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): August 28, 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 August 28, 2025, Fulcrum Therapeutics, Inc., or Fulcrum, made available an updated corporate presentation that may be used in connection with presentations at conferences and investor meetings, which can be found in the "Events and Presentations" section on the Company's website. The corporate presentation is furnished as Exhibit 99.1 to this Current Report on Form 8-K and incorporated by reference in this Item 7.01.

The information in this Item 7.01, 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 9.01 Financial Statements and Exhibits.

(d) Exhibits

99.1+	Corporate Presentation Dated August 28, 2025
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

+ Furnished 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: August 28, 2025

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

Fulcrum Therapeutics

Nasdaq FULC

August 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, fetal hemoglobin (HbF) induction, vaso-occlusive crises (VOCs), enrollment in additional cohorts and timing of data releases, timing and outcomes of meetings and filings with the U.S. Food and Drug Administration (FDA), and Fulcrum’s cash runway, 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 obtain and maintain necessary approvals from the FDA and other regulatory authorities; to continue to advance pociredir and its other product candidates in clinical trials, including enrollment and completion; 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.

Unlocking the Power of Small Molecules to Change the Course of Genetically Defined Rare Diseases

Strategic Focus

- Developing oral small molecules designed to **modify gene expression** in rare diseases with a **focus on benign hematology**

Pociredir

- Potential **best-in class** oral small molecule HbF inducer for SCD
  - Demonstrated robust and rapid increase in HbF & Hb, and decreases in VOCs, hemolysis and anemia
- **Fast Track and Orphan Designations**
- Composition of Matter and Method of Use patent coverage through 2040
- Phase 1b PIONEER data disclosure
  - ✓ Cohort 3 (12 mg): **July 2025**
  - – Cohort 4 (20 mg): **YE 2025[1]**

Discovery & Cash Position

- Advancing discovery programs for pipeline sustainability
- IND submission for Diamond Blackfan Anemia (DBA) & Other Bone Marrow Failure Syndromes (BMFS) planned in Q4 2025
- Cash position of $214.1M as of 6/30/2025 with **runway into 2028**

HbF: Fetal hemoglobin; Hb: Hemoglobin; VOC: Vaso-occlusive crisis; IND: Investigational new drug application
[1]Enrollment open with N=6 enrolled with 1 discontinuation as of July 25, 2025

Small Molecule Pipeline Across Multiple Rare Diseases

Indication	Asset / Mechanism of Action	Preclinical	Phase 1	Phase 2	Phase 3
Clinical Programs					
Sickle Cell Disease	**Pociredir** (HbF Induction)				
Discovery Programs					
DBA & Other BMFS					
Novel HbF Inducers					
Fibrotic Disorders					
Undisclosed Program					

DBA: Diamond Blackfan Anemia; BMFS: Bone Marrow Failure Syndromes

Pociredir

for Sickle Cell Disease

Fast Track Designation
Orphan Drug Designation

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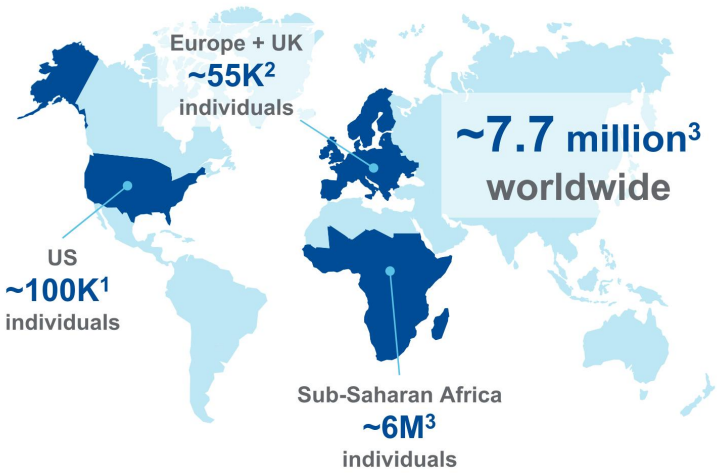
Sickle Cell Disease: Debilitating Disease with High Unmet Need

Global Impact



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 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]

