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Pociredir PIONEER Study: 20 mg Cohort Data Update

February 24, 2026

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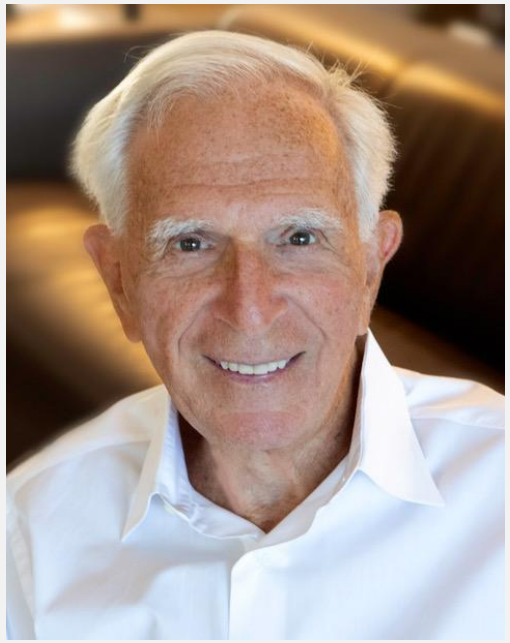
Today's Guest Speaker



Martin H Steinberg, M.D.

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

Dr. Steinberg is a practicing physician and is paid by Fulcrum Therapeutics. The views and opinions expressed by Dr. Steinberg are his own and do not necessarily reflect those of Fulcrum Therapeutics.

Agenda for Investor Call

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

20 mg cohort Demonstrates Pociredir's Best-in-Class Potential

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20 mg Cohort: Robust HbF Induction with Improvements in Markers of Hemolysis and Anemia

- **12.2%** mean absolute HbF increase from a baseline of 7.1% to **19.3%** at Week 12
- **58%** of patients (7/12) reached ≥20% HbF at Week 12
- Progression toward pan-cellularity and improvements in markers of hemolysis and anemia (>1 g/dL Hb increase)
- Continued encouraging trends in VOC reduction over 12 weeks
- Continued evidence of pociredir being generally well-tolerated at 20 mg

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20 mg cohort data as of Dec 23, 2025 Data Cut.

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Sickle Cell Disease Is a Debilitating Disease With High Unmet Need

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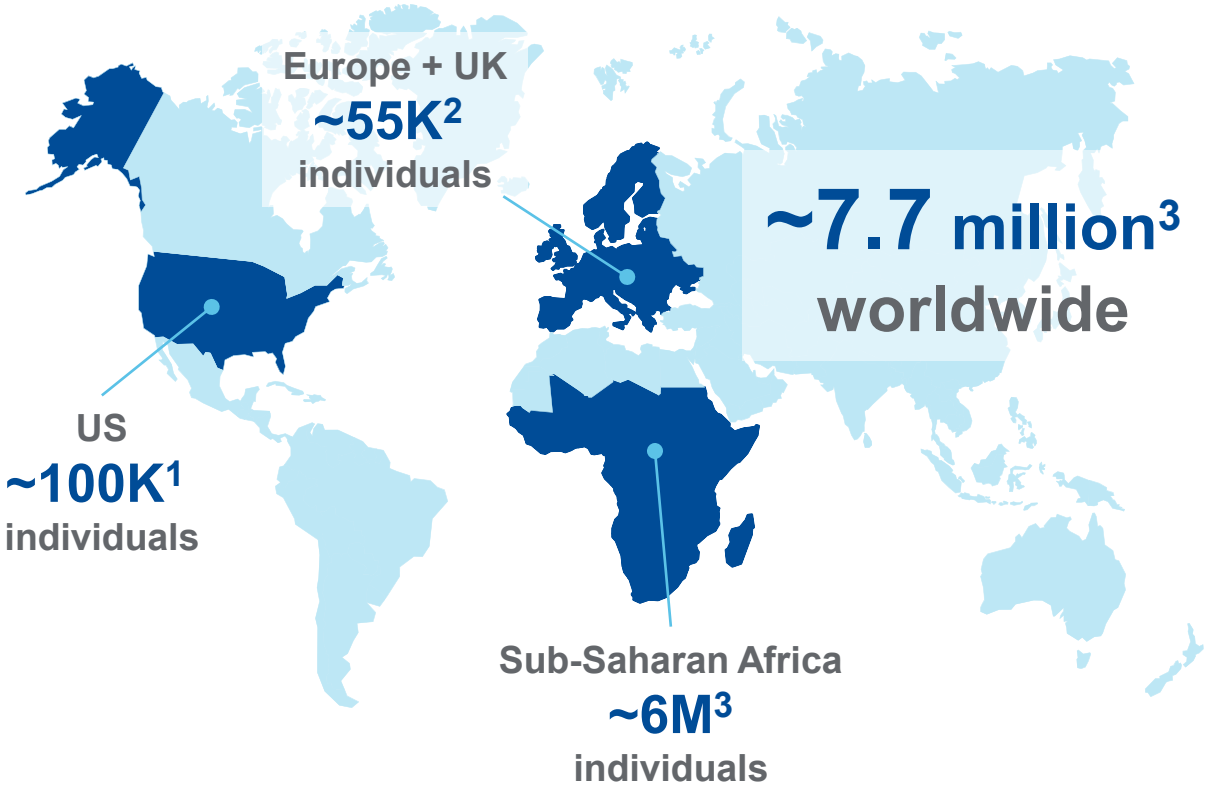
Global Impact



