Pioneer

Fulcrum Therapeutics

Pociredir Pioneer Study: 12 mg Cohort Data Release

July 29, 2025

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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

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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

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Sickle Cell Disease Is a Debilitating Disease With High Unmet Need

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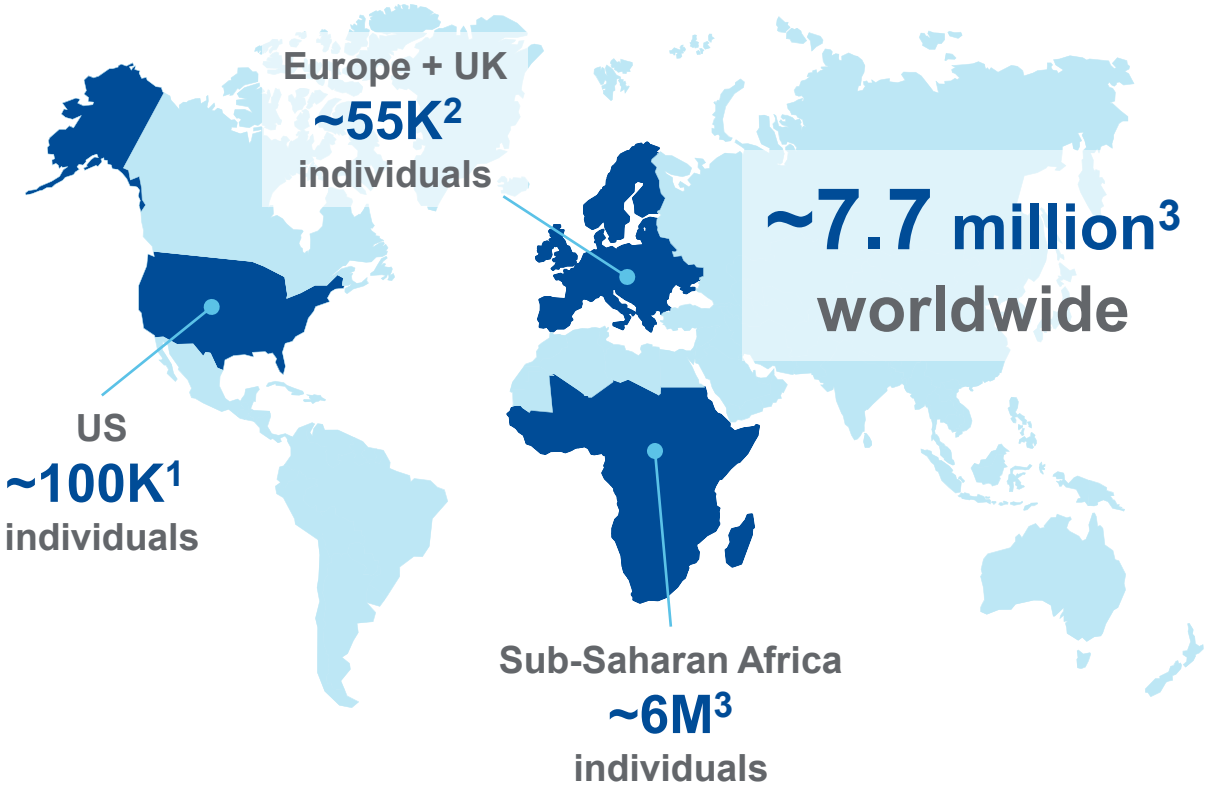
Global Impact



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]

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

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

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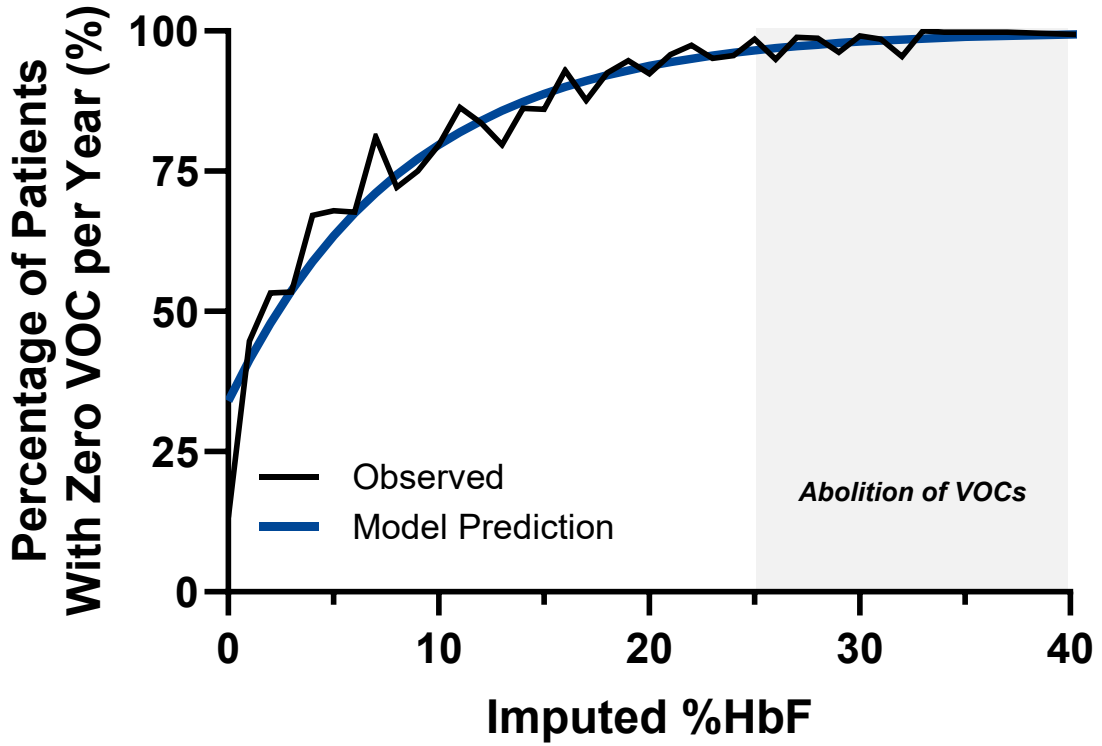
Each 1% increase in %HbF…

