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): July 29, 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 2.02 Results of Operations and Financial Condition.

On July 29, 2025, Fulcrum Therapeutics, Inc., or Fulcrum, announced its financial results for the quarter ended June 30, 2025. The full text of the press release issued in connection with the announcement is being furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

The information in this Item 2.02, including Exhibit 99.1 attached hereto, shall not be deemed "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, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

On July 29, 2025, Fulcrum announced results from the 12 mg dose cohort of its Phase 1b clinical trial of pociredir in sickle cell disease, or SCD, following conclusion of the 12-week treatment period (n=16). Results are as follows:

- Mean absolute fetal hemoglobin, or 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 vaso-occlusive crises, or 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 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 (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 adverse events, or 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); three VOCs occurred during the follow-up period as of the June 26, 2025 data cut-off date.
- 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 serious adverse events and no discontinuations due to treatment-emergent adverse events through the completion of the 12 mg dose cohort. In addition, all treatment-related adverse events 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).

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

99.1+	Press Release issued July 29, 2025, announcing financial results for the quarter ended June 30, 2025
99.2*	Presentation issued July 29, 2025, announcing results from the 12 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: July 29, 2025

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

Exhibit 99.1

Fulcrum Therapeutics Announces Recent Business Highlights and Financial Results for Second Quarter 2025

— Announced results from the 12 mg dose cohort (n=16) of the Phase 1b PIONEER trial of pociredir in sickle cell disease (SCD); pociredir was generally well-tolerated with no treatment-related serious adverse events (SAEs) —

— Observed robust and rapid pan-cellular increases in fetal hemoglobin (HbF); meaningful improvements in key markers of hemolysis and anemia; encouraging trends in vaso-occlusive crises (VOCs) —

— On track to provide clinical data from the 20 mg dose cohort by the end of 2025 —

— Ended Q2 2025 with $214.1 million in cash, cash equivalents, and marketable securities; cash runway into 2028 —

CAMBRIDGE, Mass., – July 29, 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 financial results for the second quarter of 2025 and provided a business update.

"Fulcrum has made substantial progress this quarter, having reported very promising results from the 12 mg cohort of the PIONEER trial," said Alex C. Sapir, Fulcrum's President and Chief Executive Officer. "We believe that this data demonstrates that pociredir has the potential to increase fetal hemoglobin to levels that could ameliorate SCD symptomology and transform the standard of care with a once daily oral treatment option. We look forward to reporting the 20 mg data later this year and progressing pociredir into later-stage development."

Recent Business Highlights

- Announced results from the 12 mg dose cohort of the PIONEER trial, following conclusion of the 12-week treatment period. Results included a robust mean increase of 8.6% in HbF, evidence of pan-cellular induction of HbF shown by a mean of 67% F-cells, improvements in markers of hemolysis and a 0.9 g/dL increase in total hemoglobin, and encouraging trends in VOC reductions. Pociredir was generally well-tolerated, with no drug-related SAEs and no discontinuations due to treatment-emergent adverse events through the completion of the 12 mg dose cohort. In addition, all treatment-related AEs through completion of the 12 mg dose cohort were Grade 1.
- The 20 mg dose cohort is ongoing, and Fulcrum plans to share data from this cohort by the end of 2025.
- Two abstracts were presented at the 2025 European Hematology Association (EHA) Congress in Milan, Italy, which took place June 12-15, 2025. The abstracts highlight preclinical target engagement and gene expression reversibility data of pociredir and clinical data from our previously completed Phase 1 healthy volunteer study.
- Fulcrum continues to advance its program for the potential treatment of inherited aplastic anemias, such as Diamond-Blackfan anemia (DBA), Shwachman-Diamond syndrome, and Fanconi anemia, and plans to submit an investigational new drug application (IND) for DBA during the fourth quarter of 2025.

Second Quarter 2025 Financial Results

- **Cash Position:** As of June 30, 2025, cash, cash equivalents, and marketable securities were $214.1 million, as compared to $241.0 million as of December 31, 2024. The decrease of $26.9 million is primarily due to cash used to fund operating activities in 2025.
- **Collaboration Revenue:** Collaboration revenue was zero for the three months ended June 30, 2025, as compared to $80.0 million for the three months ended June 30, 2024. The decrease of $80.0 million was primarily due to the recognition of the $80.0 million upfront license payment received from Sanofi during the second quarter of 2024.
- **R&D Expenses:** Research and development expenses were $13.0 million for the three months ended June 30, 2025, as compared to $17.3 million for the three months ended June 30, 2024. The decrease of $4.3 million was primarily due to decreased employee compensation costs as a result of the reduction in workforce implemented in the third quarter of 2024 as well as decreased costs associated with the discontinuation of our losmapimod program, partially offset by increased costs related to the advancement of the Phase 1b PIONEER trial of pociredir.
- **G&A Expenses:** General and administrative expenses were $6.8 million for the three months ended June 30, 2025, as compared to $10.2 million for the three months ended June 30, 2024. The decrease of $3.4 million was primarily due to decreased professional services costs as well as decreased employee compensation costs as a result of the reduction in workforce implemented in the third quarter of 2024.
- **Net Loss:** Net loss was $17.3 million for the three months ended June 30, 2025, as compared to net income of $55.4 million for the three months ended June 30, 2024.