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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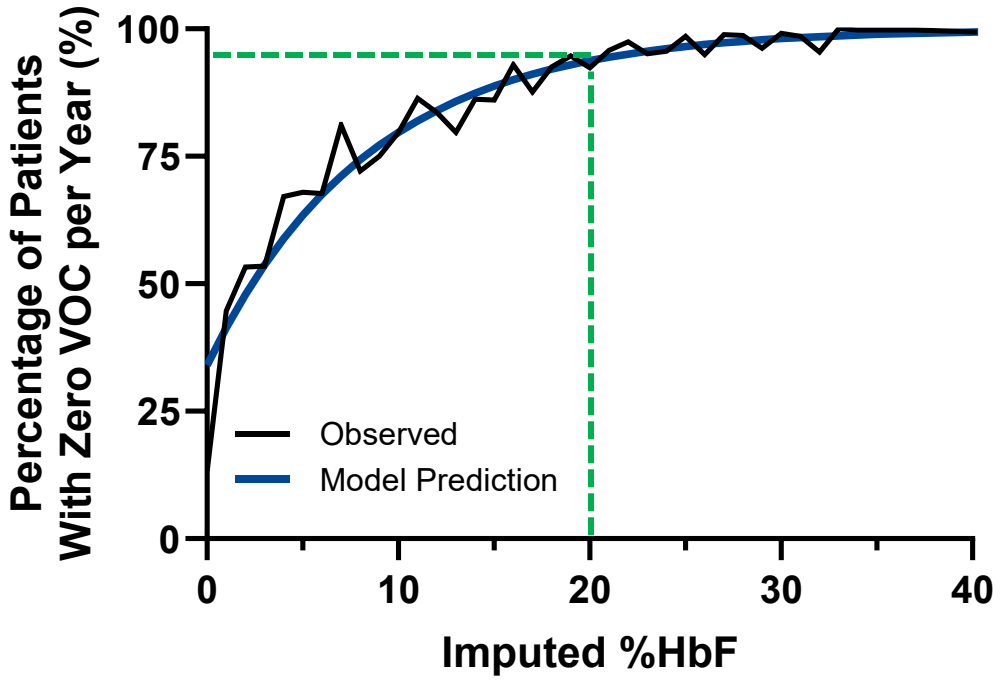
Percent Observing Zero VOC/Year by %HbF[1]



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

Each 1% increase in %HbF…

…is associated with a 4%–8% reduction in VOCs[2]

Raising HbF levels also results in:

- Reduced hemolysis
- Reduced anemia
- Fewer recurring events

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

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

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Study Design (Open Label, Dose Escalation)

4-Week Screening Period

12-Week Treatment Period (QD Capsule)

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

Completed (previously presented)

- **Cohort 4** 20 mg (n=13) — 20 mg Treatment Period Data Presented Today — Completed

4-Week Follow-Up Period

Select Inclusion Criteria

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

Key Study Endpoints

Primary
- Safety and tolerability assessments
- PK parameters

Secondary
- HbF induction
- Hemolysis
- Anemia

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

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Additional criteria apply. For more information, please see https://www.clinicaltrials.gov/study/NCT05169580.
HbF, fetal hemoglobin; HU, hydroxyurea; QD, once daily; SCD, sickle cell disease; VOC, vaso-occlusive crisis; PK, Pharmacokinetic; F-Cells, Cells expressing Fetal Hemoglobin

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

20 mg Cohort Patient Disposition as of December 23rd Data Cut

Patients Enrolled	N= 13
Patients Completing 12-week Treatment Period	N= 12
Completed Treatment Period + 4-week Follow-up	N= 7
Completed Treatment Period + 4-week Follow-up Ongoing	N= 5

- One previously disclosed patient discontinuation on Day 1 due to unrelated Grade 5 SAE[1]
- Continued high adherence (97%) to treatment schedule in the 20 mg cohort[2]
- Pharmacodynamic (PD) Analysis Set presented today is through Week 12 of treatment; Safety Data Set includes all 20 mg data as of December 23, 2025 data cut

Disposition and all subsequent data as of Dec 23, 2025, data cut
1. Grade 5 SAE determined by the investigator unrelated to treatment following complications from VOC reported on Day 1 of study. Patient excluded from the PD Analysis Set
2. Adherence measured via AiCure®, an artificial intelligence data collection tool providing real-time feedback and data collection to measure and improve study drug adherence. Dosing interruptions on study not included in AiCure adherence analysis

PIONEER Baseline Demographics and Characteristics – PD Analysis Set

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

1. n=12 PD Analysis Set

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Rapid, Robust, and Clinically Relevant increases in HbF in 12 Weeks