…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]

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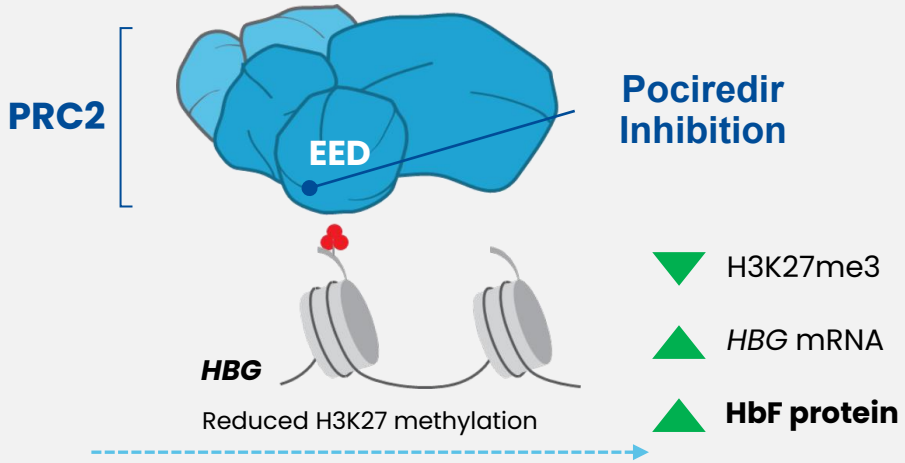
HbF, fetal hemoglobin; VOC, vaso-occlusive crisis.

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

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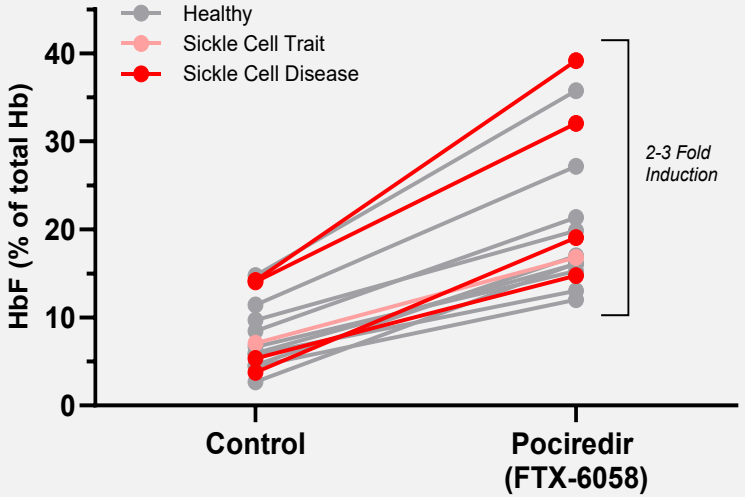
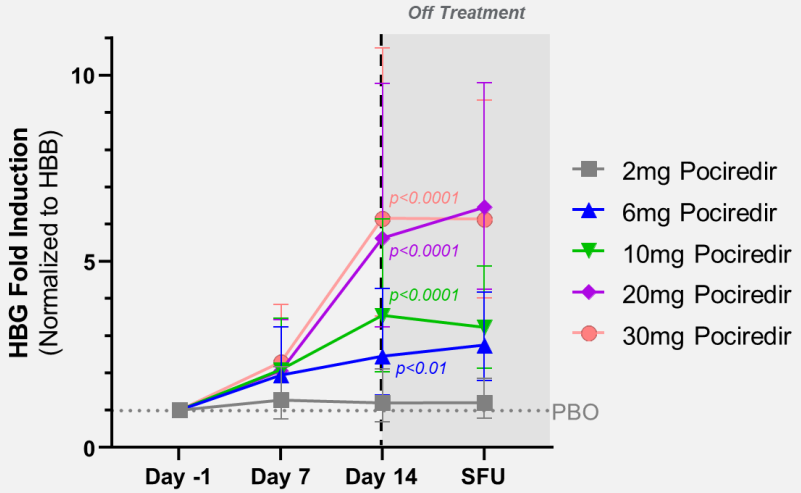
Pre-Clinical: Pociredir HbF Induction in Healthy and SCD CD34+ Donor Cells



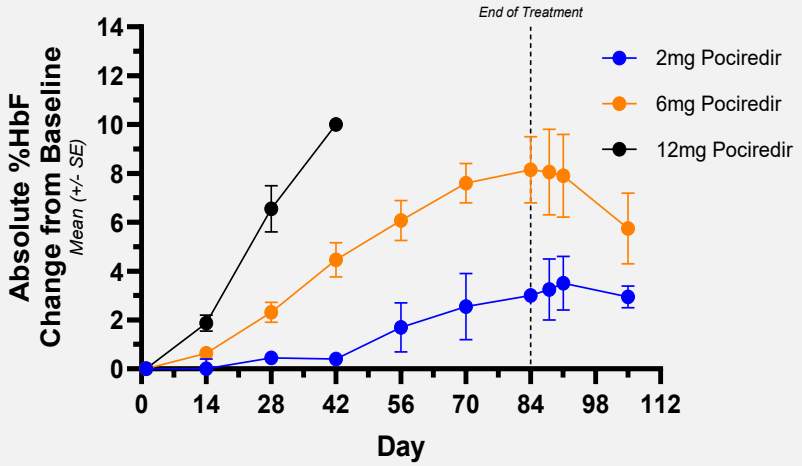
- 8 – 25% absolute increase in %HbF
- Consistent 2-3 fold induction across both healthy subject and SCD CD34+ donor-derived cells