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

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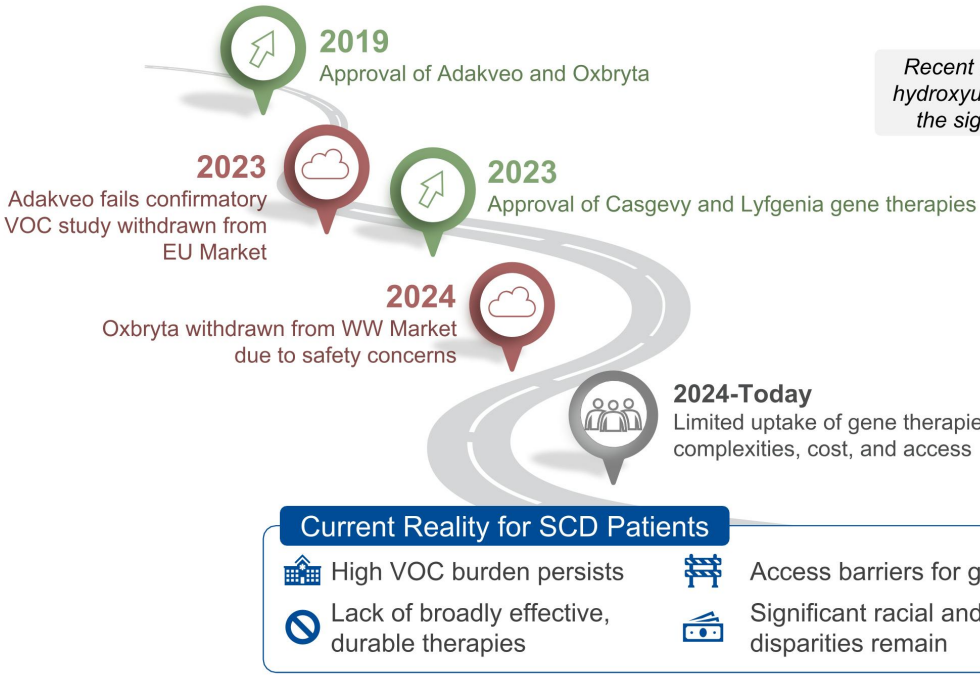
PIONEER 12 mg Cohort 3b: Addressing the Significant Unmet Need in SCD via HbF Induction

Pociredir's best-in-class potential as a once daily oral therapy for SCD informed by 12 mg cohort 3b results

- ✓ Pociredir, once-daily oral, generally well-tolerated with treatment-related AEs limited to Grade 1
- ✓ 8.6% mean absolute increase in 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 Hb with an improvement in all key markers of hemolysis
- ✓ Encouraging trends in VOC reduction over 12 weeks

SCD Unmet Need Remains High Despite Recent Therapeutic Advances



Recent additions of therapeutic options to the hydroxyurea standard of care have not satisfied the significant unmet need in SCD patients

Current Reality for SCD Patients

- High VOC burden persists
- Lack of broadly effective, durable therapies
- Access barriers for gene therapies
- Significant racial and socioeconomic disparities remain

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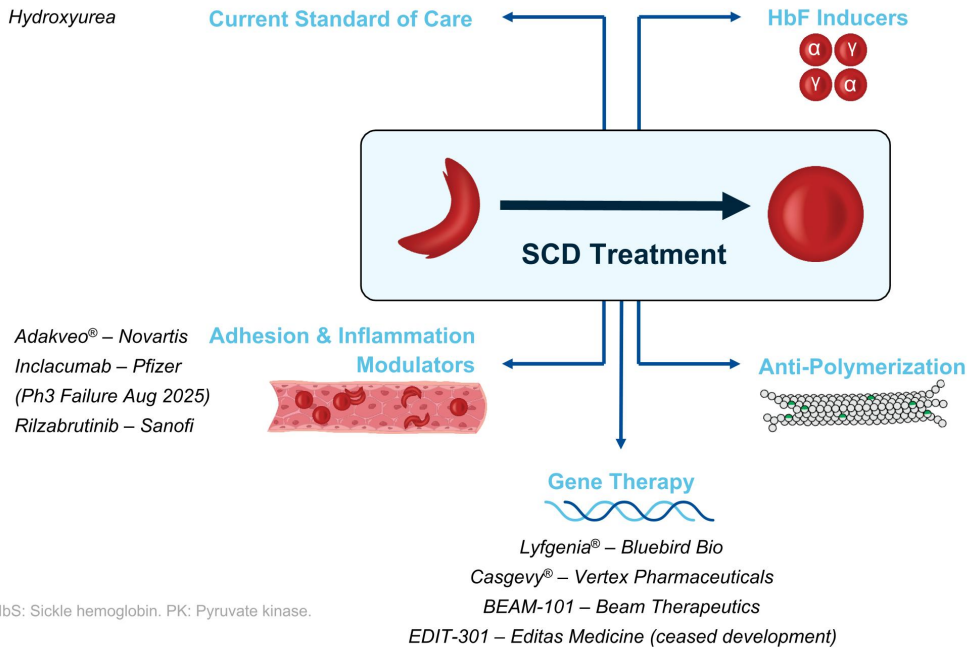
Competitive Landscape in SCD



Lyfgenia® – Bluebird Bio
Casgevy® – Vertex Pharmaceuticals
BEAM-101 – Beam Therapeutics
EDIT-301 – Editas Medicine (ceased development)

Pociredir – Fulcrum Therapeutics
BMS-986470 – Bristol Myers Squibb
ITU-512 – Novartis
Ndec (decitabine + tetrahydrouridine) – Novo Nordisk / EpiDestiny
CLY-124 – Cellarity
GSK-4172239D - GlaxoSmithKline

HbS Polymerization Inhibitors
Oxbryta® – Pfizer (withdrawn)
Osivelotor (GBT-601) – Pfizer (partial FDA clinical hold)

PK Activators
Mitapivat (AG-348) – Agios
Etavopivat (FT-4202) – Novo Nordisk
Tebapivat (AG-946) – Agios

HbS: Sickle hemoglobin. PK: Pyruvate kinase.