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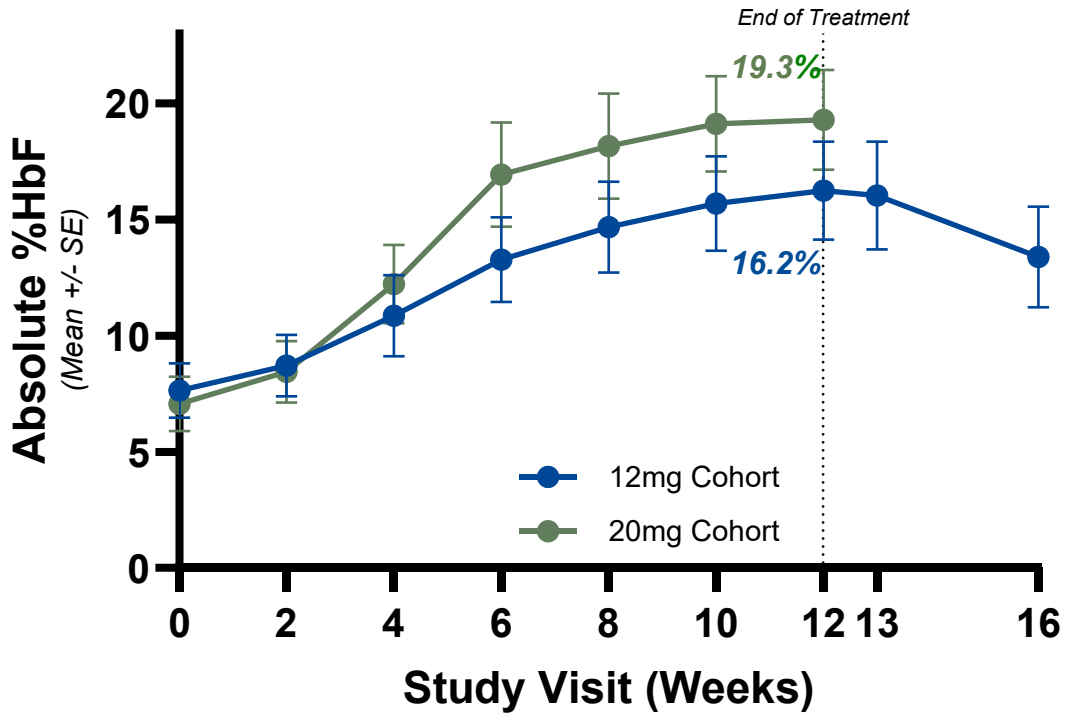
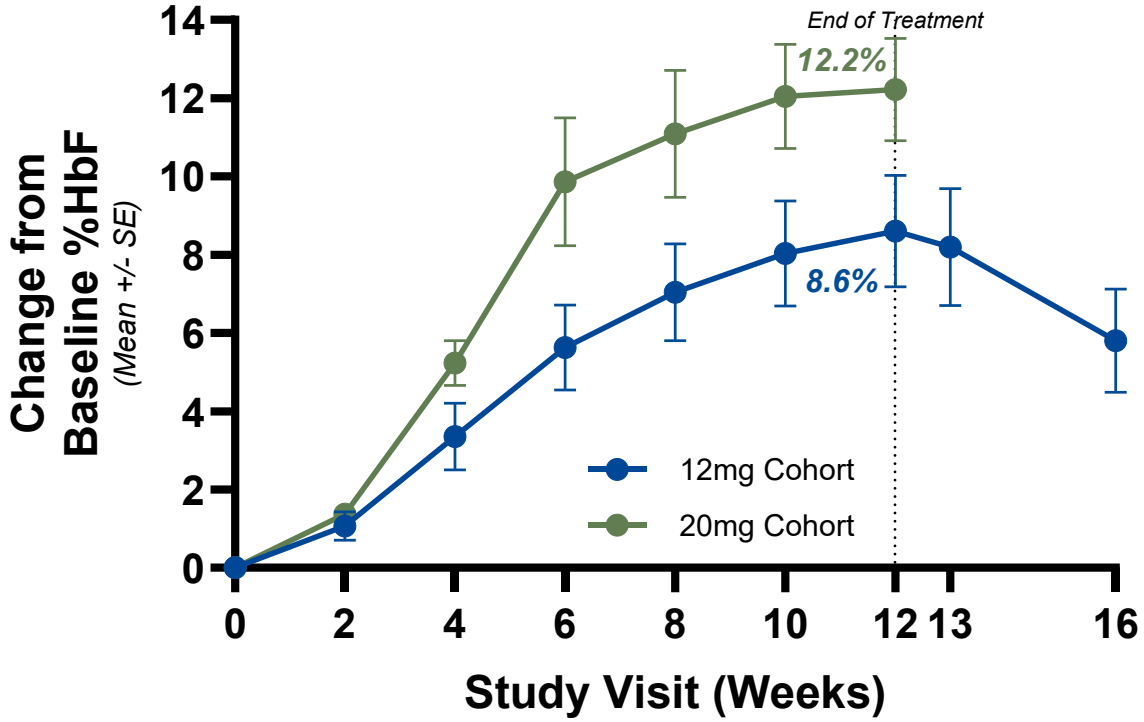
Data as of Dec 23, 2025 Data Cut

Mean Absolute %HbF



20 mg Pociredir increased %HbF from 7.1% to 19.3% at Week 12

Mean Absolute %HbF Change from Baseline



20 mg Pociredir increased %HbF by 12.2% at Week 12

12 mg cohort 3b analysis & figures includes data from all patients enrolled (n=16) regardless of transfusions during treatment period
20 mg cohort n=12. No patients received transfusions during the treatment period.