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: 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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Closing Remarks	**Alex 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)		Completed
Cohort 2 2 mg (n=2)		
Cohort 3a 12 mg (n=4)		
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

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	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

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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_{0-4h} 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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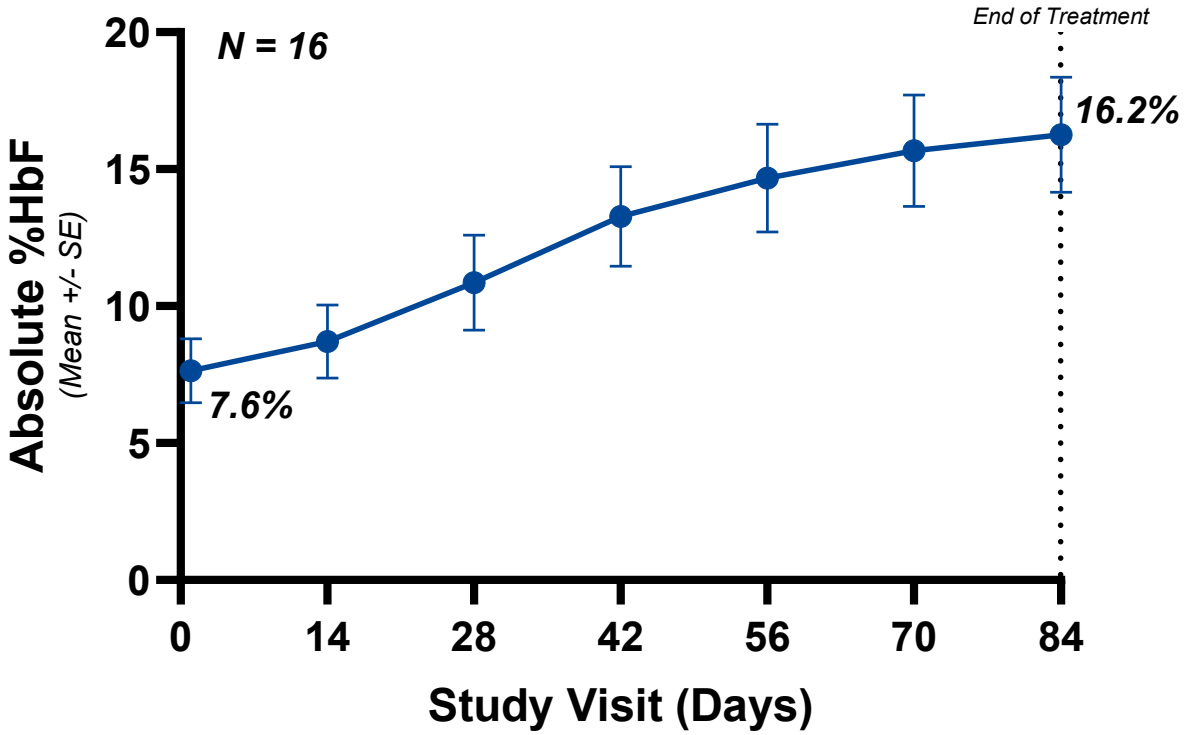
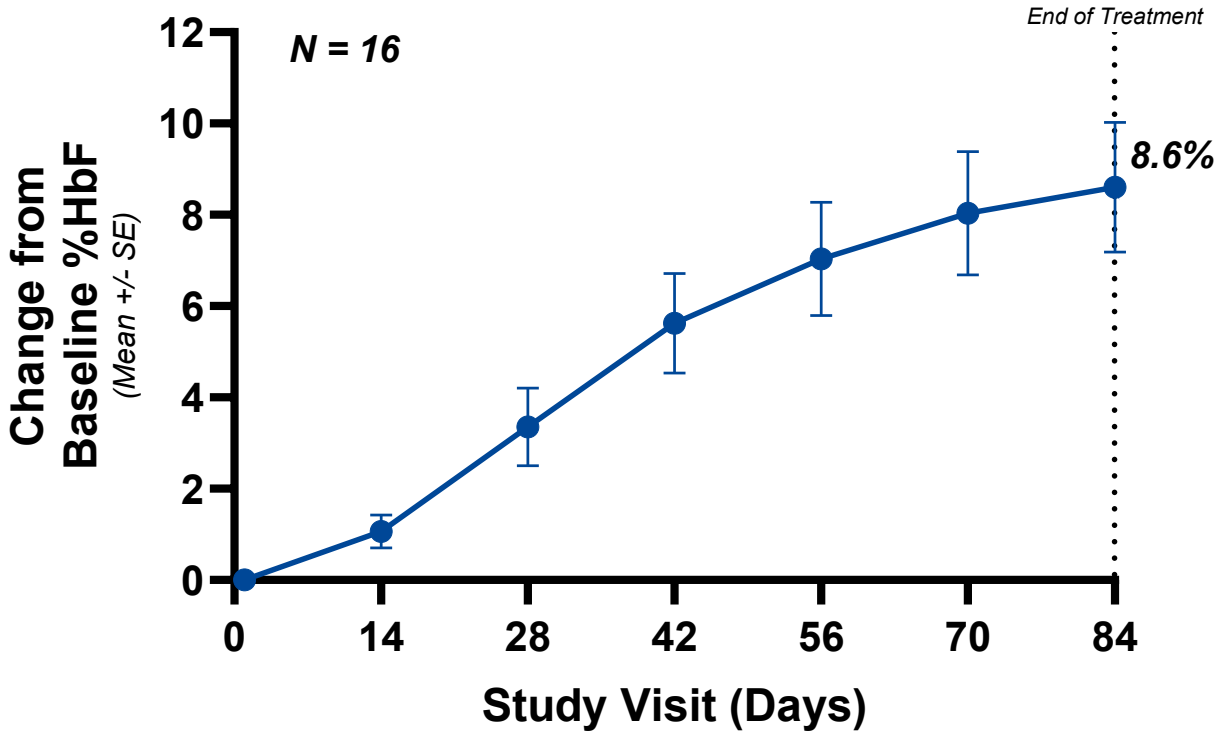
Mean Absolute %HbF