Updated Cash Runway Guidance

Based on its current operating plans, Fulcrum now expects that its current cash, cash equivalents, and marketable securities will be sufficient to fund its operating requirements into 2028.

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 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 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 Fulcrum’s Phase 1b PIONEER clinical trial of pociredir, including planned data announcement for such trial; the potential of pociredir to increase HbF to levels that could ameliorate symptoms of SCD and transform the standard of care; Fulcrum’s ability to progress its early stage development programs and planned IND filings related thereto; and its projected cash runway, 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; realizing 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.

Fulcrum Therapeutics, Inc.

Selected Consolidated Balance Sheet Data

(In thousands)

(Unaudited)

	June 30, 2025	December 31, 2024
Cash, cash equivalents, and marketable securities	$ 214,111	$ 241,021
Working capital[(1)]	210,388	238,879
Total assets	228,838	260,718
Total stockholders' equity	214,378	243,034

(1) Fulcrum defines working capital as current assets minus current liabilities.

Fulcrum Therapeutics, Inc.

Consolidated Statements of Operations

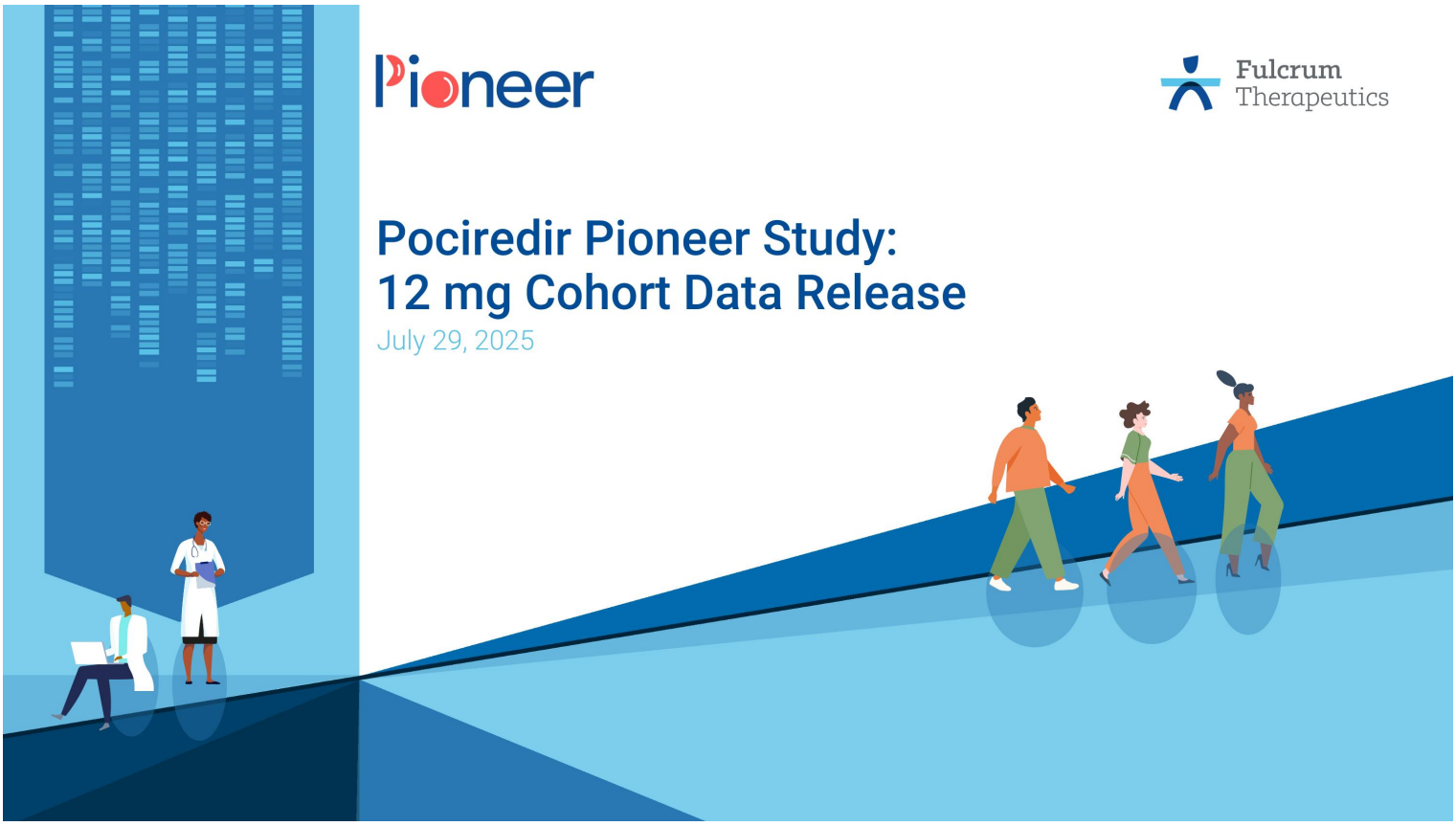
(In thousands, except per share data)

(Unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Collaboration revenue	—	80,000	—	80,000
Operating expenses:				
Research and development	12,987	17,261	26,391	37,034
General and administrative	6,828	10,247	13,827	20,308
Total operating expenses	19,815	27,508	40,218	57,342
(Loss) income from operations	(19,815)	52,492	(40,218)	22,658
Other income, net	2,519	2,917	5,267	5,881
Net (loss) income	$ (17,296)	$ 55,409	$ (34,951)	$ 28,539
Net (loss) income per share, basic	$ (0.28)	$ 0.89	$ (0.56)	$ 0.46
Net (loss) income per share, diluted	$ (0.28)	$ 0.87	$ (0.56)	$ 0.45
Weighted-average common shares outstanding, basic	62,544	62,205	62,506	62,095
Weighted-average common shares outstanding, diluted	62,544	63,587	62,506	63,684

Contact:

Alan Musso
Chief Financial Officer
amusso@fulcrumtx.com



Pioneer

Fulcrum Therapeutics

Pociredir Pioneer Study: 12 mg Cohort Data Release

July 29, 2025

Disclaimer and Notice

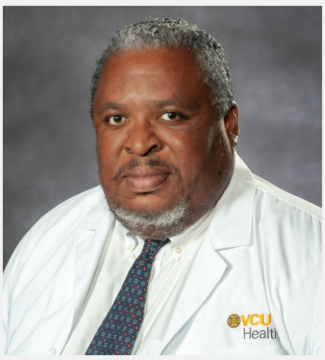
This presentation contains "forward-looking statements" of Fulcrum Therapeutics, Inc. (Fulcrum or Fulcrum Therapeutics) within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including express or implied statements regarding Fulcrum's goals for pociredir, pociredir's best-in-class potential for the treatment of sickle cell disease, pociredir's ability to induce fetal hemoglobin, vaso-occlusive crises during 12-week treatment period, enrollment in additional cohorts and 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; 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.

Unless otherwise indicated in this presentation, 12 mg data (n=16) discussed herein relates to cohort 3b. The incomplete prior 12 mg cohort (3a) conducted prior to study hold not included in this analysis.

Today's Guest Speakers

Sheinei Alan, M.D.

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



Wally Smith, M.D.

Director, VCU Adult Sickle Cell Program & Florence Neal Cooper Smith Professor of Sickle Cell Disease at Virginia Commonwealth University

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

Agenda for Investor Call

Introduction	**Alex 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 12 mg Pociredir Cohort Data Update	**Sheinei Alan, M.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	**Wally Smith, M.D.,** Director, VCU Adult Sickle Cell Program and Professor, VCU School of Internal Medicine
Q&A	**Fulcrum Management, Drs. Alan and Smith**
Closing Remarks	**Alex Sapir,** President & CEO

Addressing the Significant Unmet Need in Sickle Cell Disease via Fetal Hemoglobin (HbF) Induction

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)

Pociredir's Best-in-Class Potential as a once daily oral therapy for SCD informed by 12 mg cohort results

- ✓ Pociredir, Once-Daily Oral, generally well-tolerated with treatment-related AEs limited to Grade 1
- ✓ 8.6% mean absolute increase in Fetal Hemoglobin (HbF) at 12 weeks
- ✓ Evidence of pan-cellularity shown by a mean 67% F-Cells at 12 weeks
- ✓ 0.9 g/dL mean increase in hemoglobin (Hb) with an improvement in all key markers of hemolysis
- ✓ Encouraging trends in VOC reduction over 12 weeks

Pioneer

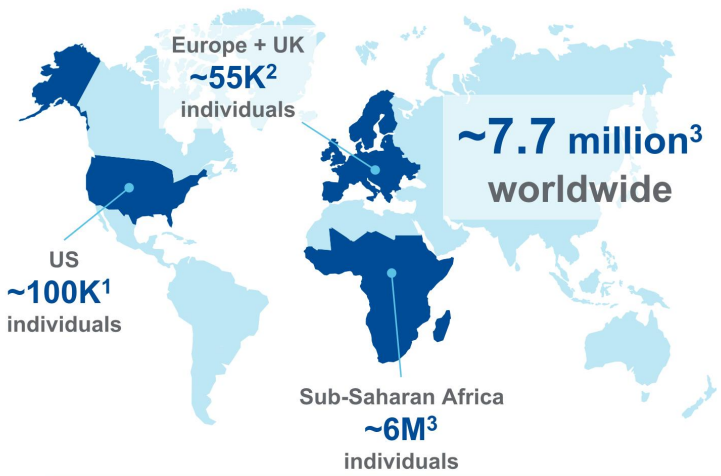
Agenda for Investor Call

Introduction	**Alex 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 12mg Pociredir Cohort Data Update	**Sheinei Alan, M.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	**Wally Smith, M.D.,** Director, VCU Adult Sickle Cell Program and Professor, VCU School of Internal Medicine
Q&A	**Fulcrum Management, Dr. Alan and Dr. Smith**
Closing Remarks	**Alex 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

Fulcrum Therapeutics

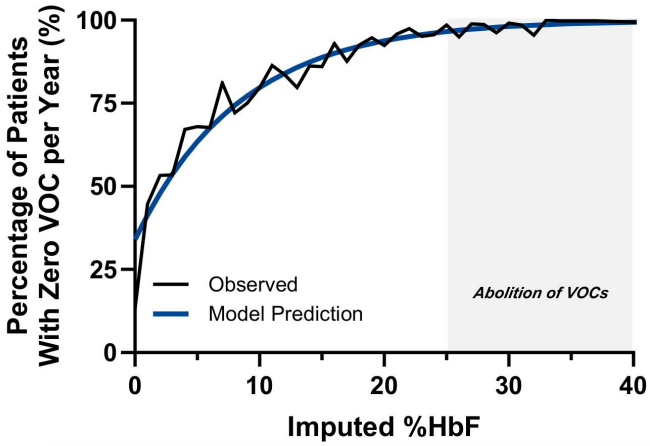
Each 1% increase in %HbF…

…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]



