities Act of 1933, as amended, or the Securities Act. The information contained in this Item 7.01 and in the accompanying Exhibit 99.1 shall not be incorporated by reference into any other filing under the Exchange Act or under the Securities Act, except as shall be expressly set forth by specific reference in such filing.

Item 8.01 Other Events.

On December 7, 2025, Fulcrum published a presentation announcing initial results of the 20 mg dose cohort of the Phase 1b PIONEER trial of pociredir in SCD in connection with a presentation at the 67th American Society of Hematology Annual Meeting. Results are as follows:

- Mean absolute fetal hemoglobin, or 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 vaso occlusive crisis, or VOCs, per year, based on real-world data presented by Fulcrum at the 20th Annual Sickle Cell & Thalassemia Conference 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 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.
- 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 serious adverse events and no discontinuations due to treatment-related adverse events as of the November 11, 2025, data cutoff.

In addition, Fulcrum now plans to submit an investigational new drug application, for its program for the potential treatment of bone marrow failure syndromes, such as Diamond-Blackfan anemia, 5q deletion syndrome, Shwachman-Diamond syndrome, and Fanconi anemia, during the second quarter of 2026.

A copy of the presentation is filed as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

Forward-Looking Statements

This Current Report on Form 8-K 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 fact, contained in this Current Report on Form 8-K are forward-looking statements, including, without limitation, 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; VOCs during the 12-week treatment period; and Fulcrum's plans to submit an investigational new drug application; among others. 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 that could cause actual results to differ from those contained in the forward-looking statements, please refer to the "Risk Factors" section of Fulcrum's most recent filings with the Securities and Exchange Commission. The forward-looking statements included in this Current Report on Form 8-K represent Fulcrum's views only as of the date hereof and should not be relied upon as representing its views as of any date subsequent to the date hereof. Fulcrum anticipates that subsequent events and developments will cause its views to change, but it undertakes no obligation to update any forward-looking statements, except as required by law.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

99.1+	Press Release issued December 6, 2025, announcing initial results from the 20 mg Dose Cohort of the Phase 1b PIONEER Trial of Pociredir in Sickle Cell Disease
99.2*	Presentation issued December 7, 2025, announcing initial results from the 20 mg Dose Cohort of the Phase 1b PIONEER Trial of Pociredir in Sickle Cell Disease
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

+ Furnished herewith.

* Filed herewith.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

FULCRUM THERAPEUTICS, INC.

Date: December 8, 2025

By: /s/ Alex C. Sapir
Name: Alex C. Sapir
Title: President and Chief Executive Officer

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

— 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., – December 6, 2025 – 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.

Contact:

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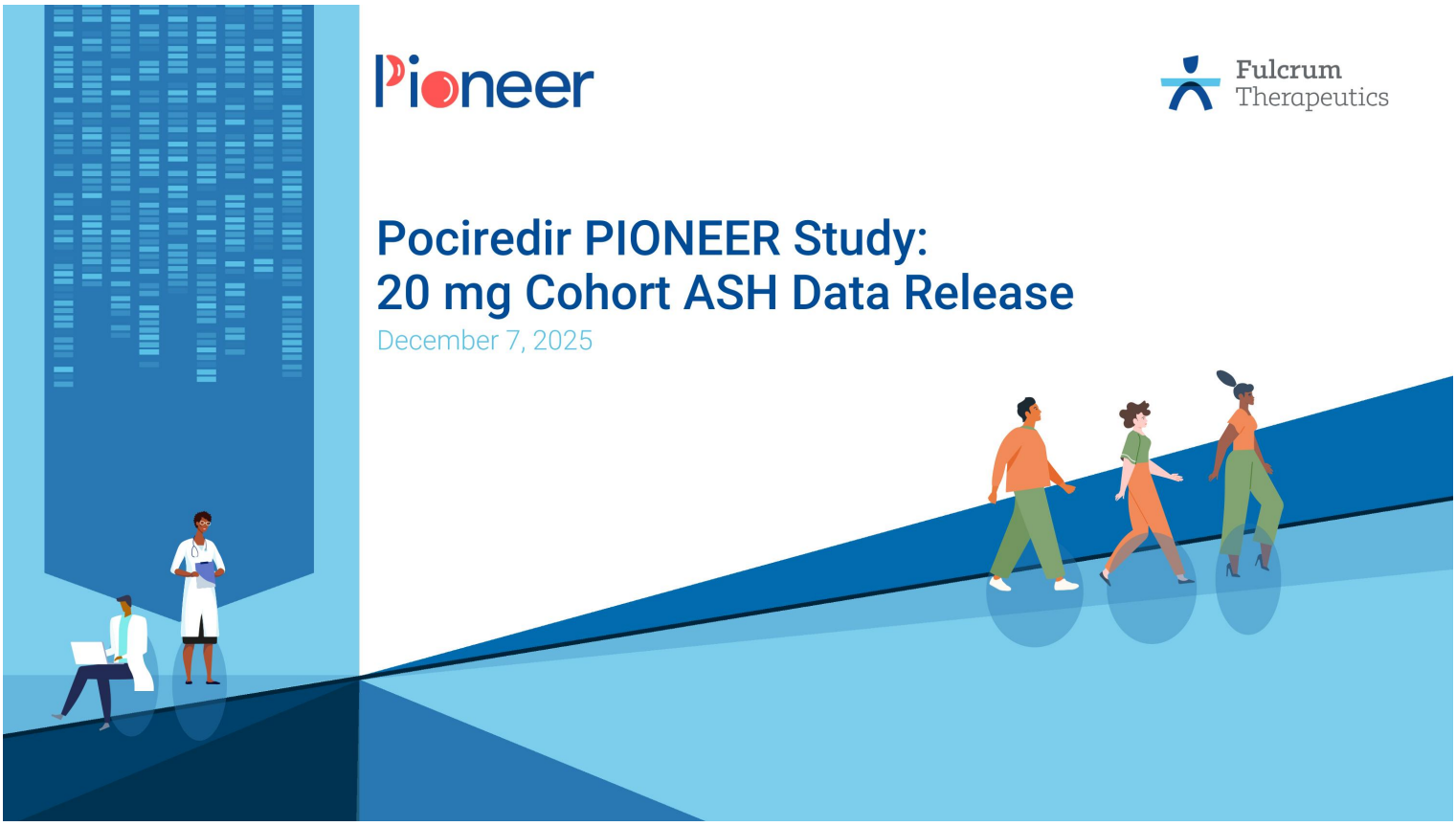
kgardner@lifesciadvisors.com
617-283-2856