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Higher HbF Levels Result in Reduced Symptomology in People Living With SCD

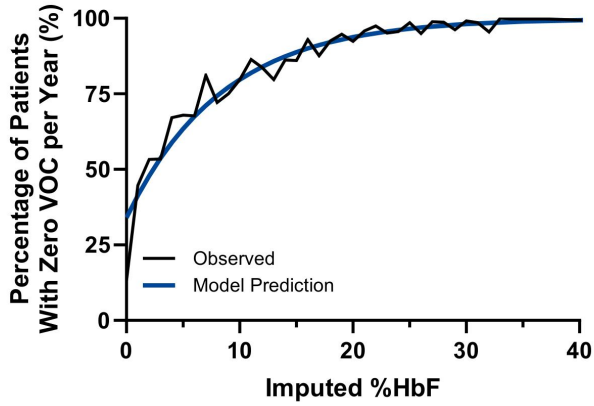
Each 1% increase in %HbF…

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

Raising HbF levels also results in:

- Reduced hemolysis
- Reduced anemia
- Fewer recurring events

Percent Observing Zero VOC/Year by %HbF[2]



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

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

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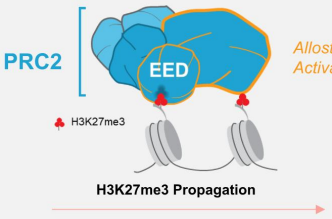
Pociredir Targets EED Resulting in HbF Increases

CRISPR + Compound Screening Engine
Experimentally screened candidate targets

Computational Data Mining
Computationally mined candidate targets

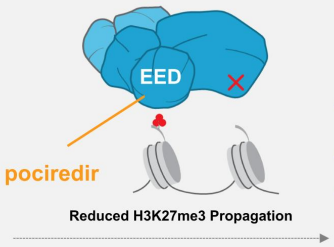
Identified Targets that Regulate HbF

Identified EED as a Novel Drug Target of Polycomb Repressor Complex 2



- ▲ H3K27me3
- ▼ HBG mRNA
- ▼ HbF Protein

Pociredir is a Potent and Selective EED Binder



- ▼ H3K27me3
- ▲ HBG mRNA
- ▲ HbF Protein

pociredir

- Highly Selective
- Clean Off-target Profile
- Composition of Matter Patent Expires 2040

EED: Embryonic Ectoderm; HbF: Fetal hemoglobin; HBG: Gamma globin gene (encodes mRNA for fetal hemoglobin)

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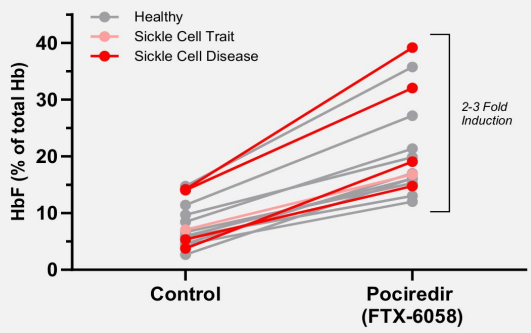
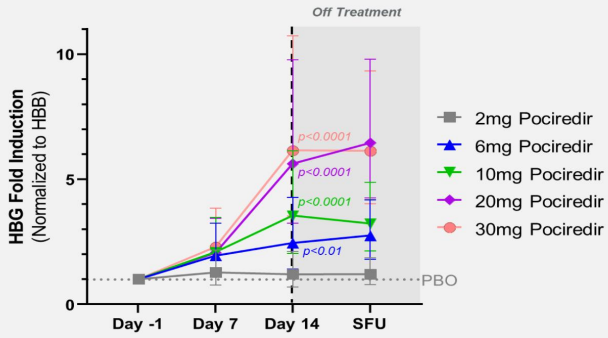
Evidence Generated to Date Highlights Pociredir's Potential as an HbF Inducer in SCD

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: HBG Induction in Healthy Volunteers



- Time- and dose-related HBG mRNA induction in healthy volunteer multiple ascending dose cohorts[1]

Previously Disclosed Fulcrum Data

1. N=6 per cohort

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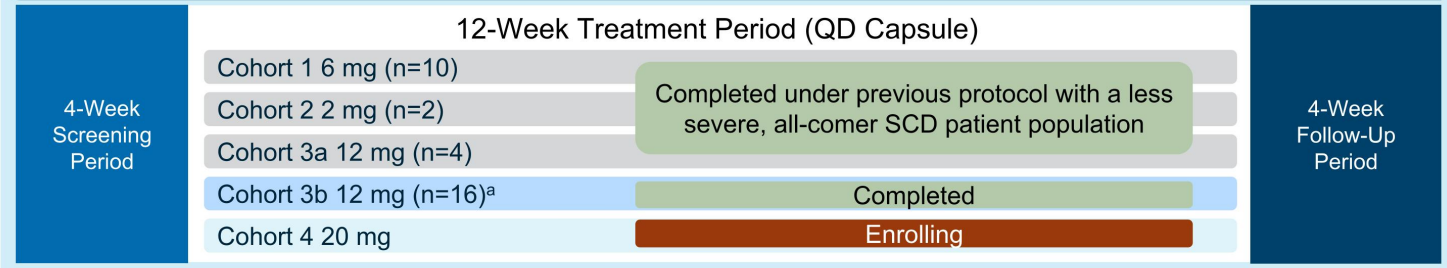
PIONEER: A Phase 1b Study in Patients With SCD