Clinically Relevant HbF Induction in all Patients

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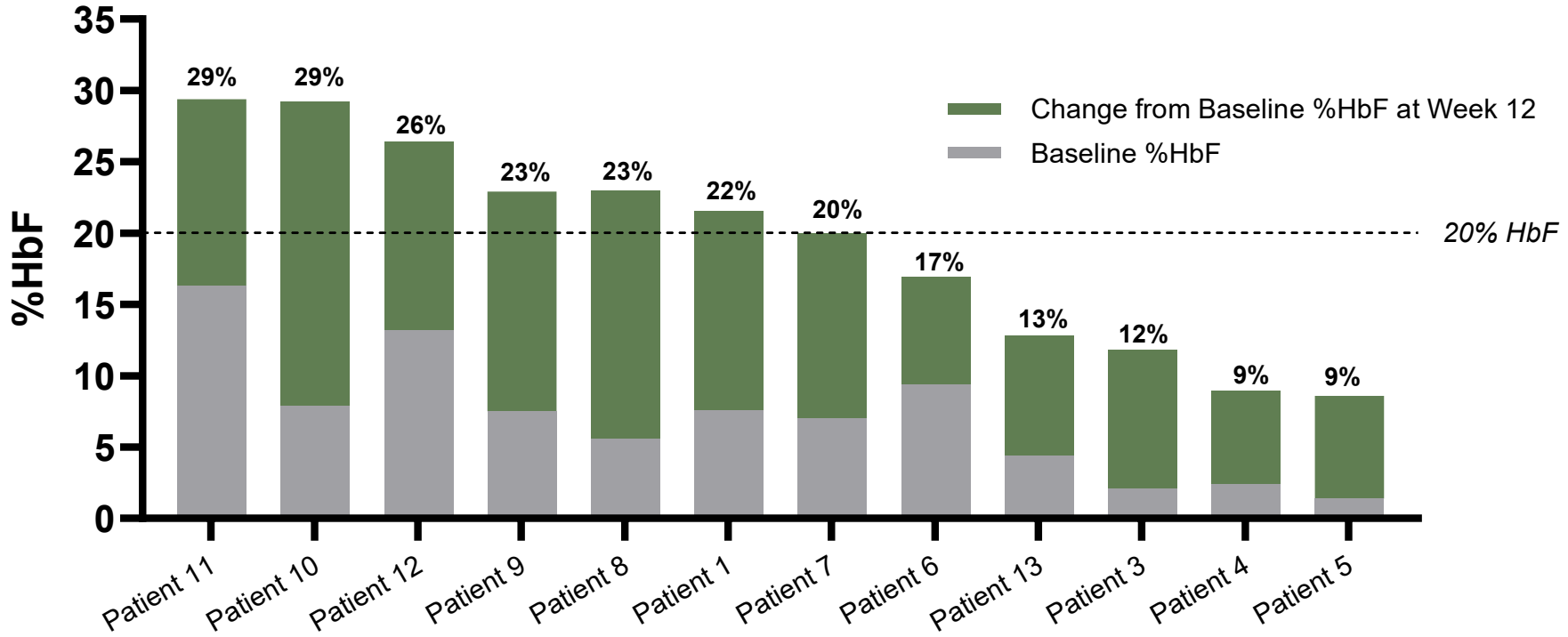
Data as of Dec 23, 2025 Data Cut

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



- 7 of 12 patients (58%) achieved a ≥20% absolute level of %HbF at their latest study visit
- All patients in the 20 mg cohort achieved at least a 6.5% absolute increase in HbF (or greater)[1]

1. No patients received transfusions during the treatment period.

Progression Toward Pan-Cellular Induction of HbF

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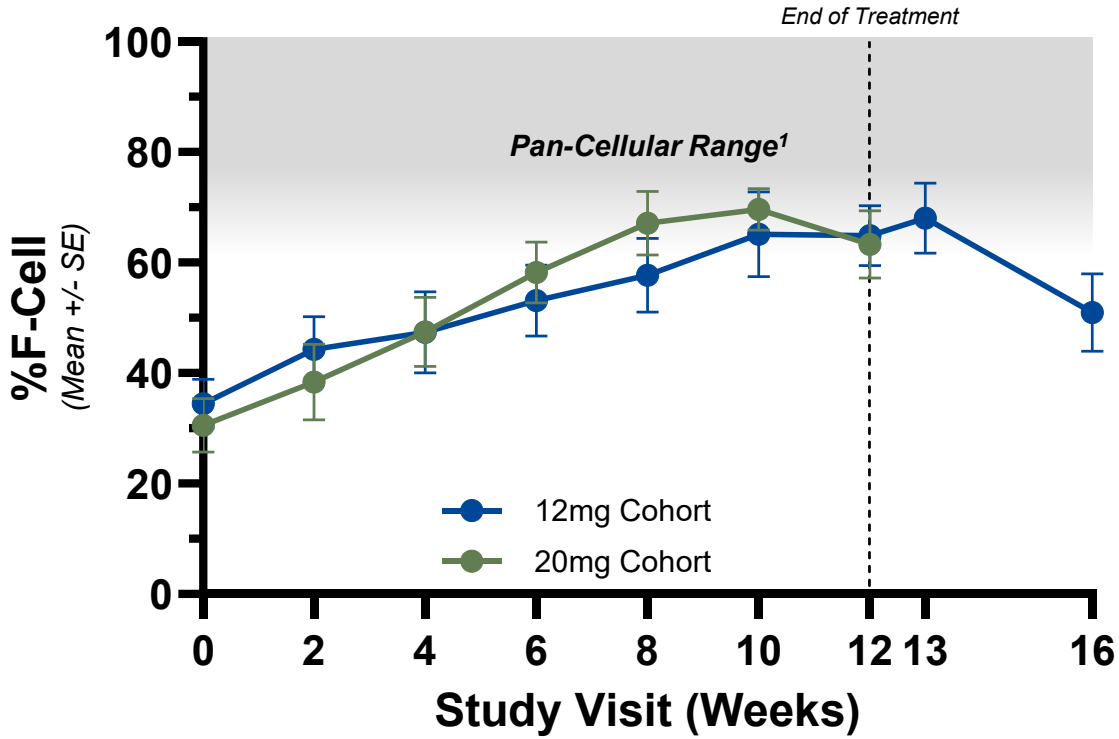
Data as of Dec 23, 2025 Data Cut