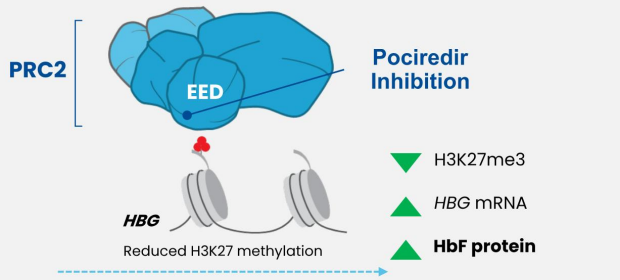
HbF levels greater than mid-20% results in near abolition of VOCs[2]

Pioneer

HbF, fetal hemoglobin; VOC, vaso-occlusive crisis.
1. Peter Bruun-Rasmussen. ASH 2024 (poster #1124).
2. Unpublished data from Fulcrum analysis of Picnic Health real-world dataset, n=673; ≥2 years ; mean HbF 8.6% - Data accepted for Publication at ASCAT 2025

Targeting EED Results in HbF Increases

Pociredir Is a Potent and Selective EED Binder



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

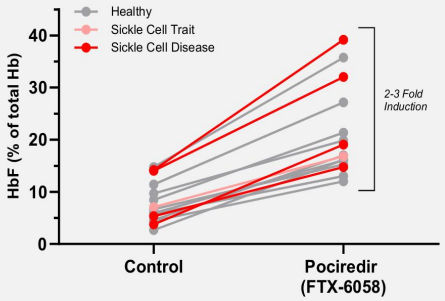
- EED inhibition targets known modulators of HbF, including *BCL11A* and *MYB*[1]
- Pociredir is a potent EED binder[1]
  - Highly selective
  - Clean off-target profile
  - Robust target engagement observed at doses as low as 2 mg

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

Evidence Generated to Date Highlights Pociredir's Potential as an HbF Inducer in SCD

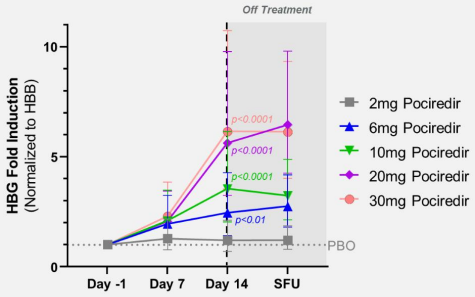
Fulcrum Therapeutics

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



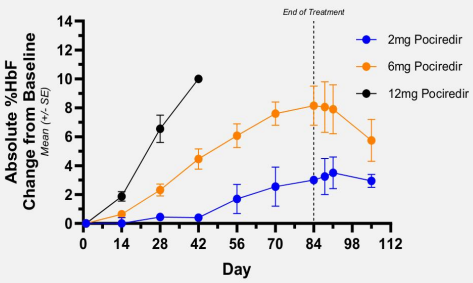
- 8 – 25% absolute increase in %HbF
- Consistent 2-3 fold induction across both healthy subject and SCD CD34+ donor-derived cells

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: Absolute %HbF Change from Baseline in SCD Patients



- Time- and Dose-related HbF induction in previous Pioneer Cohorts (2 mg, 6 mg, 12 mg)[2]
- All-comer adult SCD population with no requirement for disease severity

Previously Disclosed Fulcrum Data

1. N=6 per cohort
2. 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 cutoff of March 3, 2023. 12mg cohort N=1 at Day 42, 6mg cohort N=2 at Day 84, 2 mg cohort N=2

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Agenda for Investor Call

Introduction	**Alex 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 12 mg Pociredir Cohort Data Update	**Sheinei Alan, M.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	**Wally Smith, M.D.,** Director, VCU Adult Sickle Cell Program and Professor, VCU School of Internal Medicine
Q&A	**Fulcrum Management, Dr. Alan and Dr. Smith**
Closing Remarks	**Alex Sapir,** President & CEO

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

Fulcrum Therapeutics

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) — Completed
- **Cohort 2** 2 mg (n=2) — Completed
- **Cohort 3a** 12 mg (n=4) — Completed
- **Cohort 3b** 12 mg (n=16)[a] — 12 mg Cohort 3b data shared today — Completed
- **Cohort 4** 20 mg — Enrolling

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[a]

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.
[a] The incomplete prior 12 mg cohort (3a) conducted prior to study hold not included in this analysis
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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12 mg Cohort Patient Disposition as of June 26th Data Cut

Patients Enrolled	N= 16
Patients Completing 12-week Treatment Period	N= 16
Completed Study including Safety Follow-up (as of Jun 26)	N= 9
Patients Remaining in Safety Follow-up (as of Jun 26)	N= 7

- No patients discontinued study or treatment early. High adherence (98%) to treatment schedule[1]
- Safety Data presented includes all 12 mg data as of June 26th data cut
- Efficacy Data from the 12 mg cohort treatment period for all 16 patients will be presented today
- 12 mg cohort data including the 4-week follow-up period will be shared at a future medical meeting