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



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
HU, hydroxyurea; QD, once daily; PK, Pharmacokinetic; F-Cells, Cells expressing HbF

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

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PIONEER Phase 1b Clinical Trial Sites

Active Sites

United States

- UT Houston (PI: Idowu)
- Queens Hospital Cancer Center (PI: Ferman)
- University of North Carolina (PI: Little)
- Jacobi Medical Center (PI: Rivlin)
- Lynn Health Sciences Institute (PI: Griffin)
- Virginia Commonwealth University (PI: Smith)
- Boston Medical Center (PI: Wilks)
- University of California Los Angeles (PI: Sehl)
- University of Arkansas (PI: Birrer)
- Lady of the Lake Hospital (PI: Stagg)
- Inova Cancer Center (PI: Alan)
- Sonar Clinical Research (PI: Powell)
- University of Illinois Chicago (PI: Saraf)

South Africa

- Wits Health Consortium (PI: Mahlangu)

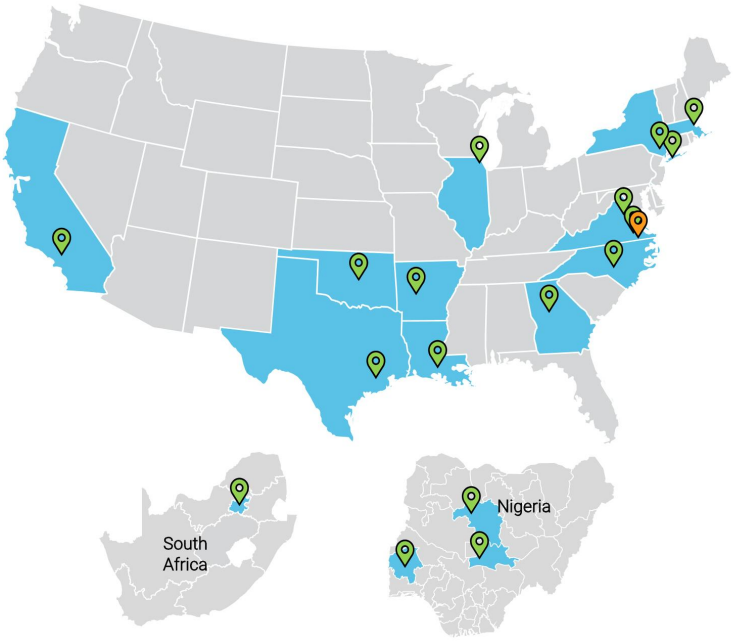
Nigeria

- National Hospital, Abuja (PI: Ojika)
- Barau Dikko Teaching Hospital, Kaduna (PI: Dogara)
- University of Ibadan (PI: Fasola)

Onboarding Sites

United States

- East Carolina University (PI: Liles)



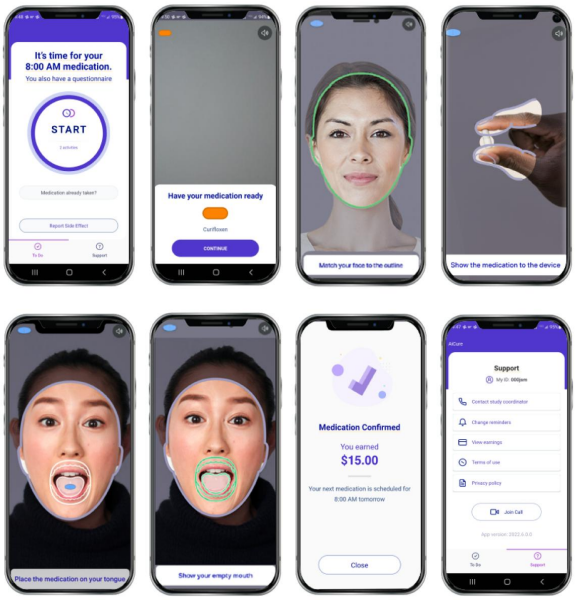
Clinical trial site status as of August 26, 2025

Utilizing Artificial Intelligence App from AiCure to Increase Study Drug Adherence

Improves Study Drug Adherence

Robust Data Collection

Real-Time Feedback to Clinical Trial Sites



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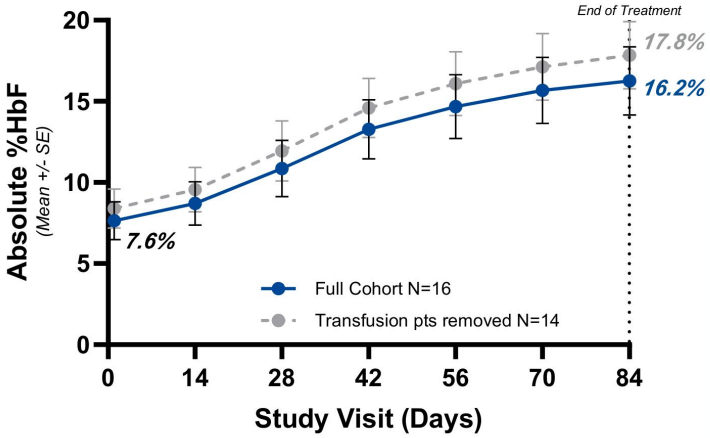
12 mg Cohort 3b Baseline Demographics and Characteristics