Mean %F-Cells



20 mg Week 12 sample size reflects missing data from two patients with higher F-cell levels at prior visits

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

1. Dai et.al., 2017; Quinn et. al., 2021
F-Cell assay utilized - fluorescent-based flow cytometry assay
12mg cohort 3b analysis & figure includes available data from all patients regardless of transfusions during treatment period;
20 mg cohort PD Analysis Set (n=12). Analysis includes data through visits with complete laboratory data. No patients received transfusions during the treatment period.
Sample size varies across timepoints due to sample availability. 12 mg n=12 at Day 84. 20 mg n=10 at Day 84.

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Consistent Reductions in Markers of Hemolysis

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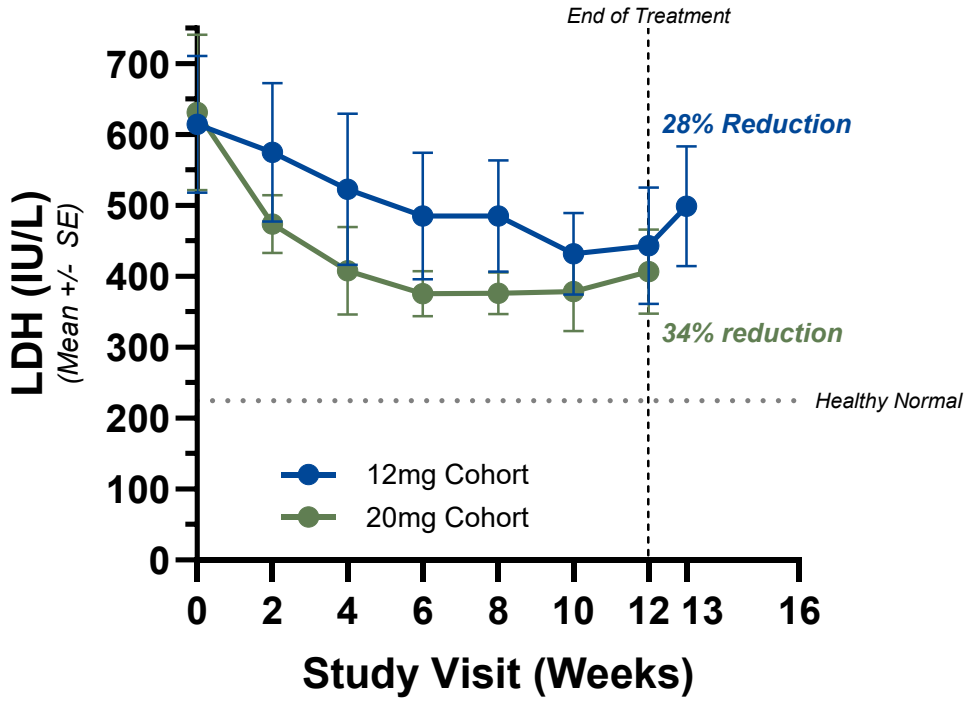
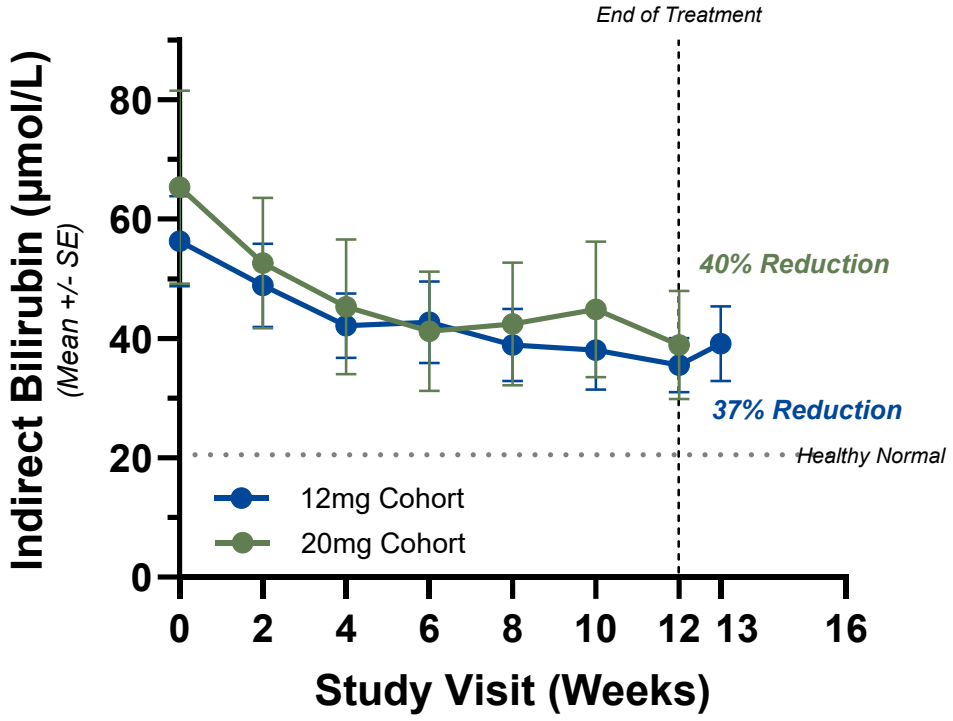
Data as of Dec 23, 2025 Data Cut