Pociredir increased %HbF from 7.6% to 16.2%

Mean Absolute %HbF Change from Baseline



Pociredir increased %HbF 8.6% by 12 weeks

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

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Pociredir 12 mg: Increased HbF in all Patients

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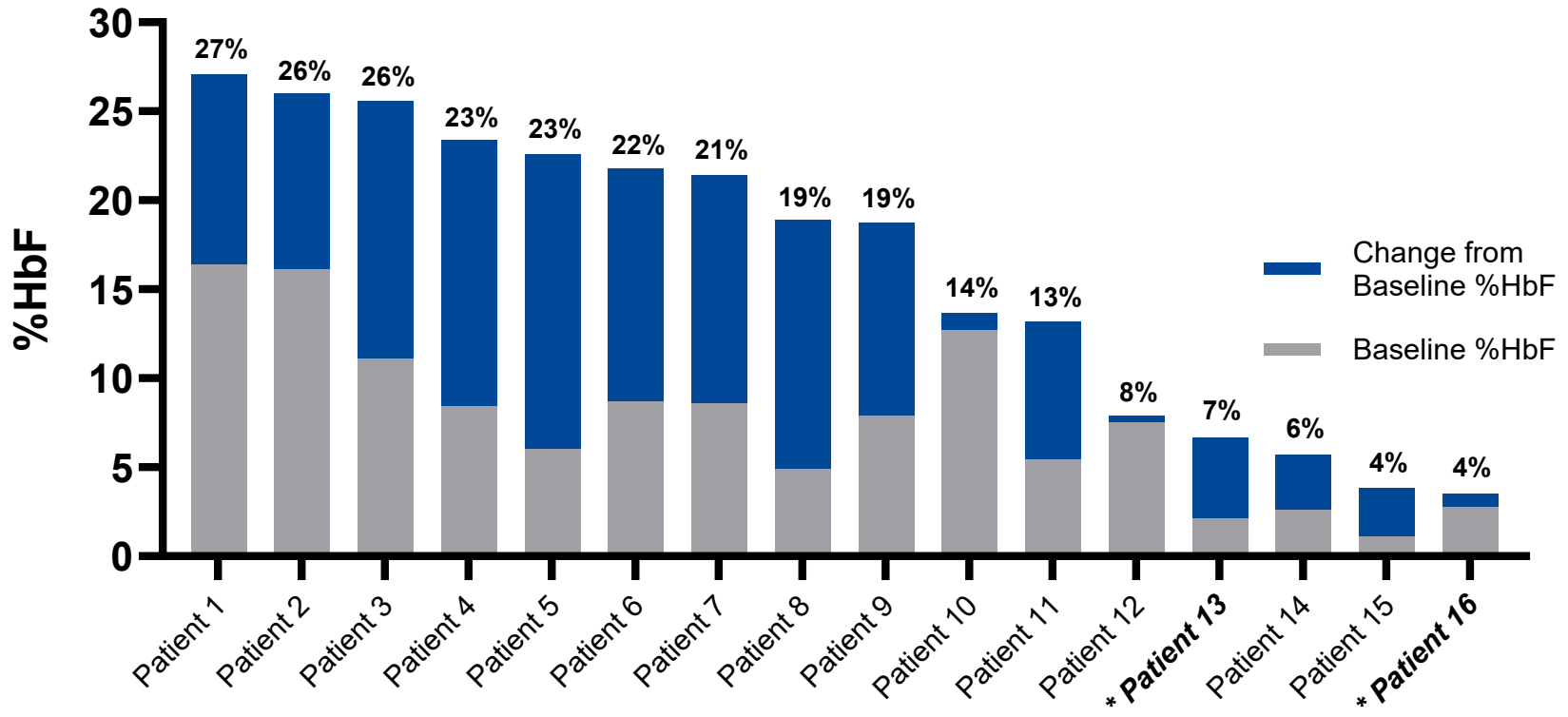
Baseline %HbF and Change from Baseline %HbF at Week 12