	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 $S\beta^0$	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

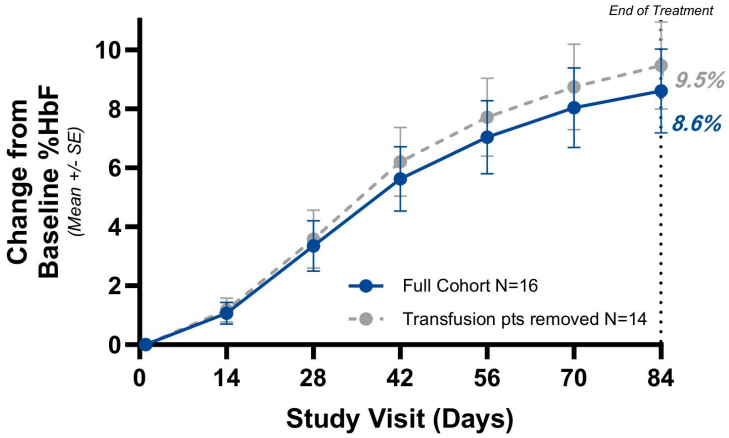
PIONEER 12 mg Cohort 3b: Achieved Robust and Clinically Relevant increases in HbF

Mean Absolute %HbF



Pociredir increased %HbF from 7.6% to 16.2%

Mean Absolute %HbF Change from Baseline

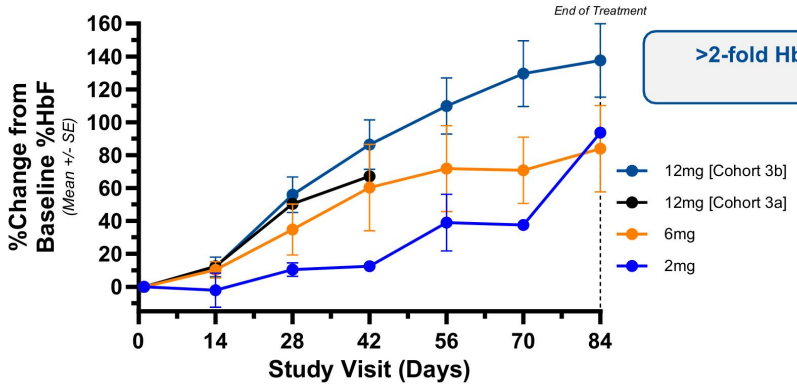


Pociredir increased %HbF 8.6% by 12 weeks

Analysis & Figure includes data from all patients enrolled (n=16) and data with transfusion patients (pts 13 and 16) removed (N=14)

PIONEER: 12 mg Cohort 3b Demonstrated Dose Response

% Change from Baseline HbF after 12 Weeks of Treatment



>2-fold HbF induction in 12 mg Cohort 3b

- **Latest 12 mg cohort data (Cohort 3b) demonstrated a clear dose-dependent increase in % change in HbF, consistent with dose response observed in phase 1 Healthy Volunteer HBG mRNA data**
- **% Change from Baseline accounts for differences in baseline HbF levels across cohorts**
  - Higher baseline HbF, smaller sample sizes, and less severe patient population in prior cohorts impair ability to make direct comparisons of Absolute HbF to the latest 12 mg cohort (Cohort 3b)

12mg cohort 3b includes data from all patients enrolled (n=16).

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 3a N=1 at Day 42, 6mg cohort N=2 at Day 84, 2 mg cohort N=1

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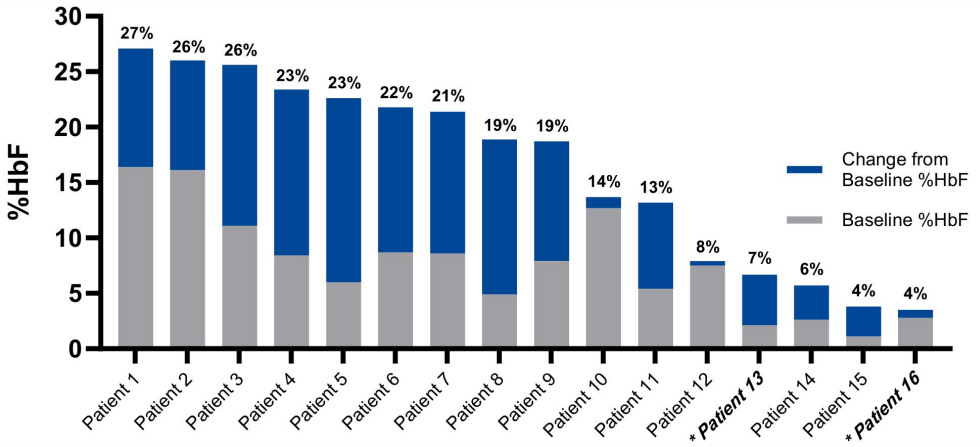
PIONEER 12 mg Cohort 3b: Increased HbF in all Patients

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**

* Patient 13 and Patient 16 received multiple transfusions over the 12-week treatment period. Transfusions increase total hemoglobin (HbA) leading to an iatrogenic reduction in %HbF.