Pociredir PIONEER Study: 20 mg Cohort ASH Data Release

December 7, 2025

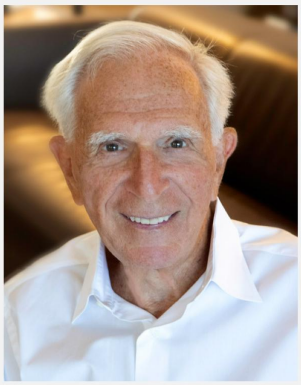
Disclaimer and Notice

This presentation contains "forward-looking statements" of Fulcrum Therapeutics, Inc. (Fulcrum or Fulcrum Therapeutics) within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including express or implied statements regarding 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 sickle cell disease, pociredir's ability to induce fetal hemoglobin, the durability or clinical relevance of early HbF and hemolysis improvements, vaso-occlusive crises during the 12-week treatment period, and the timing of data releases, as well as timing and outcomes of meetings with the U.S. Food and Drug Administration, among others. All statements, other than statements of historical facts, contained in this presentation, 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 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 pociredir and any other product candidates; obtaining, maintaining or protecting intellectual property rights related to Fulcrum's product candidates; managing expenses; 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 presentation 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. While Fulcrum may elect to update these forward-looking statements at some point in the future, Fulcrum specifically disclaims any obligation to do so.

Today's Guest Speakers

Sheinei Alan, M.D., Ph.D.

Director, Inova Adult Sickle Cell Program & Assistant Professor, UVA School of Medicine Inova Campus



Martin H. Steinberg, M.D.

Professor of Medicine, Pediatrics, Pathology and Laboratory Medicine at Boston University Chobanian & Avedisian School of Medicine

Drs. Alan and Steinberg are practicing physicians and paid Investigators in Fulcrum Therapeutics' PIONEER Study. The views and opinions expressed by Drs. Alan and Steinberg are their own and do not necessarily reflect those of Fulcrum Therapeutics.

Agenda for Investor Call

Introduction	**Alex C. Sapir,** President & CEO
Sickle Cell Disease (SCD) and the Potential of a Once Daily Oral HbF-Inducer	**Iain Fraser MBChB, D.Phil**, SVP Early Clinical Development
PIONEER Study Overview and 20 mg Pociredir Cohort Data Update	**Sheinei Alan, M.D., Ph.D.,** Director, Inova Adult Sickle Cell Program & Assistant Professor, UVA School of Medicine
Expert Perspective on Pociredir and Its Potential as a Once Daily Oral HbF-Inducer for Treating SCD	**Martin H. Steinberg, M.D.,** Professor of Medicine, Pediatrics, Pathology and Laboratory Medicine at Boston University Chobanian & Avedisian School of Medicine
Q&A	**Fulcrum Management, Drs. Alan and Steinberg**
Closing Remarks	**Alex C. Sapir,** President & CEO

Initial 20 mg cohort data raises the bar on Pociredir's Best-in-Class Potential

Fulcrum Therapeutics

Fulcrum's Goals for an HbF-Inducer in Sickle Cell Disease

- Once-Daily oral tablet with favorable tolerability
- Robust and rapid increase in HbF
- Pan-cellular HbF induction
- Improved anemia and hemolysis
- Meaningful reduction in vaso-occlusive crises (VOC)

12 mg established pociredir's Best-in-Class Potential as a QD oral therapy for SCD

- ✓ Generally well-tolerated at 12 mg
- ✓ 5.6% mean absolute increase in HbF at Week 6 and 8.6% at Week 12
- ✓ 44% of patients (7/16) reaching ≥20% HbF at Week 12
- ✓ 2.4-fold induction of HbF at Week 12 in sixteen patients
- ✓ Progression towards pan-cellularity and improvements in anemia and hemolysis
- ✓ Encouraging trends in VOC reduction over 12 weeks

Initial 20 mg cohort data raises the bar on pociredir's Best-in-Class Potential

- ✓ Continued evidence of pociredir being generally well-tolerated at 20 mg
- ✓ 9.9% mean absolute increase in HbF at Week 6 for the full cohort (n=12)
- ✓ 58% of patients (7/12) reaching ≥20% HbF at their latest study visit
- ✓ >3.75-fold induction of HbF at Week 12 in the six patients who completed the treatment period
- ✓ Continued progression towards pan-cellularity and improvements in anemia and hemolysis
- ✓ Continued encouraging trends in VOC reduction

Pioneer

20 mg cohort data as of Nov 11, 2025 Data Cut. 6 of 12 patients in the PD Analysis Set completed treatment period as of data cut

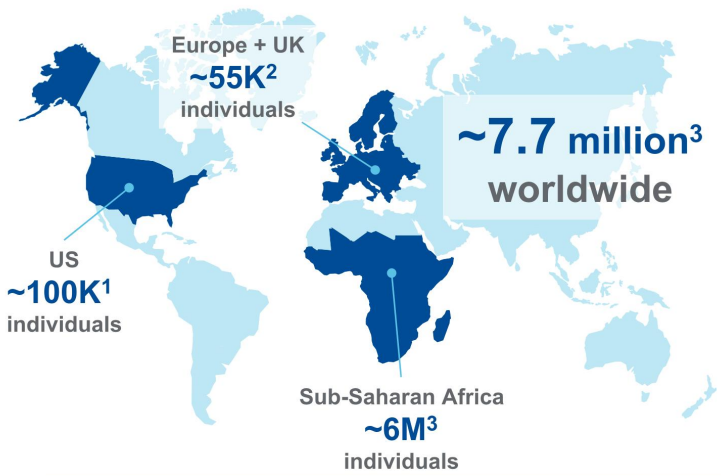
Agenda for Investor Call

Introduction	**Alex C. Sapir,** President & CEO
Sickle Cell Disease (SCD) and the Potential of a Once Daily Oral HbF-Inducer	**Iain Fraser MBChB, D.Phil**, SVP Early Clinical Development
PIONEER Study Overview and 20 mg Pociredir Cohort Data Update	**Sheinei Alan, M.D., Ph.D.,** Director, Inova Adult Sickle Cell Program & Assistant Professor, UVA School of Medicine
Expert Perspective on Pociredir and Its Potential as a Once Daily Oral HbF-Inducer for Treating SCD	**Martin H. Steinberg, M.D.,** Professor of Medicine, Pediatrics, Pathology and Laboratory Medicine at Boston University Chobanian & Avedisian School of Medicine
Q&A	**Fulcrum Management, Drs. Alan and Steinberg**
Closing Remarks	**Alex C. Sapir,** President & CEO