Disposition and all subsequent data as of June 26th, data cut

[1] Adherence measured via AiCure®, an artificial intelligence data collection tool providing real-time feedback and data collection to measure and improve study drug adherence

12 mg Cohort Baseline Demographics and Characteristics

	Pociredir 12 mg; N=16 % or mean (SD)
Sex, % Male	44%
Age, Years	34.3 (12.25)
Country	
US	62.5%
South Africa	37.5%
Genotype	
Hb SS	87.5%
Hb Sβ^0	12.5%
Baseline HbF (%)	7.6% (4.7)
Baseline Hb (g/dL)	7.8 (1.8)
Baseline VOCs	
Reporting over 6 months (N=6)	2.83
Reporting over 12 months (N=10)	5.20

Dose-Related Pociredir Exposure PK in Sickle Cell Disease Patients

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Pociredir PK Data from Ph 1 Healthy Volunteer study Demonstrated[1]:

- PK supports once-daily oral dosing ($t_{1/2}$ ~ 5.6-7.3 hrs), with dose-dependent increases in plasma exposure
  - Dose-related induction of HBG mRNA over range of 2 mg - 30 mg
- No food effect or induction of CYP3A

Plasma PK Comparison between 6 mg and 12 mg 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)

Plasma PK in 12 mg QD cohort showed dose-related increase in exposure from 6 mg QD cohort

[1] Minitti et. al., EHA 2025

Pociredir 12 mg: Achieved Robust and Clinically Relevant increases in Fetal Hemoglobin (HbF)

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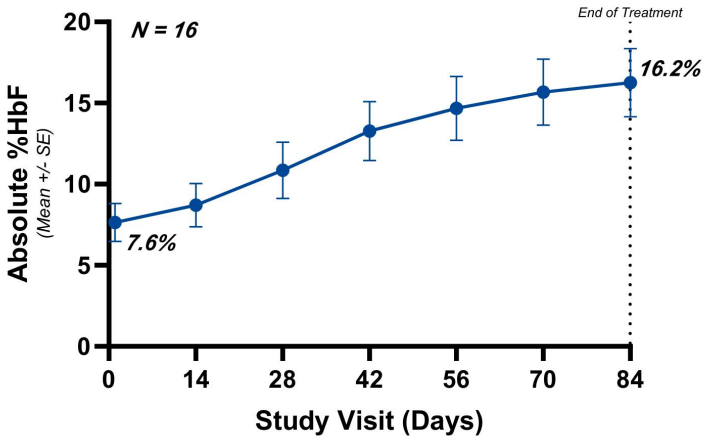
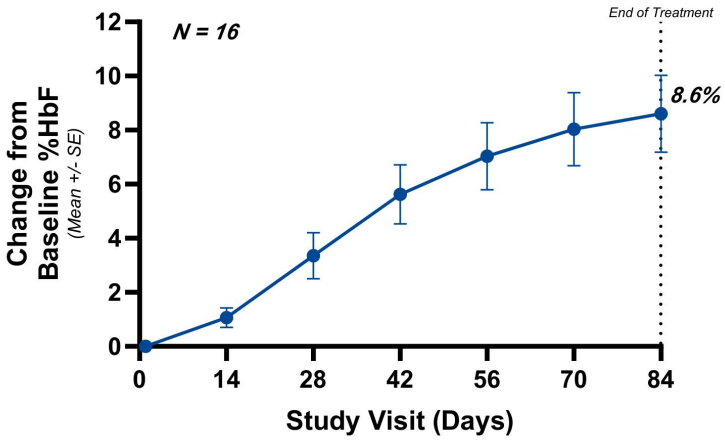
Mean Absolute %HbF



Pociredir increased %HbF from 7.6% to 16.2%

Mean Absolute %HbF Change from Baseline



Pociredir increased %HbF 8.6% by 12 weeks

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Analysis & Figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
Excluding Patients with multiple transfusions (patients 13 and 16) yields: 17.8% Mean Absolute %HbF and 9.5% Mean Absolute Change from Baseline at Week 12

Pociredir 12 mg: Increased HbF in all Patients

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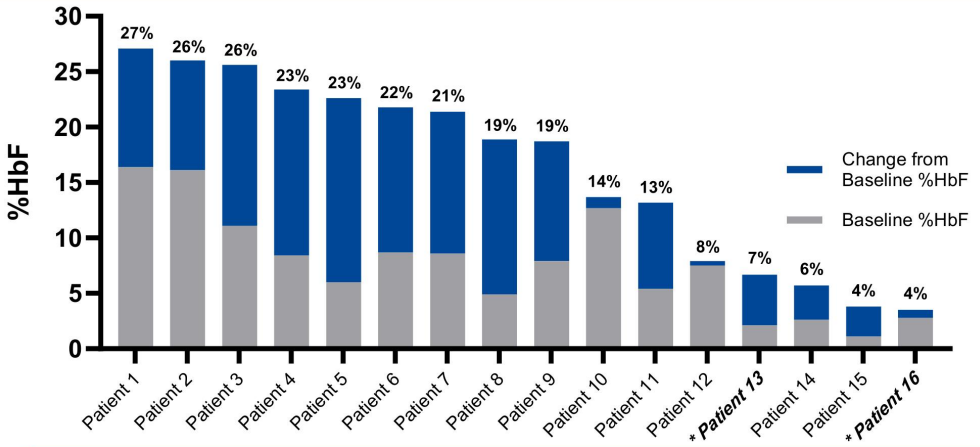
Baseline %HbF and Change from Baseline %HbF at Week 12