- 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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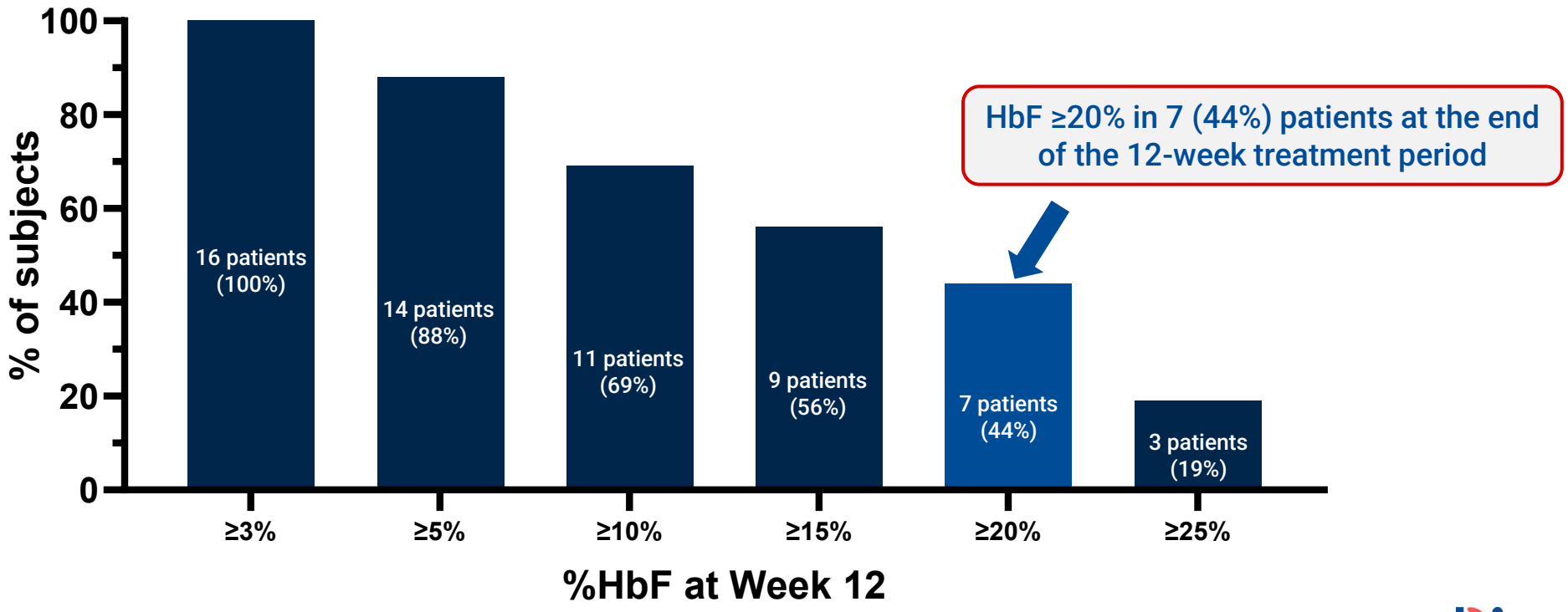
%HbF Threshold Achieved after 12 Weeks of Treatment



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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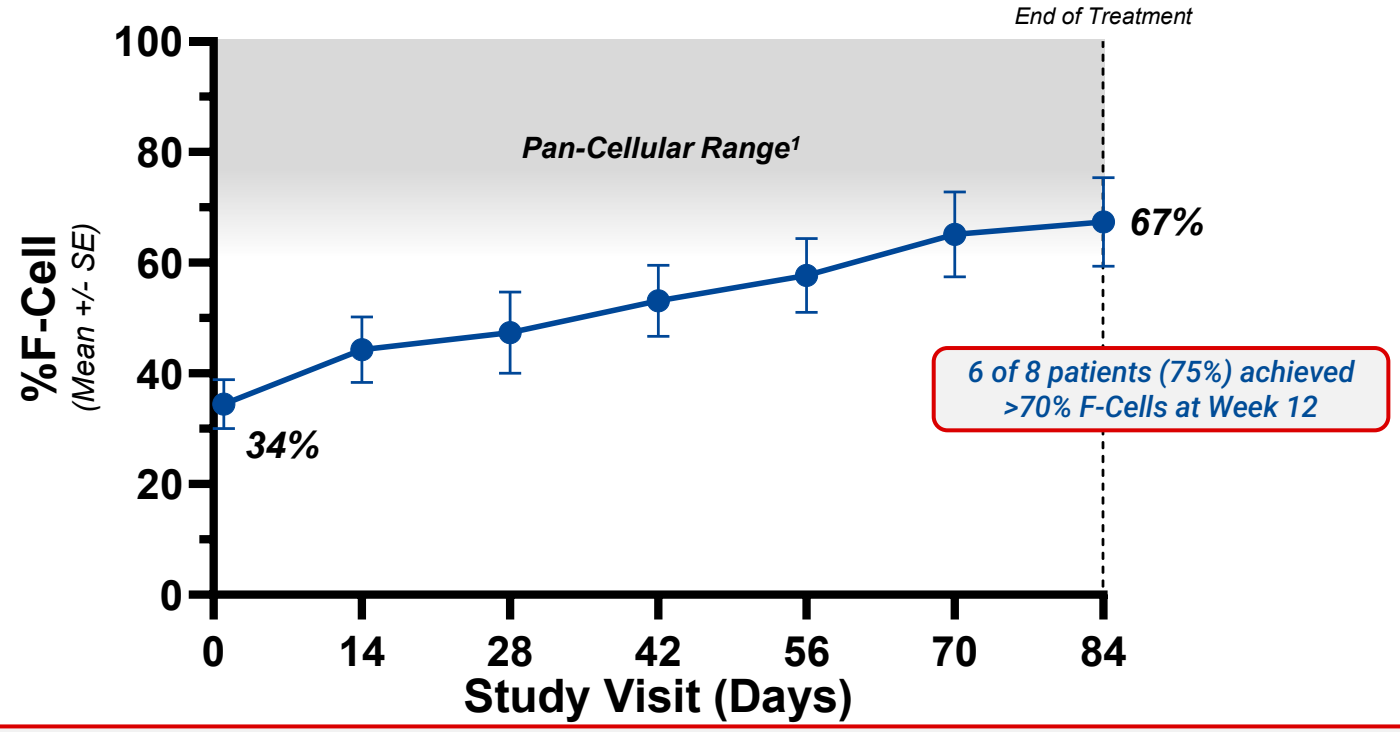
Mean %F-Cells