Sickle Cell Disease Is a Debilitating Disease With High Unmet Need

Fulcrum Therapeutics

Global Impact



Disease

- Sickle Cell Disease (SCD) is driven by abnormal, sickle-shaped RBCs with a shortened lifespan that rupture and block blood vessels causing extreme pain for the patient

Debilitating Symptoms

- Painful Vaso-Occlusive Crises (VOCs) contribute to >75% of SCD-related hospitalizations[4]
- Acute manifestations also include stroke, pulmonary hypertension, priapism, leg ulcers, and splenic sequestration
- Chronic anemia and hemolysis result in end-organ damage

Patients with SCD face a substantial reduction in life expectancy (>20 years), with a mortality rate up to 9× higher than the general population[5]

Pioneer

1. American Society of Hematology; CDC
2. EMA, Piel et al., 2013, Inusa et al. 2019
3. GBD 2021, Piel et al.,2013, Makani et al. 2013
4. Shah, et.al. 2019
5. GBD 2021, CDC

RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis

Higher HbF Levels Result in Reduced Symptomology in People Living With Sickle Cell Disease

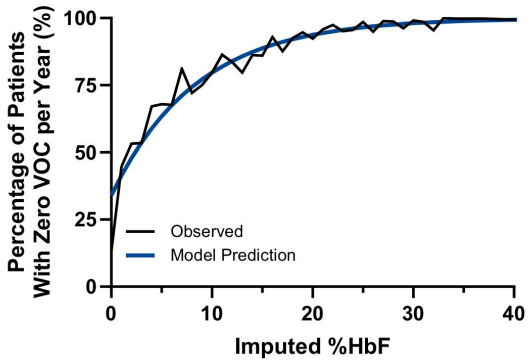
Each 1% increase in %HbF…

…is associated with a 4%–8% reduction in VOCs[1]

Raising HbF levels also results in:

- Reduced hemolysis
- Reduced anemia
- Fewer recurring events

Probability of Observing Zero VOC/Year by %HbF[2]



HbF level	% of Patients reporting zero VOCs *(Model Prediction)*
15%	89%
20%	94%
25%	97%

HbF, fetal hemoglobin; VOC, vaso-occlusive crisis.

1. Peter Bruun-Rasmussen. ASH 2024 (poster #1124).
2. Data from Fulcrum analysis of Picnic Health real-world dataset, n=673; ≥2 years ; mean HbF 8.6% - Alan et al., 20th Annual Sickle Cell & Thalassaemia Conference. Br J Haematol, 207: S5-S135. 2025

Targeting EED Results in HbF Increases

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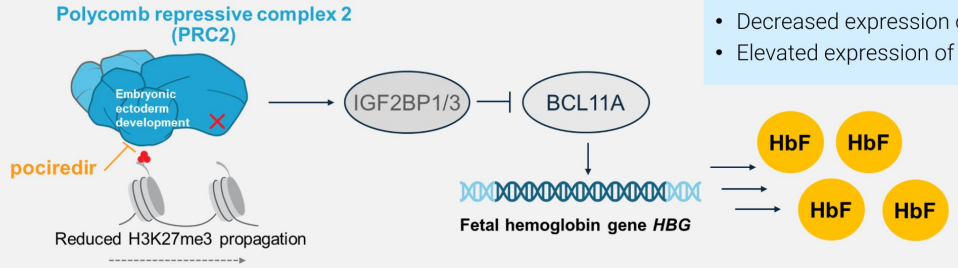
Pociredir Is a Potent and Selective EED Binder



- Decreased expression of HbF repressors and regulators
- Elevated expression of HbF mRNA and protein

- EED inhibition targets known modulators of HbF, including *BCL11A* and *MYB*[1]
- Pociredir is a potent EED binder[1]
  - Highly selective
  - Clean off-target profile
  - Robust target engagement observed at doses as low as 2 mg

EED, embryonic ectoderm; HbF, fetal hemoglobin; mRNA, messenger RNA; PRC2, polycomb repressive complex 2.
1. Stuart B, et.al., Hemasphere 2022

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Previously Disclosed Data Highlights Pociredir's Potential as an HbF Inducer in SCD

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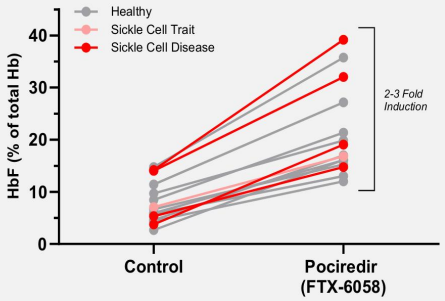
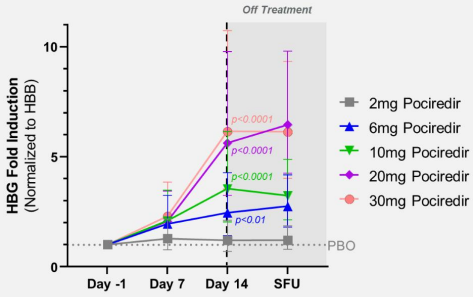
Pre-Clinical: Pociredir HbF Induction in Healthy and SCD CD34+ Donor Cells



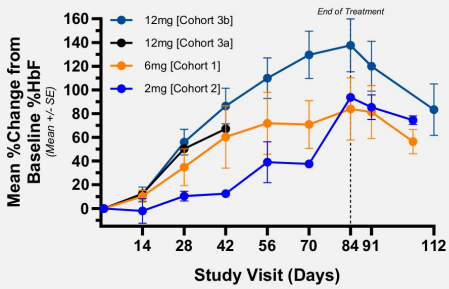
- 8 – 25% absolute increase in %HbF
- Consistent 2-3 fold induction across both healthy subject and SCD CD34+ donor-derived cells