Mean Lactate Dehydrogenase (LDH)



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

Mean Indirect Bilirubin



Indirect bilirubin increases with red blood cell destruction

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

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Improved Erythropoiesis and Normalization of Red Blood Cell Morphology

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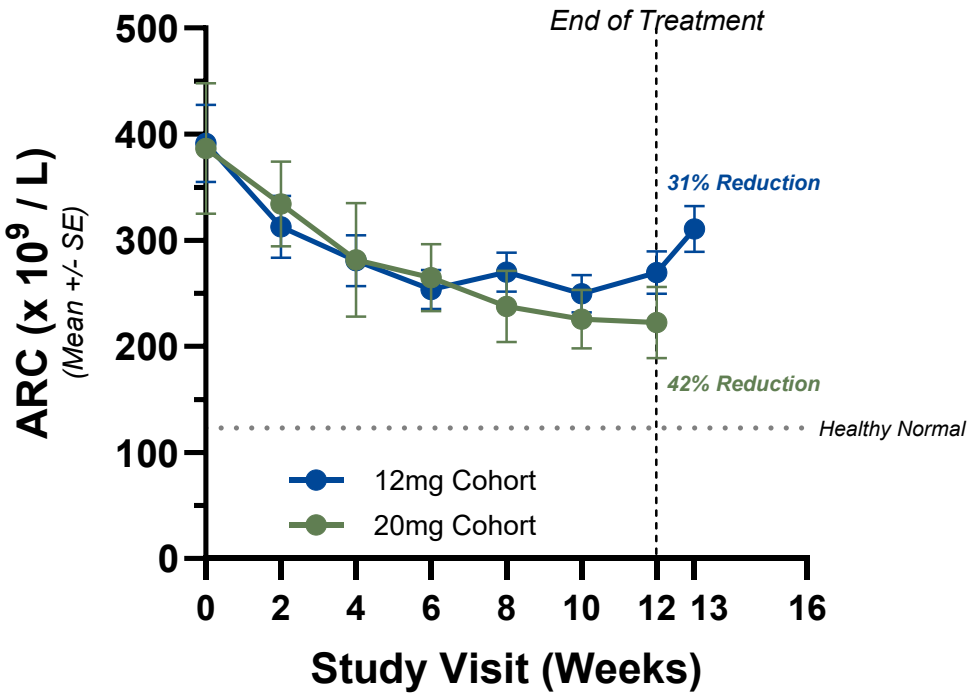
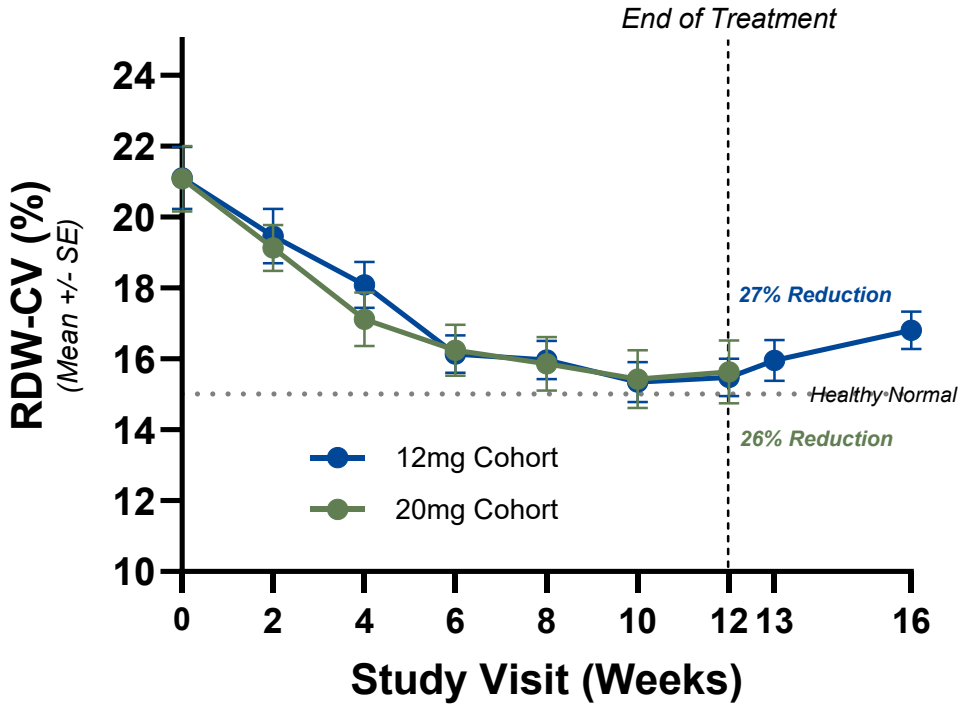
Data as of Dec 23, 2025 Data Cut

Mean Absolute Reticulocyte Count (ARC)



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

Mean Red Cell Distribution Width (RDW-CV)



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

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

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Reduction in Anemia: >1 g/dL Increase in Hemoglobin in 12 Weeks, With no Transfusions