Additional potential factors influencing %HbF induction levels include patient haplotype and residual HbF induction following an HU-washout

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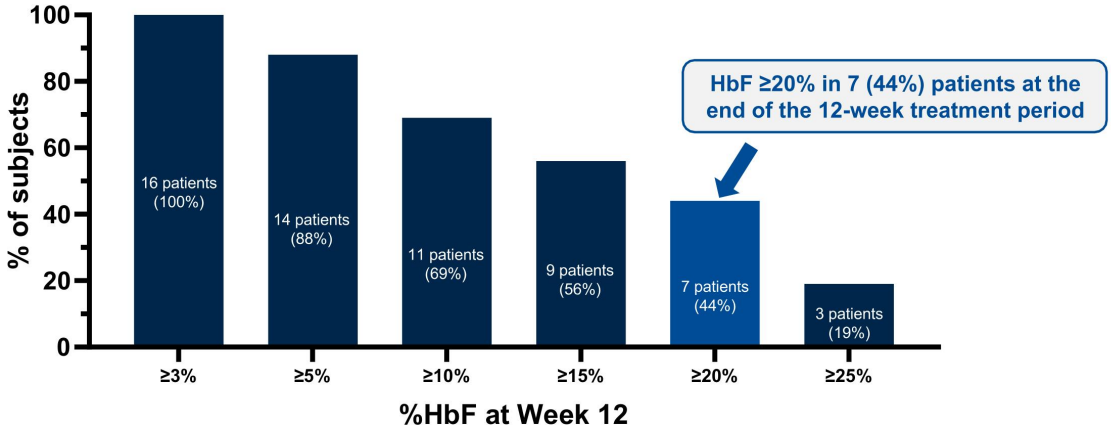
PIONEER 12 mg Cohort 3b: Meaningful Thresholds of %HbF Reached

%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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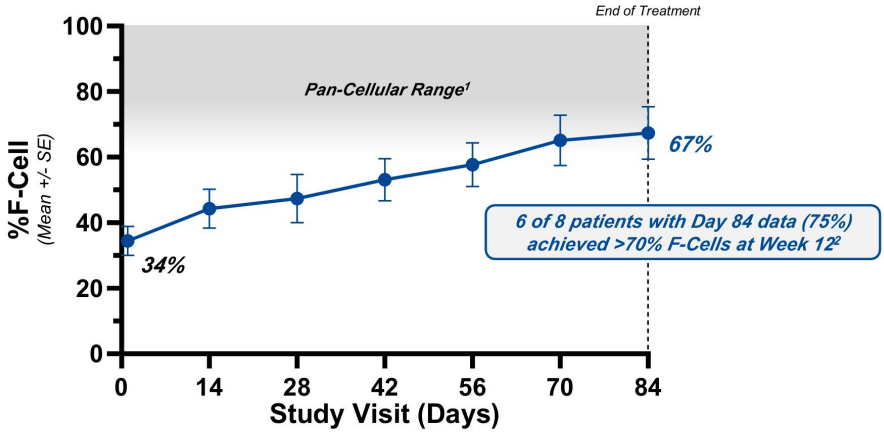
PIONEER 12 mg Cohort 3b: F-cell Data Consistent with Pan-Cellular Induction

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]

F-Cell assay utilized - fluorescent-based flow cytometry assay
Analysis & Figure includes data from all patients enrolled (n=16) and data with transfusion patients (pts 13 and 16) removed (N=14). 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
1. Dai et.al., 2017; Quinn et. al., 2021
2. Full cohort 6 of 8 patients >70% F-Cells at Week 12; Patients with Transfusion removed yields 6 of 7 patients >70% F-Cells at Week 12

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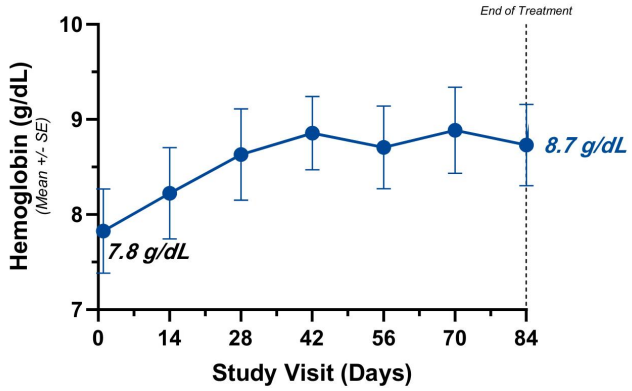
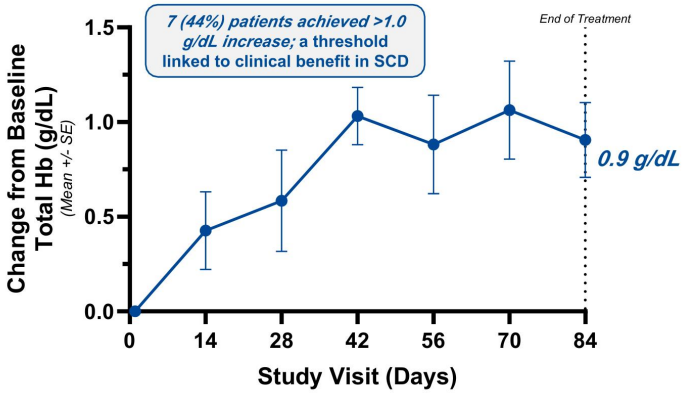
PIONEER 12 mg Cohort 3b: Reductions in Anemia