Phase 1: Gamma Globin (HBG) Induction in Healthy Volunteers



- Time- and Dose-related HBG mRNA Induction in Healthy Volunteer Multiple Ascending Dose Cohorts[1]

Phase 1b: Mean % Change from Baseline %HbF in SCD Patients



- Time- and Dose-related HbF induction in previous PIONEER Cohorts[2]
- Cohorts 1-3a conducted in all-comer adult SCD population with no requirement for disease severity

1. n=6 per cohort
2. n=16 12mg cohort 3b. Previously-conducted incomplete 12 mg cohort due to U.S. FDA full clinical hold for pociredir on February 23, 2023, which was lifted August 23, 2023. Safety data collection continued with data cut of March 3, 2023. 12mg cohort 3a n=1 at Day 42, 6mg cohort n=5 at Day 84, 2 mg cohort n=1 at Day 84.

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Agenda for Investor Call

Introduction	**Alex C. Sapir,** President & CEO
Sickle Cell Disease (SCD) and the Potential of a Once Daily Oral HbF-Inducer	**Iain Fraser MBChB, D.Phil**, SVP Early Clinical Development
PIONEER Study Overview and 20 mg Pociredir Cohort Data Update	**Sheinei Alan, M.D., Ph.D.,** Director, Inova Adult Sickle Cell Program & Assistant Professor, UVA School of Medicine
Expert Perspective on Pociredir and Its Potential as a Once Daily Oral HbF-Inducer for Treating SCD	**Martin H. Steinberg, M.D.,** Professor of Medicine, Pediatrics, Pathology and Laboratory Medicine at Boston University Chobanian & Avedisian School of Medicine
Q&A	**Fulcrum Management, Drs. Alan and Steinberg**
Closing Remarks	**Alex C. Sapir,** President & CEO

PIONEER: A Phase 1B Study in Patients With SCD[1]

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Study Design (Open Label, Dose Escalation, ≈10 Patients per Cohort)

4-Week Screening Period

12-Week Treatment Period (QD Capsule)

- **Cohort 1** 6 mg (n=10)
- **Cohort 2** 2 mg (n=2)
- **Cohort 3a** 12 mg (n=4)
- **Cohort 3b** 12 mg (n=16)

Completed (previously presented)

- **Cohort 4** 20 mg (n=13) — Initial 20 mg Cohort 4 data presented today — In Progress

4-Week Follow-Up Period

Select Inclusion Criteria

- SCD Patients 18-65 years
- Discontinued HU for ≥60 days
- Severe SCD as defined by ≥4 VOCs over 12 months or ≥2 VOCs over 6 months

Key Study Endpoints

Primary
- Safety and tolerability assessments
- PK parameters

Secondary
- HbF induction
- Hemolysis
- Anemia

Exploratory
- Globin gene expression
- % F-cells
- Incidence of VOCs

Additional criteria apply. For more information, please see https://www.clinicaltrials.gov/study/NCT05169580.

HbF, fetal hemoglobin; HU, hydroxyurea; QD, once daily; SCD, sickle cell disease; VOC, vaso-occlusive crisis; PK, Pharmacokinetic; F-Cells, Cells expressing Fetal Hemoglobin

1. Adapted from Alan S, et al. *J Sick Cell Dis.* 2025;2(Suppl 1)

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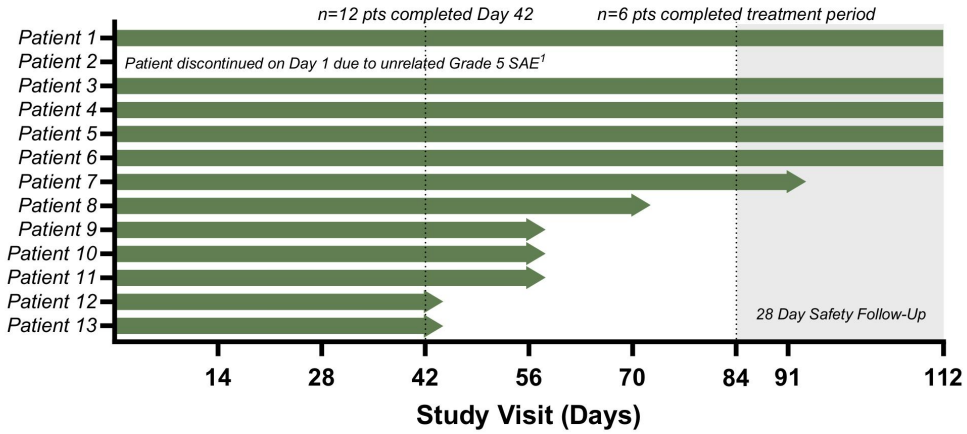
20 mg Cohort Patient Disposition (Data Cut: Nov 11, 2025)



- 20 mg Pharmacodynamic (PD) Analysis Set includes n=12 patients. 6 of 12 patients (50%) have reached 12 weeks and 12 of 12 patients (100%) had reached at least 6 weeks as of data cut.
- Safety Analysis Set to be presented includes all 12 mg (n=16) and 20 mg (n=13) data as of data cut
- Continued high adherence (97%) to treatment schedule in the 20 mg cohort[2]

Disposition and all subsequent data as of Nov 11, 2025, data cut
1. Grade 5 SAE determined by the investigator unrelated to treatment following complications from VOC reported on Day 1 of study. Patient excluded from the PD Analysis Set
2. Adherence measured via AiCure®, an artificial intelligence data collection tool providing real-time feedback and data collection to measure and improve study drug adherence. Dosing interruptions on study not included in AiCure adherence analysis

PIONEER Baseline Demographics and Characteristics – PD Analysis Set

	Pociredir 12 mg; n=16 % or mean (SD)	Pociredir 20 mg; n=12[1] % or mean (SD)
Sex, % Male	44%	17%
Age, Years	34.3 (12.25)	32.3 (6.98)
Country		
US	62.5%	58.3%
South Africa	37.5%	8.3%
Nigeria	0%	33.3%
Genotype		
Hb SS	87.5%	83.3%
Hb $S\beta^0$	12.5%	8.3%
Hb $S\beta^+$	0%	8.3%
Baseline HbF (%)	7.6% (4.7)	7.1% (4.4)
Baseline Hb (g/dL)	7.8 (1.8)	7.3 (1.2)
Baseline VOCs		
Reporting over 6 months	2.83 (N=6)	2.40 (N=5)
Reporting over 12 months	5.20 (N=10)	6.71 (N=7)