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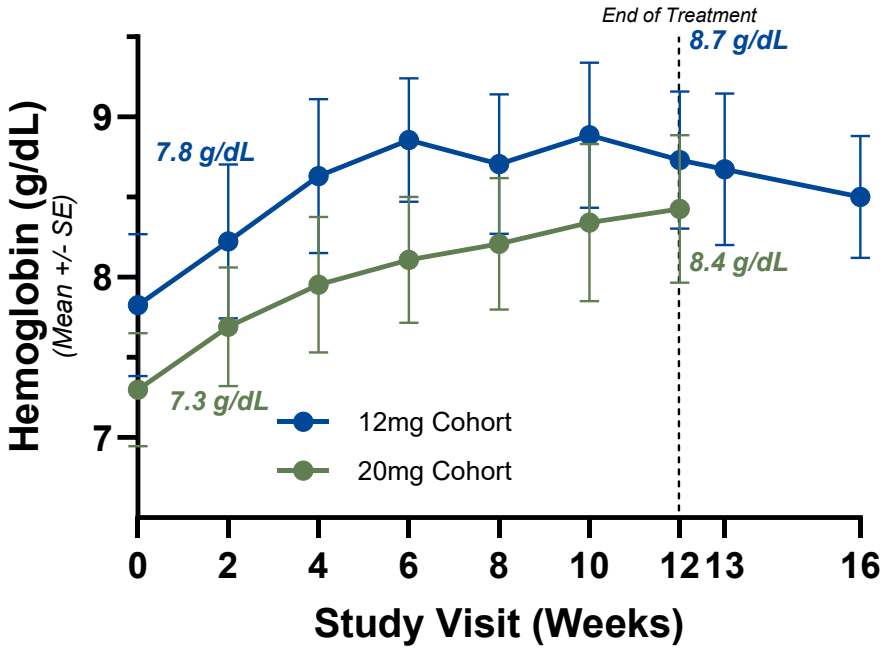
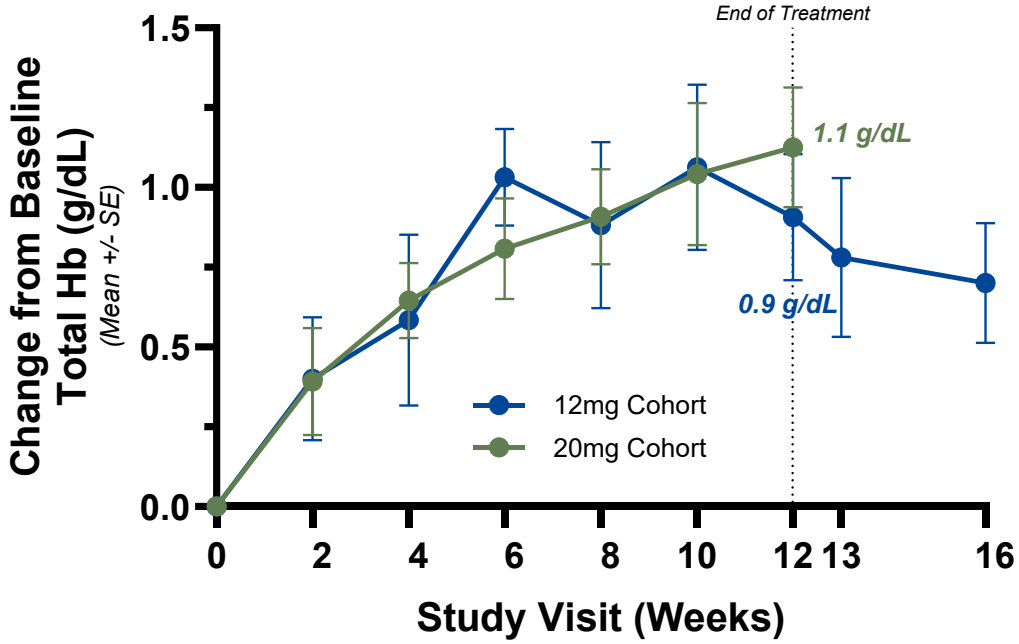
Data as of Dec 23, 2025 Data Cut

Mean Hemoglobin



Mean Change from Baseline Hemoglobin



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

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

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

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7 of 12 Patients (58%) in this Severe SCD Population Reported no VOCs During the Treatment Period

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Data as of Dec 23, 2025 Data Cut

Baseline

Reported Baseline VOCs

n=12 PD Analysis Set

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

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

Study Treatment Period

N=12 PD Analysis Set

Observed VOCs in the Treatment Period

6 VOCs observed in 5 patients[2]

Exploratory 12-week VOC findings support continued evaluation of pociredir in a potential registration-enabling study

Note: 1 additional VOC observed in patient who discontinued on Day 1 due to Grade 5 SAE. Patient not included in PD Analysis Set.

