Fulcrum Therapeutics

Nasdaq FULC

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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 disease with a **focus on benign hematology**

Pociredir

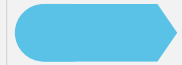
- Potential **best-in class** oral HbF inducer for SCD
  - Robust, rapid, and clinically relevant increases in HbF with early evidence of improvements in hemolysis, anemia, and VOCs
- **Fast Track and Orphan Drug Designations**
- Composition of matter and method of use coverage through 2040
- Phase 1b PIONEER completed in **Q1 2026**
- Update on next trial design in **Q2 2026** following receipt of End-of-Phase meeting minutes
- Initiate a potential registration-enabling trial in **2H 2026**

Pipeline Sustainability & Capital Strength

- Advancing discovery programs focused on benign hematological diseases to provide **long-term pipeline sustainability**
- **$352.3 million** of cash as of 12/31/2025
  - **Cash runway into 2029**
  - Fully funded to support anticipated Pociredir registrational milestones

HbF: Fetal hemoglobin; VOC: Vaso-occlusive crisis

Small Molecule Pipeline

Indication	Asset / Mechanism of Action	Preclinical	Phase 1	Phase 2	Phase 3
Clinical Programs					
Sickle Cell Disease	**Pociredir** (HbF Induction)				
Discovery Programs					
Sickle Cell Disease	Novel HbF Inducers				
Castration Resistant Prostate Cancer					

Pociredir

for Sickle Cell Disease

Fast Track Designation

Orphan Drug Designation

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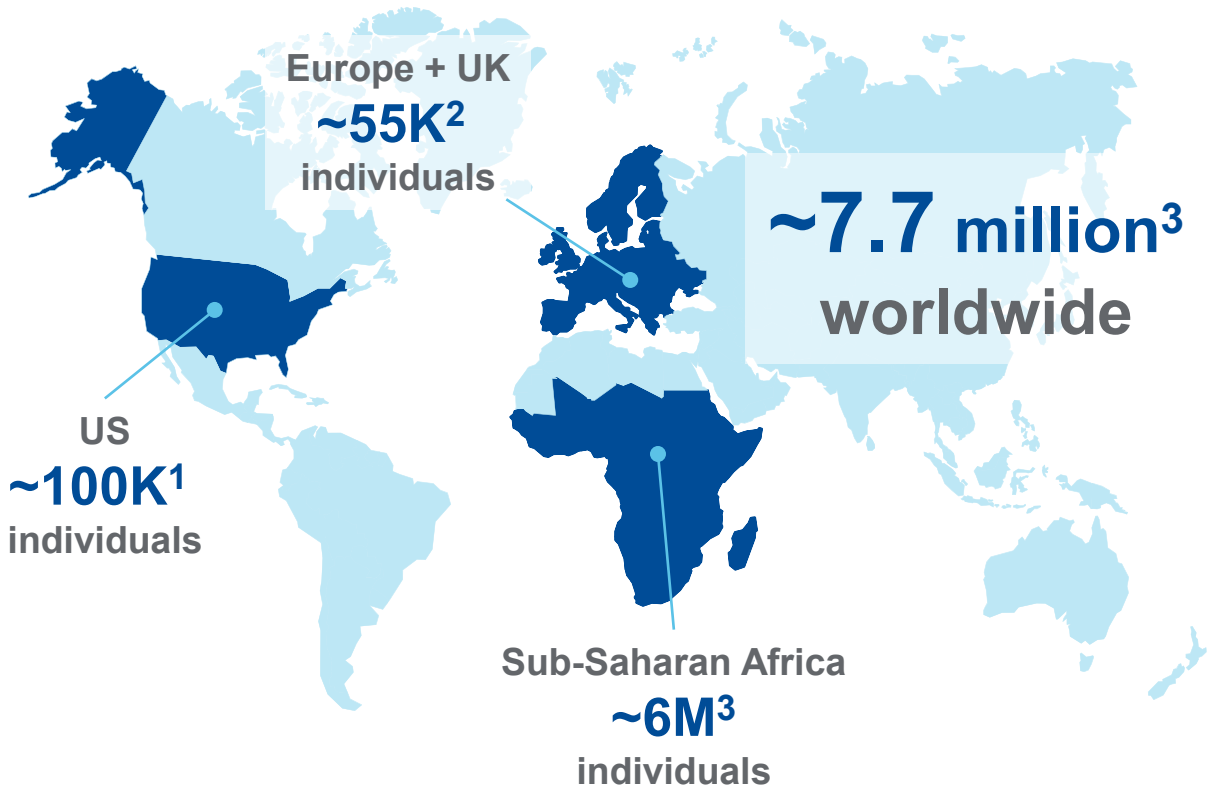
Sickle Cell Disease: Debilitating Disease with High Unmet Need