1. n=12 PD Analysis Set

Dose-Dependent Pociredir PK Exposure in Sickle Cell Disease Patients

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Plasma PK Comparison between cohorts in PIONEER Study

Dose (PIONEER Study)	Number of Patients	Mean C_{max} ng/mL (%CV)	Median T_{max} hrs (range)	Mean $AUC_{0\text{-}4h}$ ng·hr/mL (%CV)
6 mg (Day 1)	9	18.1 (20.9)	2.0 (2.0-4.0)	45.2 (24.7)
12 mg (Day 1)	16	38.5 (38.9)	3.0 (2.0-4.0)	94.8 (45.4)
20 mg (Day 1)	12	69.4 (54.7)	3.0 (1.0-4.0)	168.0 (58.0)

Consistent with previously reported healthy volunteer data, dose-dependent increases in C_{max} and AUC observed across the 6 mg, 12 mg, and 20 mg cohorts

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Pociredir 20 mg: Building on the Robust and Clinically Relevant increases in Fetal Hemoglobin (HbF)

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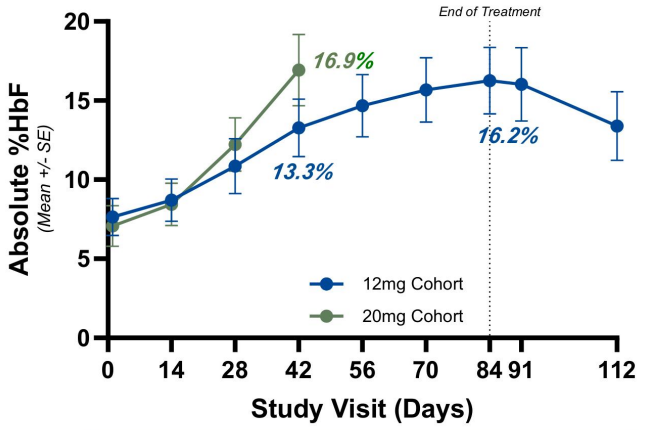
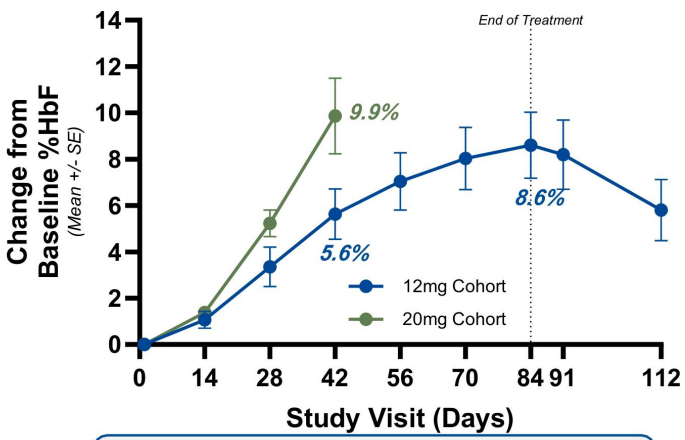
Data as of Nov 11, 2025 Data Cut

Mean Absolute %HbF



20 mg Pociredir increased %HbF from 7.1% to 16.9% at Week 6

Mean Absolute %HbF Change from Baseline



20 mg Pociredir increased %HbF by 9.9% at Week 6

12 mg cohort 3b analysis & figures includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
In progress 20 mg cohort PD Analysis Set (n=12). Analysis includes data through visits with complete laboratory data. No patients received transfusions during the treatment period.

Pociredir 20 mg: Clinically Relevant HbF Induction in all Patients

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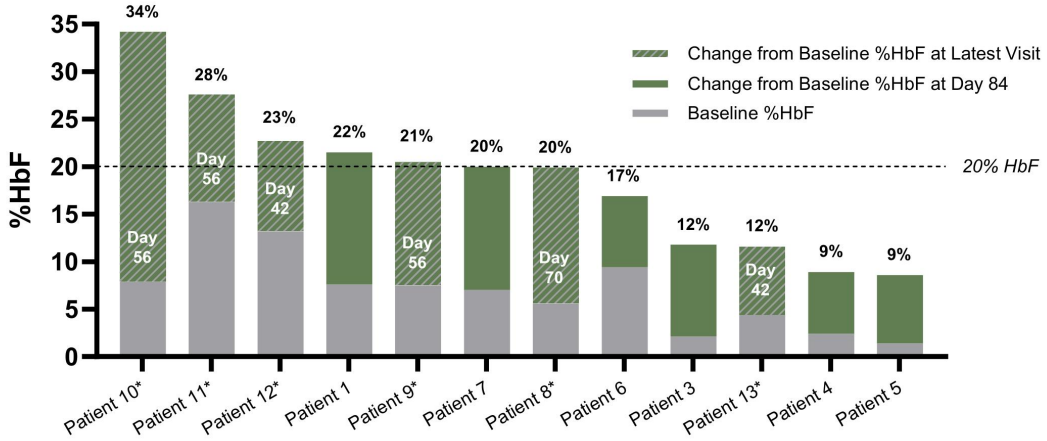
Data as of Nov 11, 2025 Data Cut

Baseline %HbF and Change from Baseline %HbF at Latest Timepoint



- As of data cut, 7 of 12 patients (58%) achieved a ≥20% absolute level of %HbF at their latest study visit
- All patients in the 20 mg cohort[1] achieved a ≥6.5% absolute HbF increase from baseline

*Patients yet to complete Day 84 treatment visit. Latest visit indicated and Change from Baseline %HbF from latest study visit included.
1. In progress 20 mg cohort PD Analysis Set (n=12). No patients received transfusions during the treatment period.