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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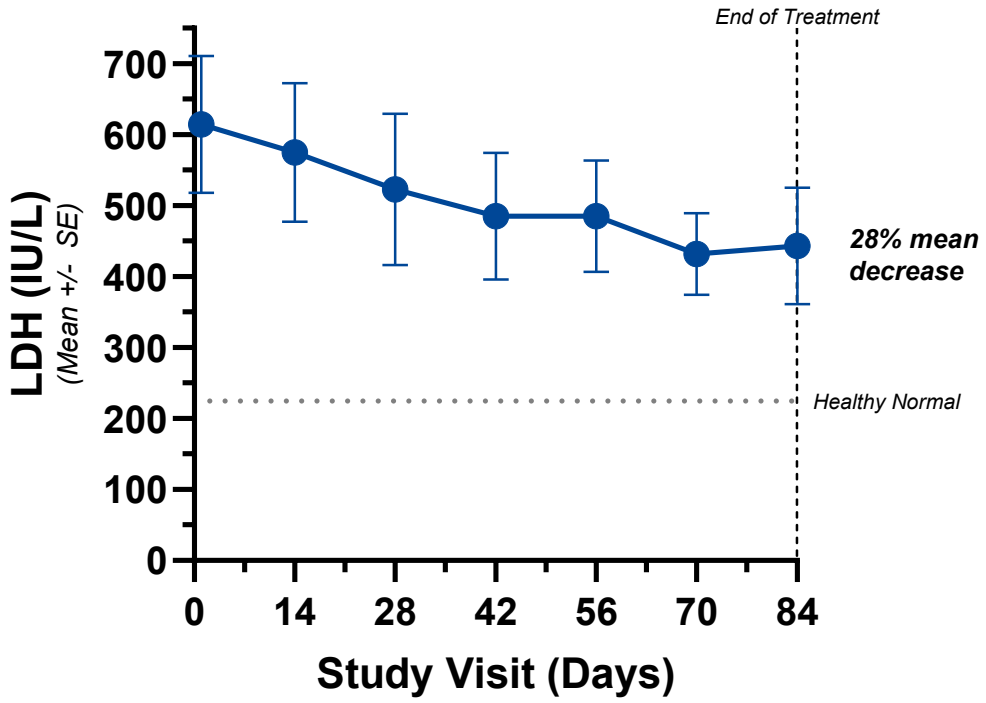
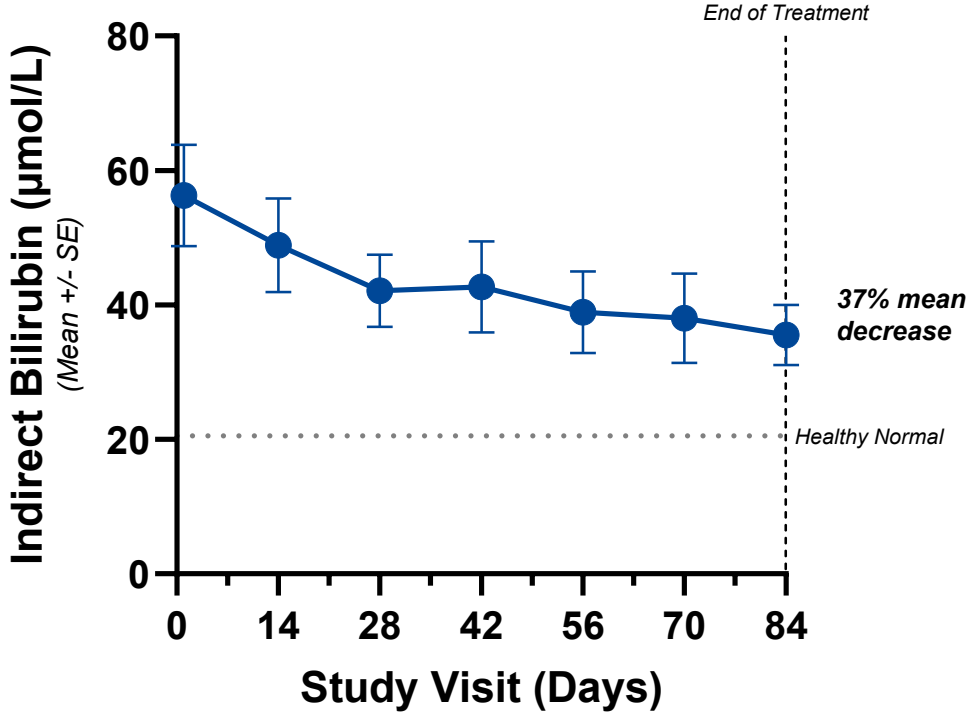
Mean Lactate Dehydrogenase (LDH)