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) and data with transfusion patients (pts 13 and 16) removed (N=14)
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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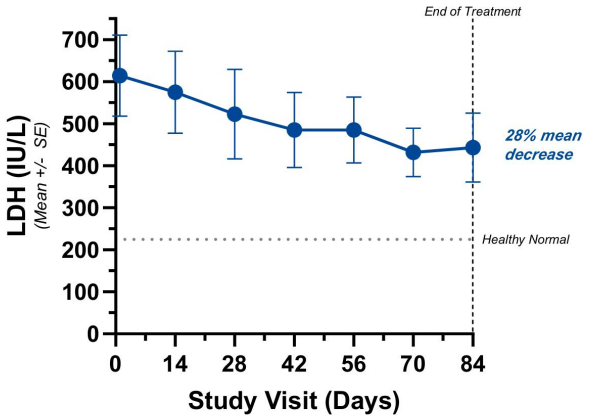
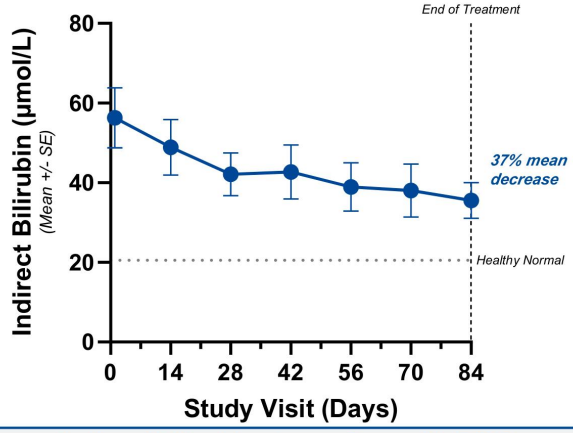
PIONEER 12 mg Cohort 3b: Reductions in Hemolysis

Mean Lactate Dehydrogenase (LDH)



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

Mean Indirect Bilirubin



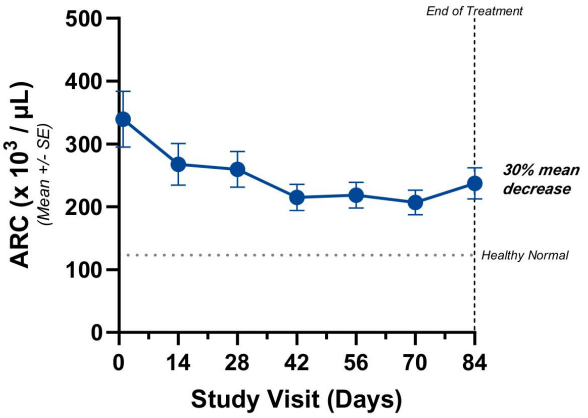
Indirect bilirubin rises often with RBC destruction

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

Fulcrum Therapeutics

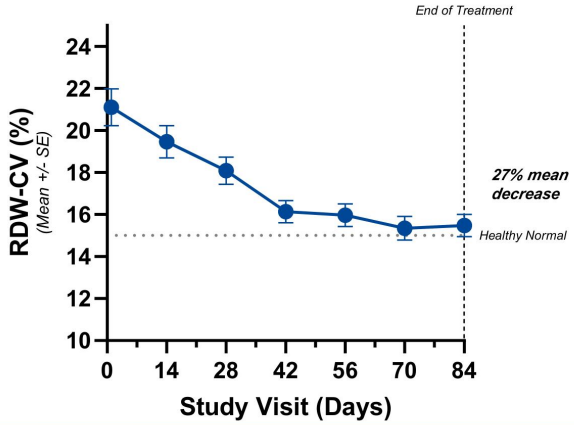
PIONEER 12 mg Cohort 3b: Improvements in RBC Morphology and Erythropoiesis

Mean Absolute Reticulocyte Count (ARC)



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

Mean Red Cell Distribution Width (RDW-CV)