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Pociredir 20 mg: Demonstration of Dose-Response

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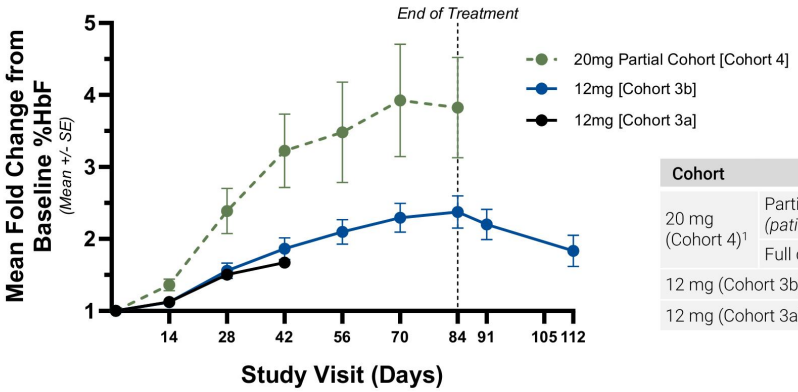
Data as of Nov 11, 2025 Data Cut

Mean Fold Change from Baseline HbF after 12 Weeks of Treatment



Cohort		Mean Baseline %HbF
20 mg (Cohort 4)[1]	Partial cohort n=6 *(patients completing treatment period)*	5.0
	Full cohort n=12	7.1
12 mg (Cohort 3b)[2] n=16		7.6
12 mg (Cohort 3a)[3] n=3		14.8

- **Mean fold change from baseline accounts for variability across cohort baselines to evaluate dose response**
- **Patients with complete 12-week data (n=6) in the 20 mg cohort achieved >3.75-fold induction of HbF, demonstrating a clear dose-response vs. prior 12 mg cohorts**

Mean fold change from baseline calculated by taking the mean of individual patients' fold change from baseline at each timepoint.
1. In progress 20 mg cohort PD Analysis Set (n=12). Figure & analysis includes n=6 patients who completed 12 weeks as of data cut. No patients received transfusions during the treatment period.
2. 12 mg Cohort 3b analysis & figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
3. Previously-conducted incomplete 12 mg cohort due to U.S. FDA full clinical hold for pociredir on February 23, 2023 which was lifted August 23, 2023. PD Analysis Set

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Pociredir 20 mg: F-cell Data Demonstrated Progression Towards Pan-Cellular Induction

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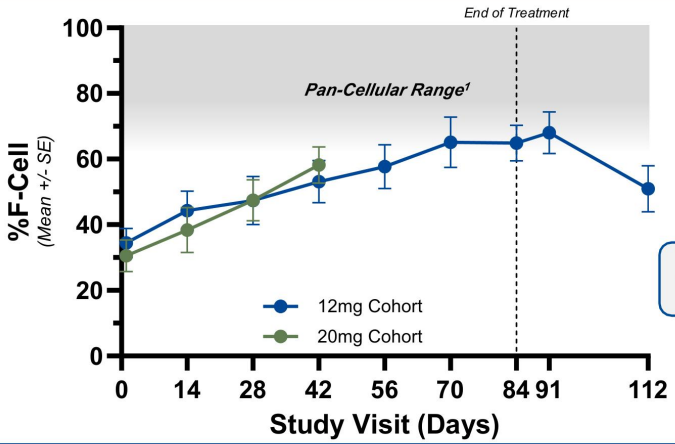
Data as of Nov 11, 2025 Data Cut

Mean %F-Cells



Consistent with 12 mg cohort, 20 mg cohort demonstrated similar progression towards Pan-Cellularity through 6 weeks of treatment

F-Cells are red blood cells that contain HbF, which increases their resistance to sickling and hemolysis. A higher proportion of F-cells is associated with improved red blood cell health.[1]

1. Dai et.al., 2017; Quinn et. al., 2021

F-Cell assay utilized - fluorescent-based flow cytometry assay

12mg cohort 3b analysis & figure includes available data from all patients regardless of transfusions during treatment period;

In progress 20 mg cohort PD Analysis Set (n=12). Analysis includes data through visits with complete laboratory data. No patients received transfusions during the treatment period.

Sample size varies across timepoints due to sample availability. 12 mg n=12 at Day 84. 20 mg n=9 at Day 42

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Pociredir 20 mg: Consistent reductions in Markers of Hemolysis

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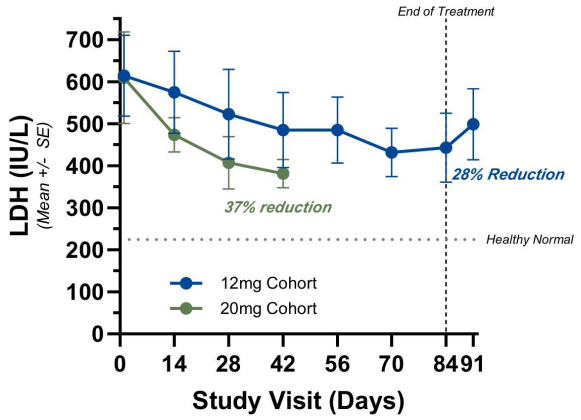
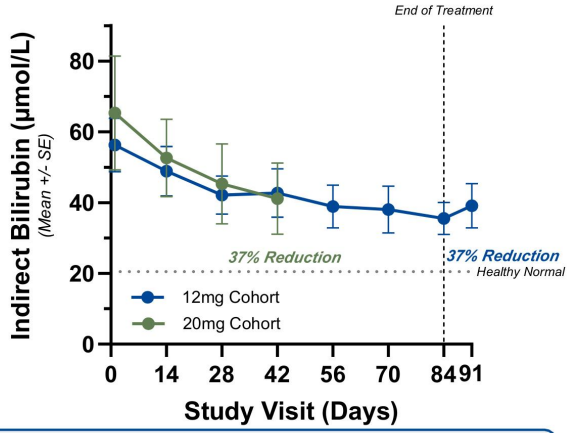
Data as of Nov 11, 2025 Data Cut

Mean Lactate Dehydrogenase (LDH)



LDH is an intracellular enzyme released into the blood in response to cell damage

Mean Indirect Bilirubin



Indirect bilirubin rises with red blood cell destruction

12 mg cohort 3b analysis & figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
In progress 20 mg cohort PD Analysis Set (n=12). Analysis includes data through visits with complete laboratory data. No patients received transfusions during the treatment period.