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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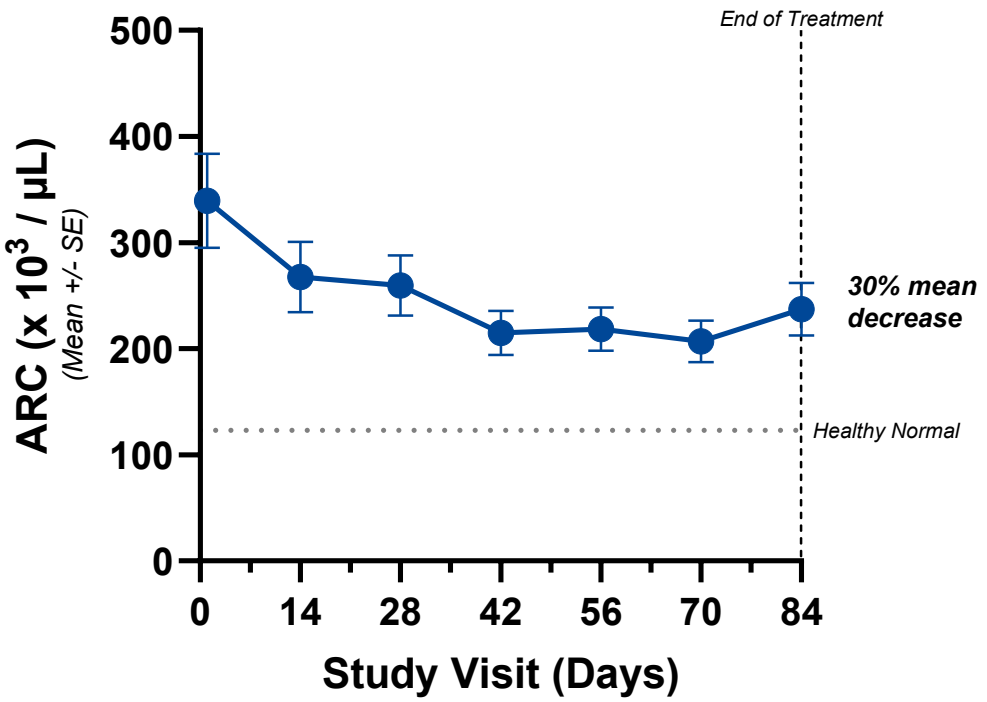
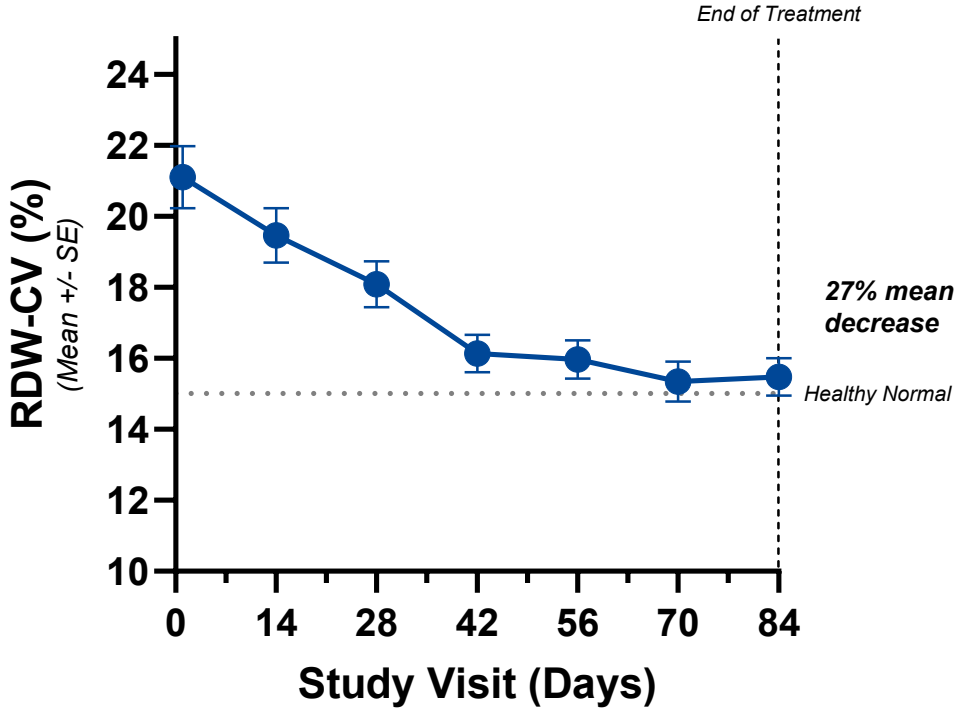
Mean Absolute Reticulocyte Count (ARC)



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: 259x10^3 /µL ARC and 15.0% RDW-CV

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Pociredir 12 mg: Reductions in Anemia