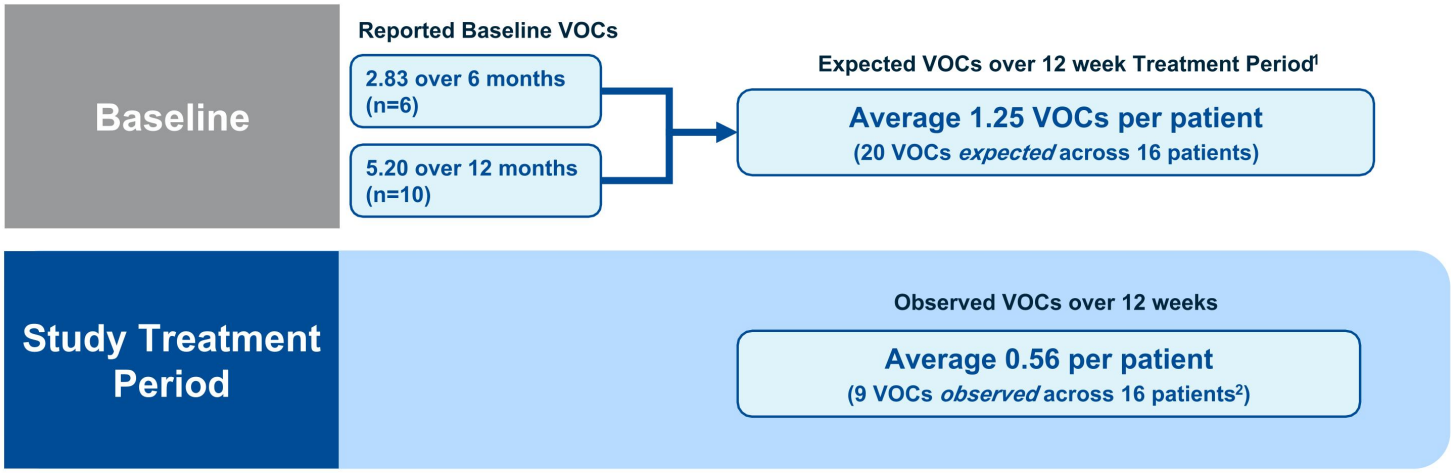


Decreased RDW-CV indicates a more uniform RBC population

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

Fulcrum Therapeutics

PIONEER 12 mg Cohort 3b: Encouraging VOC Trends in this Severe SCD Population



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

[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

PIONEER Ph1b Cohorts 1-3a – Pociredir Was Generally Well-tolerated with No Serious Treatment-Related AEs in the All-Comer SCD Population

Number of Patients with:	Pociredir (n=16) n (%)
Any TEAE	10 (62.5)
Any treatment-related TEAE	5 (31.3)
Any SAE*	4 (25.0)
Any TEAE leading to treatment discontinuation	0
Any lab-related TEAE	0
Patients with TEAE (by Maximum Severity)	
Mild	4 (25.0)
Moderate	5 (31.3)
Severe	1 (6.3)
Most Common TEAEs	
Pain crisis	4 (25.0)
Headache	3 (18.8)

* In 3 (of 4) patients, SAE began prior to first dose of study drug

Cohorts 1-3a were all-comer SCD patients, with no inclusion criteria related to disease severity

- 23 TEAEs in 10/16 (62.5%) patients
  - 8/23 were treatment-related TEAEs in 5/16 (31.3%) patients: (headache [x2], lip numbness, diarrhea, fatigue, somnolence, nausea, tinnitus)#
- 4/23 TEAEs (in 4 patients) were characterized as VOC (pain crisis) per protocol definition
  - None reported as related to study drug
  - Two VOCs occurred in patients documented non-adherent to study drug
- Single SAE in patient on study drug*
  - VOC with chest syndrome, reported as not related to study drug

TEAE: Treatment-emergent Adverse Event; SAE: Serious adverse event

All mild in severity, non-serious and resolved while patient remained on study drug

Fulcrum Therapeutics

PIONEER Ph1b 12 mg Cohort 3b – Pociredir was Generally Well-tolerated with No Serious Treatment-related AEs in the Severe SCD Population

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

AE > 10% of Patients with event[2] (preferred term)			Treatment related AEs		
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 VOCs reported on study at data cut
  - 3 of 12 VOCs occurred off drug during the study follow-up period
- Following the 12 mg cohort, pociredir has been dosed in 135 adults as of June 26, 2025
  - 103 healthy subjects
  - 32 SCD patients

Data as of June 26, 2025 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

PIONEER Ph1b 12 mg Cohort 3b – Pociredir Achieves Target Product Profile and Addresses Unmet Need in Sickle Cell Disease

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

Strong 12 mg Cohort 3b Data Driving Continued Pociredir Development

Key Next Steps

1. Continued 20 mg dose cohort enrollment
   - N=6 enrolled as of July 25, 2025 - 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.

Well-Positioned for Transformational Year in 2025

Pociredir: Best-in-class potential

- Oral small molecule HbF inducer with proof-of-concept
  - Robust and rapid increase in HbF & Hb, and decreases in vaso-occlusive crises, hemolysis and anemia in cohort 3b
- Potential to be broadly protective of SCD symptomology
- Planned timing for Phase 1b PIONEER data disclosure
  - ✓ cohort 3b (12 mg): July 2025
  - – cohort 4 (20 mg): YE 2025

Preclinical Programs

- Advanced preclinical program for the potential treatment of DBA & Other BMFS
- Foundation for pipeline sustainability in benign hematology
- IND submission planned in Q4

Cash Position

- $214.1 million as of June 30, 2025
- Estimated 2025 cash burn of $55 - $65 million
- Cash runway into 2028