- All 16 patients saw an increase in HbF
- 8 of 16 patients (50%) achieved a >10% absolute increase in %HbF by week 12

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* Patient 13 and Patient 16 received multiple transfusions over the 12-week treatment period. Transfusions will increase total hemoglobin (HbA) leading to an iatrogenic reduction in %HbF. Subsequent slides include sensitivity analysis in footnotes excluding Patient 13 and Patient 16

Pociredir 12 mg: Meaningful Thresholds of %HbF Reached

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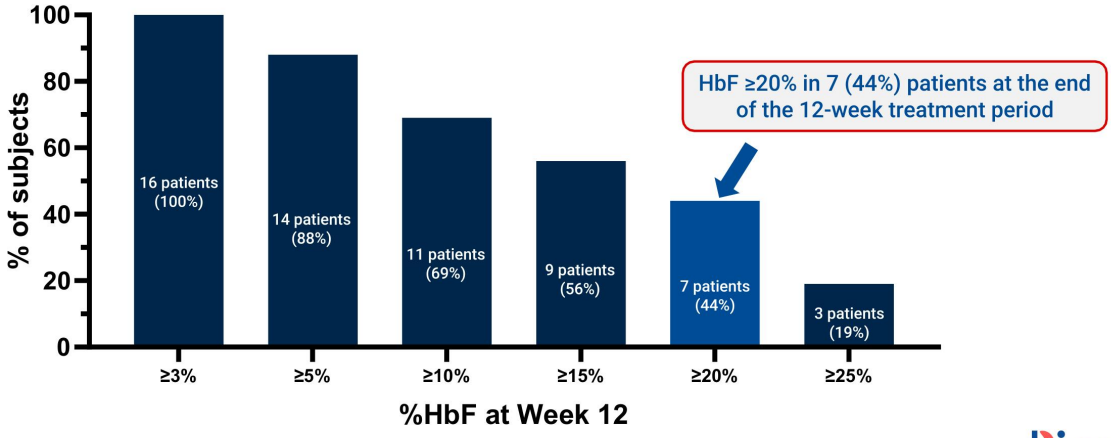
%HbF Threshold Achieved after 12 Weeks of Treatment



Analysis & Figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
Excluding patients with multiple transfusions (patients 13 and 16) yields: HbF ≥ 20% in 7 of 14 (50%) patients at the end of the 12-week treatment period

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Pociredir 12 mg: F-cell Data Consistent with Pan-Cellular Induction

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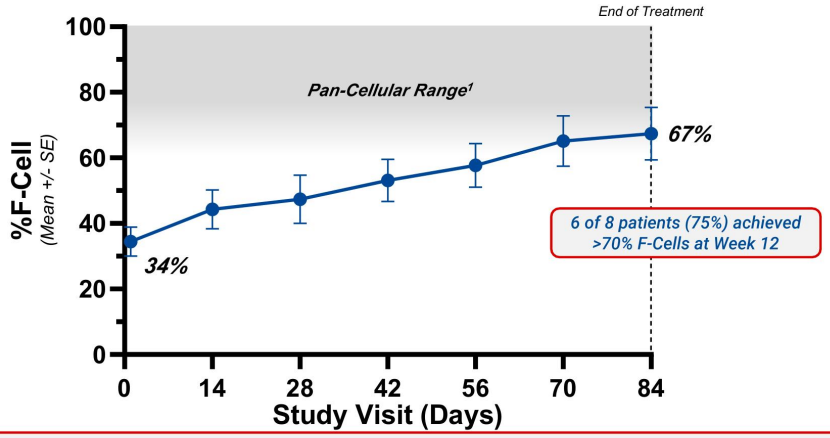
Mean %F-Cells



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
Analysis & Figure includes available data from all patients enrolled (n=16) regardless of transfusions during treatment period; Sample size varies across timepoints due to sample availability. N=8 at Week 12
Excluding patients with multiple transfusions (patients 13 and 16) yields: 72% Mean F-Cells at Week 12; 6 of 7 patients >70% F-Cells at Week 12

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Pociredir 12 mg: Reductions in Hemolysis

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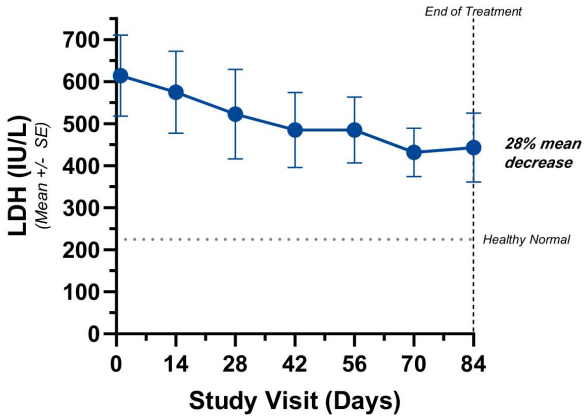
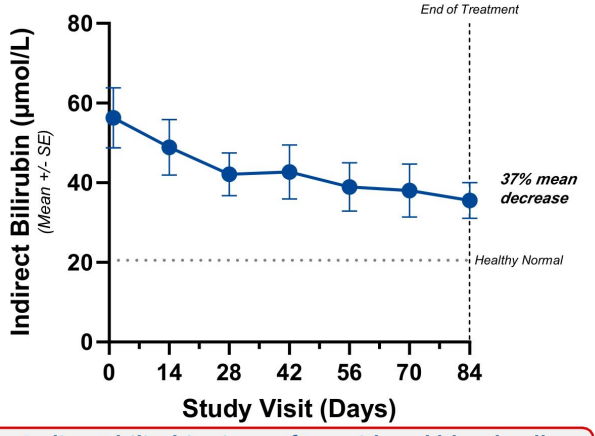
Mean Lactate Dehydrogenase (LDH)