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Pociredir 20 mg: Consistent Improvements in Red Blood Cell Morphology and Erythropoiesis

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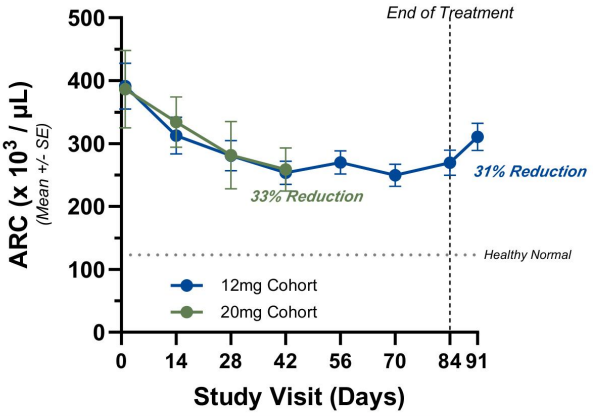
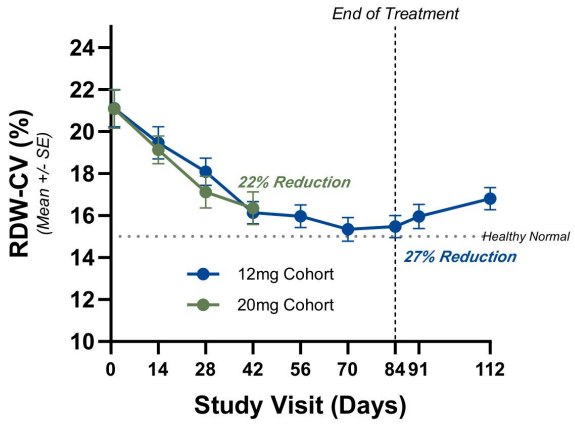
Data as of Nov 11, 2025 Data Cut

Mean Absolute Reticulocyte Count (ARC)



Reductions in reticulocytes accompanied by increases in hemoglobin indicate reduced stress erythropoiesis

Mean Red Cell Distribution Width (RDW-CV)



Normalization of RDW-CV indicates a more uniform red blood cell population

12 mg cohort 3b analysis & figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
In progress 20 mg cohort PD Analysis Set (n=12). Analysis includes data through visits with complete laboratory data. No patients received transfusions during the treatment period.

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Pociredir 20 mg: Reduction in Anemia

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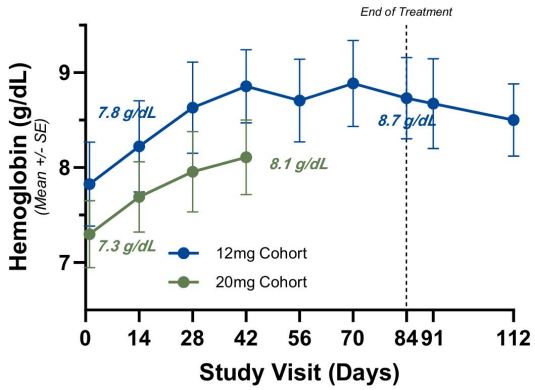
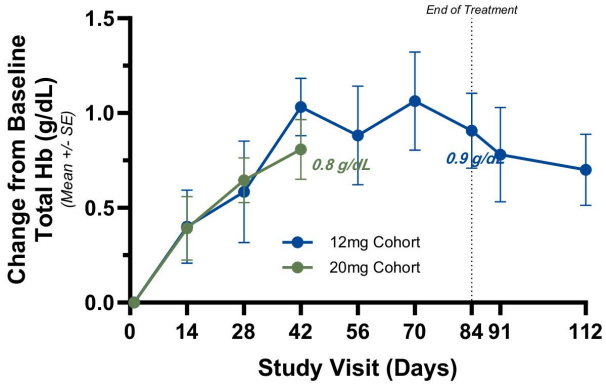
Data as of Nov 11, 2025 Data Cut

Mean Hemoglobin



Mean Change from Baseline Hemoglobin



Increases in hemoglobin are associated with improvements in fatigue, decreased risk of stroke, and improved overall survival[1]

12 mg cohort 3b analysis & figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
In progress 20 mg cohort PD Analysis Set (n=12). Analysis includes data through visits with complete laboratory data. No patients received transfusions during the treatment period.

1. Ataga, Am J Hematol. 2020; Adams, N Engl J Med. 1998, Mehari, Blood. 2012, Platt N Engl J Med. 1994,

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Pociredir 20 mg: Encouraging VOC Trends in a Severe SCD Population

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Data as of Nov 11, 2025 Data Cut

Baseline

Reported Baseline VOCs

- 2.40 over 6 months (n=5)
- 6.71 over 12 months (n=7)

→ 16 VOCs *expected* across the 12 patients over the 12-week Treatment Period[1]

Study Treatment Period

Observed VOCs in the Treatment Period as of Nov 11, 2025 Data Cut[2]

5 VOCs observed in 4 patients[3]

As of the Nov 11, 2025 data cut, 8 of 12 patients (67%) reported no VOCs in the 12-week treatment period

1. Expected VOCs derived from reported baseline VOCs for the PD Analysis Set – ((2.40 VOCs / 26 weeks)*5 patients) + ((6.71 / 52 weeks)*7 patients)) * 12 weeks
2. Nov 11, 2025 data cut includes 82% (59 of 72) of the post-baseline study visits in the treatment period
3. Additional 1 VOC observed in Safety Follow-up period as of data cut

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Pociredir 20 mg: Generally Well-tolerated with No Serious Treatment-related Adverse Events

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Data as of Nov 11, 2025 Data Cut

Adverse Event (AE)*	Cohort 4 (20 mg) n=13 (%)[a]
Patients with Adverse Events Regardless of Causality	11 (85)
Treatment-related AE	3 (23)
Grade ≥ 3 AEs	4 (31)
Grade ≥ 3 Treatment-related AEs	1 (8)
Serious adverse event (SAE)	4 (31)
SAEs consistent with VOC/SCD complications	4 (31)
Treatment-related SAE	0 (0)
AE with treatment interruption	1 (8)
AE with treatment discontinuation	1 (8)[b]