1. Expected VOCs derived from reported baseline VOCs for the PD Analysis Set – ((2.40 VOCs / 26 weeks)*5 patients) + ((6.71 / 52 weeks)*7 patients)) * 12 weeks
2. 3 additional VOCs were observed in Safety Follow-up period as of data cut

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

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Data as of Dec 23, 2025 Data Cut

Adverse Event (AE)*	Cohort 4 (20 mg) n=13 (%)[a]
Patients with Adverse Events Regardless of Causality	11 (85)
Treatment-related AE	3 (23)
Grade ≥ 3 AEs	5 (38)
Grade ≥ 3 Treatment-related AEs	1 (8)
Serious adverse event (SAE)	6 (46)
SAEs consistent with VOC/SCD complications	6 (46)
Treatment-related SAE	0 (0)
TEAE with treatment discontinuation	1 (8)
TEAE leading to death	1 (8)[b]

AE > 10% of Patients (n) with event*			Treatment-related AEs		
Preferred term	**n (%)**	**Highest Grade**	**Preferred term**	**# of AEs**	**Grade**
SCA with crisis	4 (31)	4	Reticulocytopenia (ARC)	1	3
Pain (extremity)	2 (15)	2	Insomnia	1	1
Fatigue	3 (23)	2	Upper respiratory tract infection	1	2
Malaria	3 (23)	2	Rash (Macular)	1	1
Arthralgia	2 (15)	1	Catarrh	1	1
Headache	2 (15)	1			
Pyrexia	3 (23)	1			
Bone pain	3 (23)	3			

- 3 patients reported treatment-related AEs
  - All treatment-related AEs resolved during treatment period
  - Grade 3 Reticulocytopenia alongside broader CBC reductions in the context of a viral infection (presumed Parvo B19) and amoxicillin treatment. 14-day pociredir treatment interruption. Continued normalization of CBCs following re-exposure to pociredir.
- No dose limiting toxicities or dose discontinuations due to treatment-related AE
- A total of 10 VOCs reported at data cut
  - 3 of the 10 VOCs occurred in the safety follow-up period
  - 1 VOC occurred in a patient prior to receipt of study drug (death determined unrelated to treatment)

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

a. Safety Analysis Set

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

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

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Data as of Dec 23, 2025 Data Cut

Adverse Event (AE)*	Cohort 3b (12 mg) n=16 (%)[1]	Cohort 4 (20 mg) n=13 (%)[1]
Patients with Adverse Events (AE) Regardless of Causality	15 (94)	11 (85)
Treatment-related AE	3 (19)	3 (23)
Grade ≥ 3 AEs	8 (50)	5 (38)
Grade ≥ 3 Treatment-related AEs	0 (0)	1 (8)
Serious adverse event (SAE)	5 (31)	6 (46)
SAEs consistent with VOC/SCD complications	5 (31)	6 (46)
Treatment-related SAE	0 (0)	0 (0)
AE with treatment interruption	1 (6)	1 (8)
AE with treatment discontinuation	0 (0)	1 (8)[2]

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

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

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Pociredir: Potential to Transform the Treatment of SCD

Connecting the Dots from HbF Induction to Reduced VOCs

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Robust and Rapid HbF Induction	Pan-cellular Distribution Across RBCs	Reduced Hemolysis & Improved Erythropoiesis	Improvements in Anemia	Early Signal of Clinical Benefit
• Mean absolute HbF 19.3% at Week 12 (+12.2%) • 7/12 patients reached ≥ 20% HbF	• F-Cell proportion doubled to ~63% by Week 12	• 34-42% reductions in LDH, bilirubin, and reticulocytes • Improved RDW uniformity	• ↑1.1 g/dL in hemoglobin at Week 12 • Consistent anemia improvement by Week 12	• 7/12 (58%) patients reported zero VOCs during the 12-week treatment period • No treatment-related SAEs observed

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Closing Remarks	**Alex C. Sapir,** President & CEO

Expert Perspective on HbF Induction and Potential Clinical Impact in SCD

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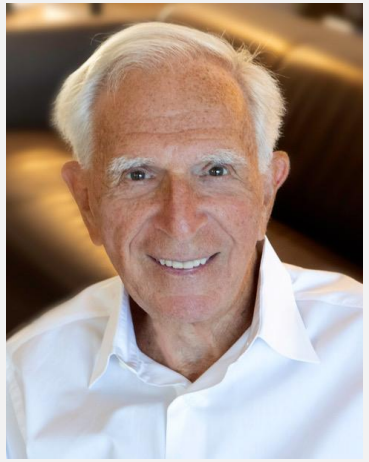

Martin H Steinberg, M.D.

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

Key Perspectives from Dr. Steinberg:

- **Inducing HbF** across as many RBCs as possible (i.e., pan-cellular) represents a potentially transformative approach for treating SCD
- **HbF levels achieved with pociredir exceed** those historically observed with hydroxyurea
- **Increases in HbF** translates into decreased hemolysis and increased hemoglobin
- **An oral HbF inducer** offers a scalable treatment option for SCD patients who currently have limited treatment options

The views expressed are those of Dr. Steinberg based on his clinical experience and interpretation of the PIONEER data.

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Preparing for Potential Registration-Enabling Trial While Engaging FDA on Trial Design

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Q1 2026 PIONEER Data ✓	H1 2026 Regulatory Alignment	H1 2026 Initiate PIONEER Open-Label Extension Study	H2 2026 Registration-Enabling Trial Initiation
Completed 20mg cohort and shared updated results	Provide update on next trial design in Q2 2026 following receipt of FDA End-of-Phase meeting minutes Engage with EMA for protocol assistance (mid-2026)	Activating sites for open-label extension (OLE) study to evaluate safety and durability of response	Potential initiation of global registration-enabling trial (pending regulatory feedback)

$352.3M Cash Position as of 12/31/2025 with Runway into 2029

Fully Funded to Support Anticipated Registrational Milestones

Pioneer

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Q&A

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