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

Mean Indirect Bilirubin



Indirect bilirubin rises often with red blood cell destruction

Analysis & Figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
Excluding patients with multiple transfusions (patients 13 and 16) yields: 339 IU/L LDH and 35 µmol/L Indirect Bilirubin

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Pociredir 12 mg: Improved Red Blood Cell Morphology and Erythropoiesis

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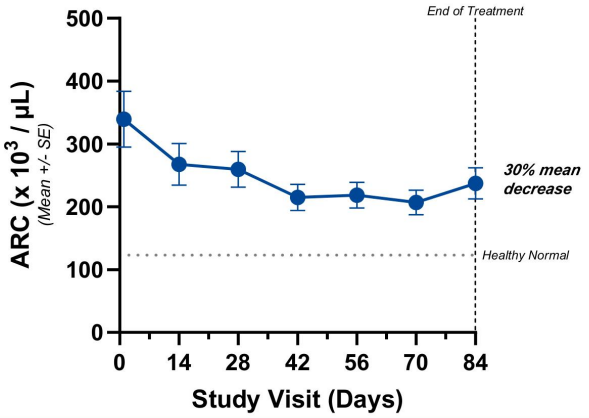
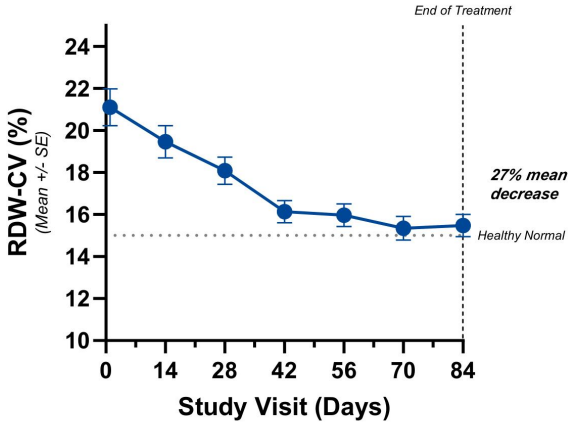
Mean Absolute Reticulocyte Count (ARC)



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

Mean Red Cell Distribution Width (RDW-CV)



Decreased RDW-CV indicates a more uniform red blood cell population

Analysis & Figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
Excluding patients with multiple transfusions (patients 13 and 16) yields: 259x10³ /µL ARC and 15.0% RDW-CV

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Pociredir 12 mg: Reductions in Anemia

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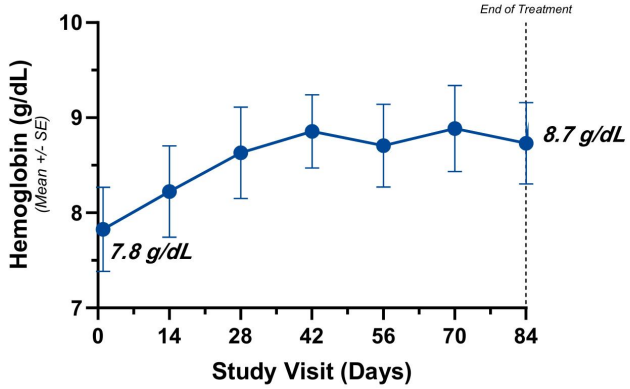
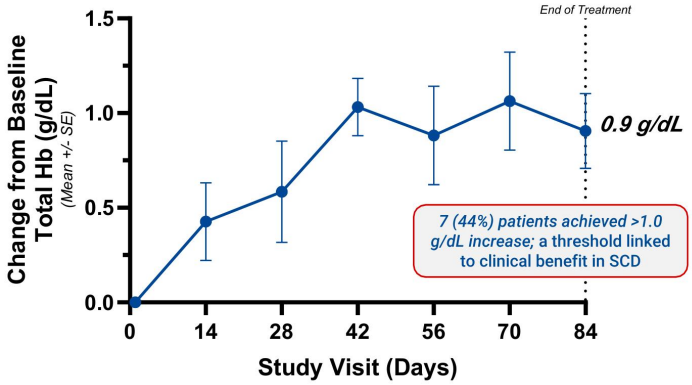
Mean Hemoglobin



Mean Change from Baseline Hemoglobin



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

Analysis & Figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
Excluding patients with multiple transfusions (patients 13 and 16) yields: 9.2 g/dL Hb and 1.0 g/dL Change from Baseline Hb

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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Encouraging VOC Trends in this Severe SCD Population

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Baseline

Reported Baseline VOCs

- 2.83 over 6 months (n=6)
- 5.20 over 12 months (n=10)