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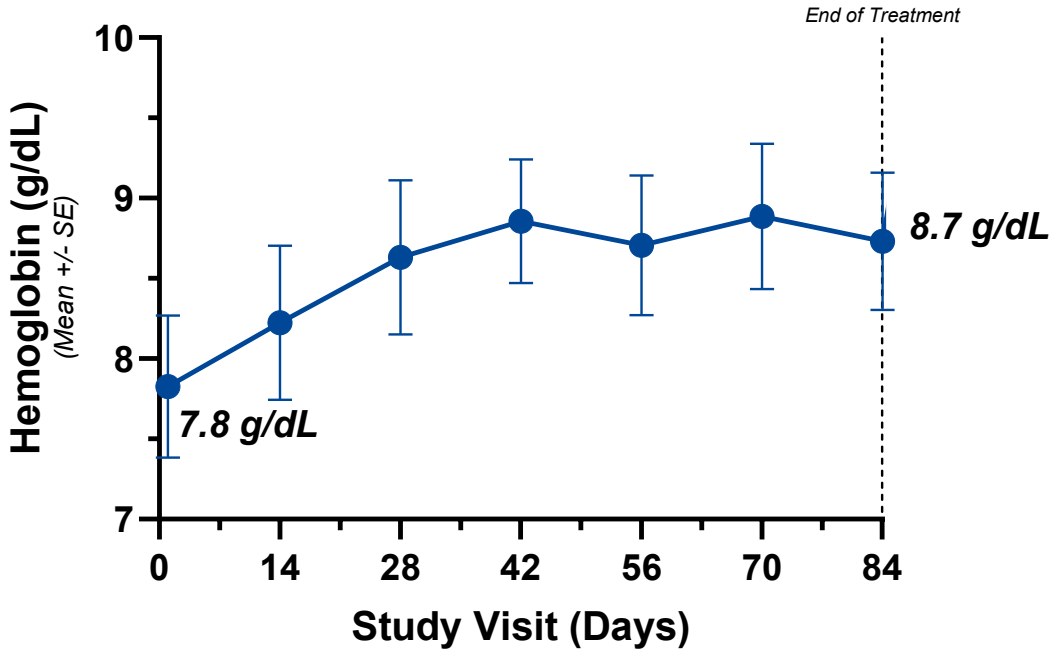
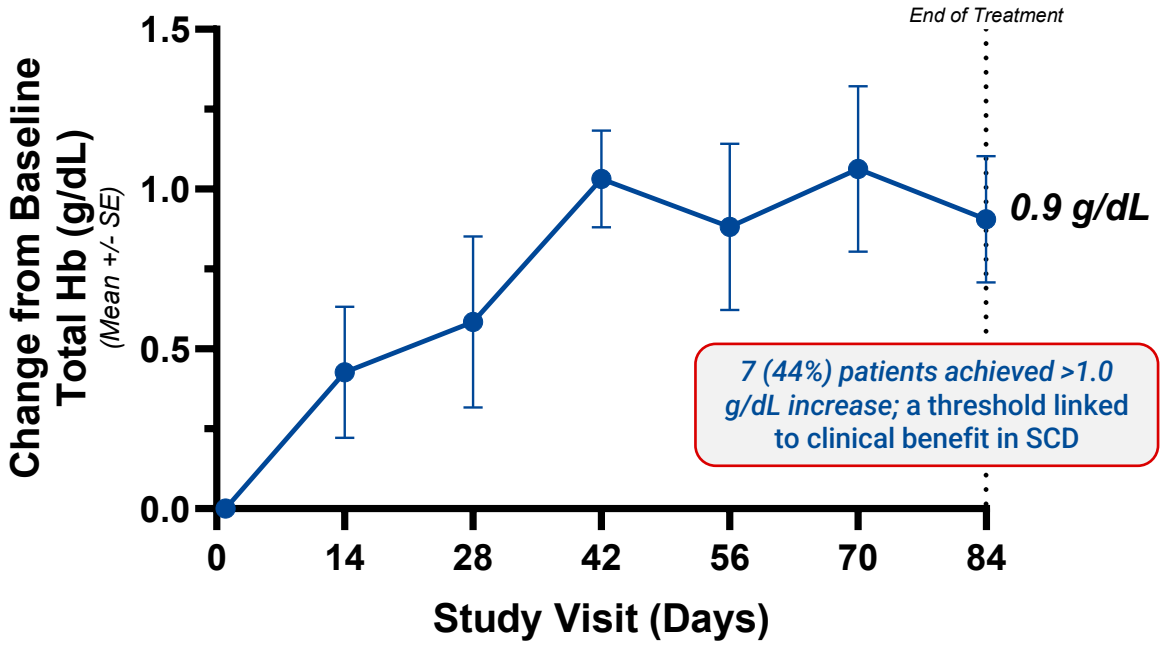
Mean Hemoglobin



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)

[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

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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

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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

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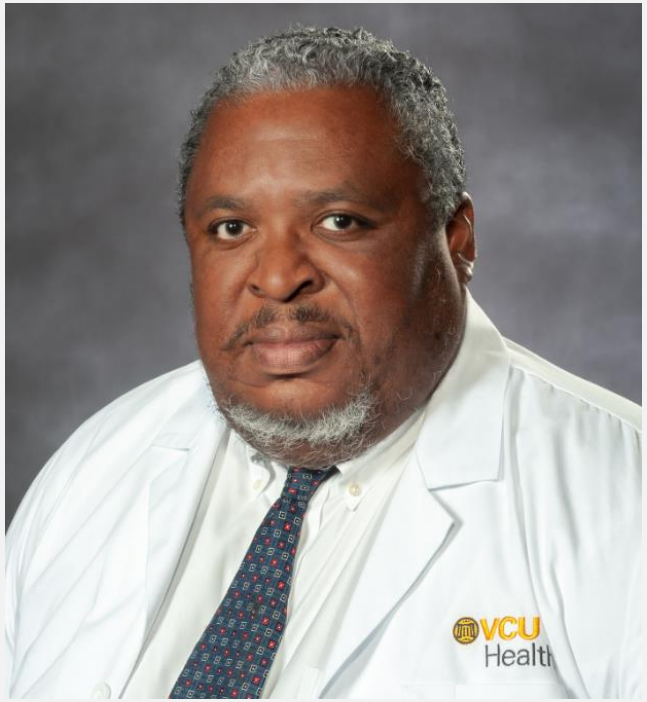

Wally Smith, M.D.
Director, VCU Adult Sickle Cell Program &
Professor School of Medicine at Virginia Commonwealth University

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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

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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

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We thank the patients and their caregivers who participated in Pioneer, and our investigators and their teams