AE > 10% of Patients (n) with event*			Treatment-related AEs		
Preferred term	**n (%)**	**Highest Grade**	**Preferred term**	**# of AEs**	**Grade**
VOC	5 (38)	3	Reticulocytopenia (ARC)	1	3
Pain (back, extremity)	2 (15)	2	Insomnia	1	1
Fatigue	3 (23)	2	Iron overload	1	1
Malaria	3 (23)	2			
Arthralgia	2 (15)	1			
Headache	2 (15)	1			
Urinary tract infection	2 (15)	2			
Bone pain	2 (15)	2			

- 3 patients reported treatment-related AEs
  - All treatment-related AEs resolved during treatment period
  - Grade 3 Reticulocytopenia alongside broader CBC reductions in the context of a viral infection (presumed Parvo B19) and amoxicillin treatment. 14-day pociredir treatment interruption. Continued normalization of CBCs following re-exposure to pociredir.
- No dose limiting toxicities or dose discontinuations due to treatment-related AE
- A total of 6 VOCs reported on study at data cut
  - 1 of the 6 VOCs occurred in the safety follow-up period

*AEs in table are treatment-emergent AEs. AEs could be reported multiple times as individual symptoms during an event such as a VOC.

a. Safety Analysis Set

b. One discontinuation due to death (Grade 5 SAE). Death determined by the investigator unrelated to treatment following complications from VOC reported on Day 1 of study. Previously undisclosed hospital admissions for VOC on Days -7 and -1 prior to treatment. Cause of death: acute respiratory distress syndrome

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PIONEER 12mg and 20mg Safety Data to Date: Generally Well-tolerated with No Serious Treatment-related Adverse Events

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Data as of Nov 11, 2025 Data Cut

Adverse Event (AE)*	Cohort 3b (12 mg) n=16 (%)[a]	Cohort 4 (20 mg) n=13 (%)[a]
Patients with Adverse Events (AE) Regardless of Causality	15 (94)	11 (85)
Treatment-related AE	3 (19)	3 (23)
Grade ≥ 3 AEs	8 (50)	4 (31)
Grade ≥ 3 Treatment-related AEs	0 (0)	1 (8)
Serious adverse event (SAE)	5 (31)	4 (31)
SAEs consistent with VOC/SCD complications	5 (31)	4 (31)
Treatment-related SAE	0 (0)	0 (0)
AE with treatment interruption	1 (6)	1 (8)
AE with treatment discontinuation	0 (0)	1 (8)[b]

- AE profile consistent with severe sickle cell disease
- No dose limiting toxicities or dose discontinuations due to treatment related adverse events
- Following this 20 mg cohort, pociredir has been dosed in 148 adults to date
  - 103 healthy subjects
  - 45 patients with SCD

* AEs in table are treatment-emergent AEs.
a. Safety Analysis Set
b. One discontinuation due to death (Grade 5 SAE). Death determined by the investigator unrelated to treatment following complications from VOC reported on Day 1 of study. Previously undisclosed hospital admissions for VOC on Days -7 and -1 prior to treatment. Cause of death: acute respiratory distress syndrome

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Initial 20 mg cohort data raises the bar on Pociredir's Best-in-Class Potential

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12 mg established pociredir's Best-in-Class Potential as a QD oral therapy for SCD

- Generally well-tolerated at 12 mg
- 5.6% mean absolute increase in HbF at Week 6 / 8.6% at Week 12
- 44% of patients (7/16) reaching ≥20% HbF at Week 12
- 2.4-fold induction of HbF at Week 12 in 16 patients
- Demonstrated pan-cellularity and improvements in anemia and hemolysis
- Encouraging trends in VOC reduction over 12 weeks

Initial 20 mg cohort data raises the bar on pociredir's Best-in-Class Potential

- Continued evidence of pociredir being generally well-tolerated at 20 mg
- 9.9% mean absolute increase in HbF at Week 6 for the full cohort (n=12)
- 58% of patients (7/12) reaching ≥20% HbF at their last study visit
- >3.75-fold induction of HbF at 12 weeks in the six patients who completed the treatment period
- Continued progression towards pan-cellularity and improvements in anemia and hemolysis
- Continued encouraging trends in VOC reduction

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20 mg cohort data as of Nov 11, 2025 Data Cut. 6 of 12 patients in the PD Analysis Set completed treatment period as of data cut

Agenda for Investor Call

Introduction	**Alex C. Sapir,** President & CEO
Sickle Cell Disease (SCD) and the Potential of a Once Daily Oral HbF-Inducer	**Iain Fraser MBChB, D.Phil**, SVP Early Clinical Development
PIONEER Study Overview and 20 mg Pociredir Cohort Data Update	**Sheinei Alan, M.D., Ph.D.,** Director, Inova Adult Sickle Cell Program & Assistant Professor, UVA School of Medicine
Expert Perspective on Pociredir and Its Potential as a Once Daily Oral HbF-Inducer for Treating SCD	**Martin H. Steinberg, M.D.,** Professor of Medicine, Pediatrics, Pathology and Laboratory Medicine at Boston University Chobanian & Avedisian School of Medicine
Q&A	**Fulcrum Management, Drs. Alan and Steinberg**
Closing Remarks	**Alex C. Sapir,** President & CEO

Expert Perspective on HbF Induction and Clinical Benefit in SCD Patients

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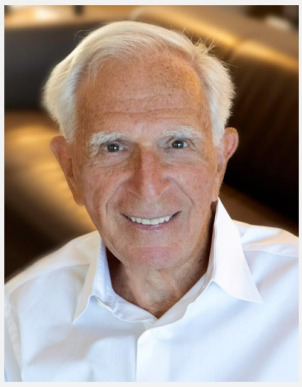

Martin H. Steinberg, M.D.

Professor of Medicine, Pediatrics, Pathology and Laboratory Medicine at Boston University Chobanian & Avedisian School of Medicine

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20 mg cohort advancing Pociredir to next program milestones

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Key Next Steps

1. Complete 20 mg Cohort and share updated results in Q1 2026
2. Prepare for End of Phase 1 meeting with FDA anticipated in H1 2026
3. Begin enrolling PIONEER patients in Open Label Extension (OLE) study in H1 2026
4. Continue finalizing a planned registrational study (pending regulatory feedback) to commence in H2 2026

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Q&A

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We thank the patients, caregivers, investigators and their staff who participated in PIONEER