Expected VOCs over 12 weeks Treatment Period[1]

Average 1.25 VOCs per patient
(20 VOCs *expected* across 16 patients)

Study Treatment Period

Observed VOCs over 12 weeks

Average 0.56 per patient
(9 VOCs *observed* across 16 patients[2])

Eight of 16 patients (50%) reported no VOCs during the course of the treatment period (12 weeks)

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[1] Expected VOCs derived from Reported Baseline VOCs – ((2.83 VOCs / 26 weeks)*6 patients) + ((5.20 / 52 weeks)*10 patients)) * 12 weeks
[2] Additional 3 VOCs observed in Safety Follow-up period as of June 26th data cut

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

Event	Patients n=16 (%)
All Adverse Events (AE) Regardless of Causality	15 (94)
Treatment-related AE	3 (19)
Grade ≥ 3 AEs	7 (44)
Grade ≥ 3 Treatment-related AEs	0 (0)
Serious adverse event (SAE)	5 (31)
SAEs consistent with VOC/SCD complications	5 (31)
Treatment-related SAE	0
AE with treatment interruption	1 (6)

AE > 10% of Patients with event[2] (preferred term)			Treatment related AE		
Preferred term	**n (%)**	**Highest Grade**	**Preferred term**	**n**	**Grade**
VOC	8 (50)	3	Headache	1	1
Pain (back, extremity)	5 (31)	2	Nausea	1	1
Fatigue	4 (25)	2	Paresthesia (face)	1	1
Arthralgia	3 (19)	2	Diarrhea	1	1
Diarrhoea	2 (13)	2	Rhinorrhea	1	1
Constipation	2 (13)	2			
Vomiting	2 (13)	2			
Urinary tract infection	2 (13)	3			
Rash	2 (13)	2			
Acne	2 (13)	2			
Oedema peripheral	2 (13)	2			

- 3 patients reported treatment-related AEs; all were Grade 1 in severity
  - All related AEs resolved during treatment period
- No dose limiting toxicities or dose discontinuations due to related AE[1]
- A total of 12 VOC reported on study at data cut
  - 3 of 12 VOCs occurred off drug during the study follow-up period
- Following this 12 mg cohort, pociredir has been dosed in 135 adults to date
  - 103 healthy subjects
  - 32 SCD patients

Data as of June 26th Data Cut

[1] One discontinuation due to death (Grade 5 SAE) in 20 mg cohort. 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

[2] AEs (preferred terms) could be reported multiple times as individual symptoms during an event such as a VOC.

Addressing the Significant Unmet Need in Sickle Cell Disease via Fetal Hemoglobin (HbF) Induction

Fulcrum Therapeutics

Pociredir's Best-in-Class Potential as a once daily oral therapy for SCD informed by 12 mg cohort results

- ✓ Pociredir, once-daily oral, generally well-tolerated with treatment-related AEs limited to Grade 1
- ✓ 8.6% mean absolute increase in Fetal Hemoglobin (HbF) at 12 weeks
- ✓ Evidence of pan-cellularity as shown by a mean 67% F-Cells at 12 weeks
- ✓ 0.9 g/dL mean increase in hemoglobin (Hb) with an improvement in all key markers of hemolysis
- ✓ Encouraging trends in VOC reduction over 12 weeks

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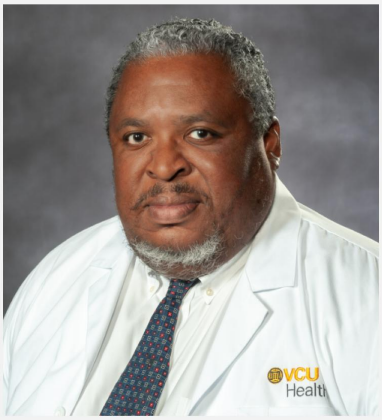
Agenda for Investor Call

Introduction	**Alex 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 12 mg Pociredir Cohort Data Update	**Sheinei Alan, M.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	**Wally Smith, M.D.,** Director, VCU Adult Sickle Cell Program and Professor, VCU School of Internal Medicine
Q&A	**Fulcrum Management, Dr. Alan and Dr. Smith**
Closing Remarks	**Alex Sapir,** President & CEO

Expert Perspective on HbF Induction and Clinical Benefit in SCD Patients



Wally Smith, M.D.
Director, VCU Adult Sickle Cell Program &
Professor School of Medicine at Virginia Commonwealth University

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Q&A

Strong 12 mg Data Driving Continued Pociredir Development

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Key Next Steps

1. **Continued 20 mg dose cohort enrollment**
   - N=6 enrolled as of July 25th - 1 discontinued[1]
2. **20 mg data release expected by the end of 2025**
3. **End of Phase 1 meeting with FDA anticipated in early 2026 to discuss initiation of next study**

[1] One discontinuation due to death (Grade 5 SAE) in 20 mg cohort. 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

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Addressing the Significant Unmet Need in Sickle Cell Disease via Fetal Hemoglobin (HbF) Induction

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)

Pociredir's Best-in-Class Potential as a once daily oral therapy for SCD informed by 12 mg cohort results

- ✓ Pociredir, Once-Daily Oral, generally well-tolerated with treatment-related AEs limited to Grade 1
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We thank the patients and their caregivers who participated in Pioneer, and our investigators and their teams