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 9X 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

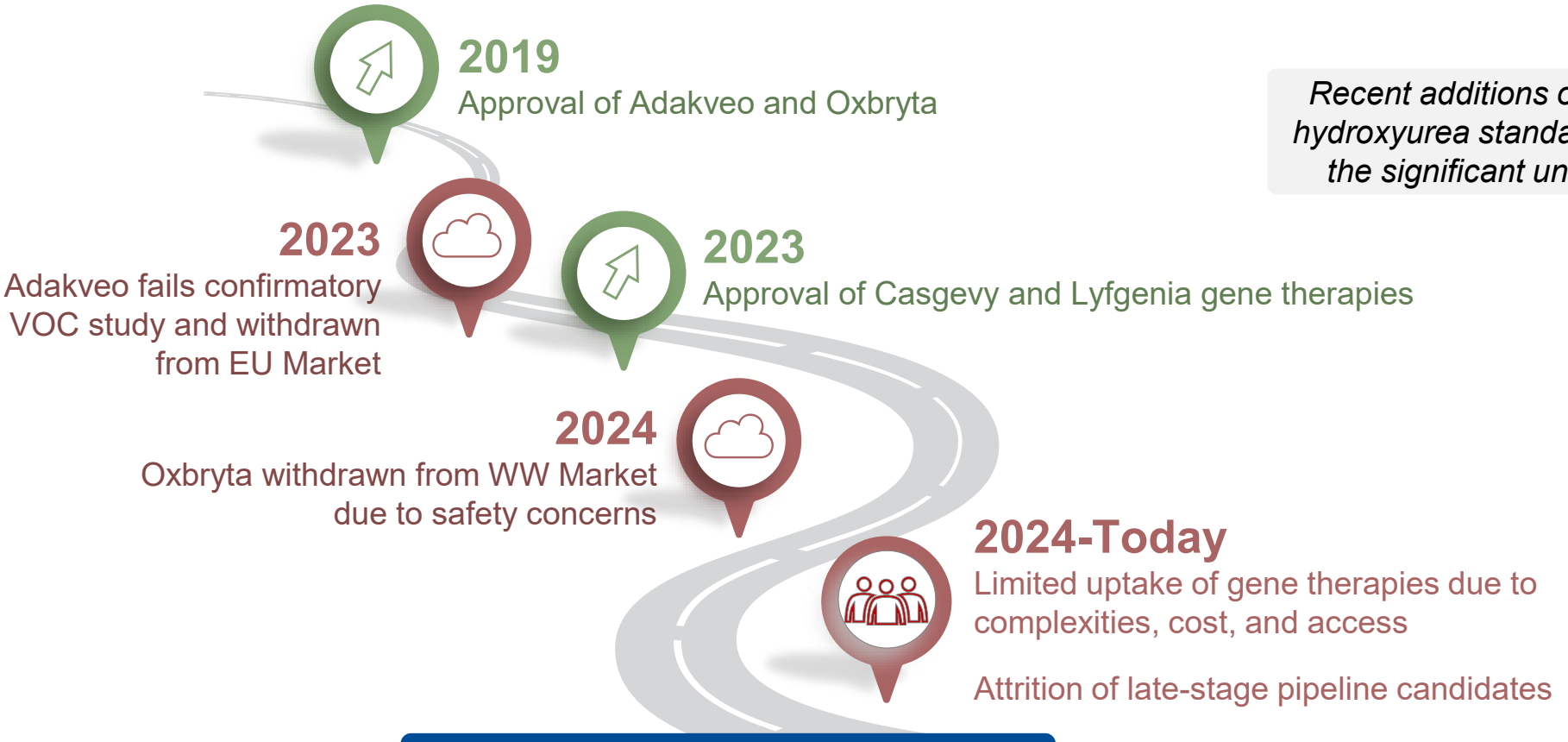
20 mg cohort Demonstrates Pociredir's Best-in-Class Potential

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

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

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 oral therapies
- Access barriers for gene therapies
- Significant racial and socioeconomic disparities remain

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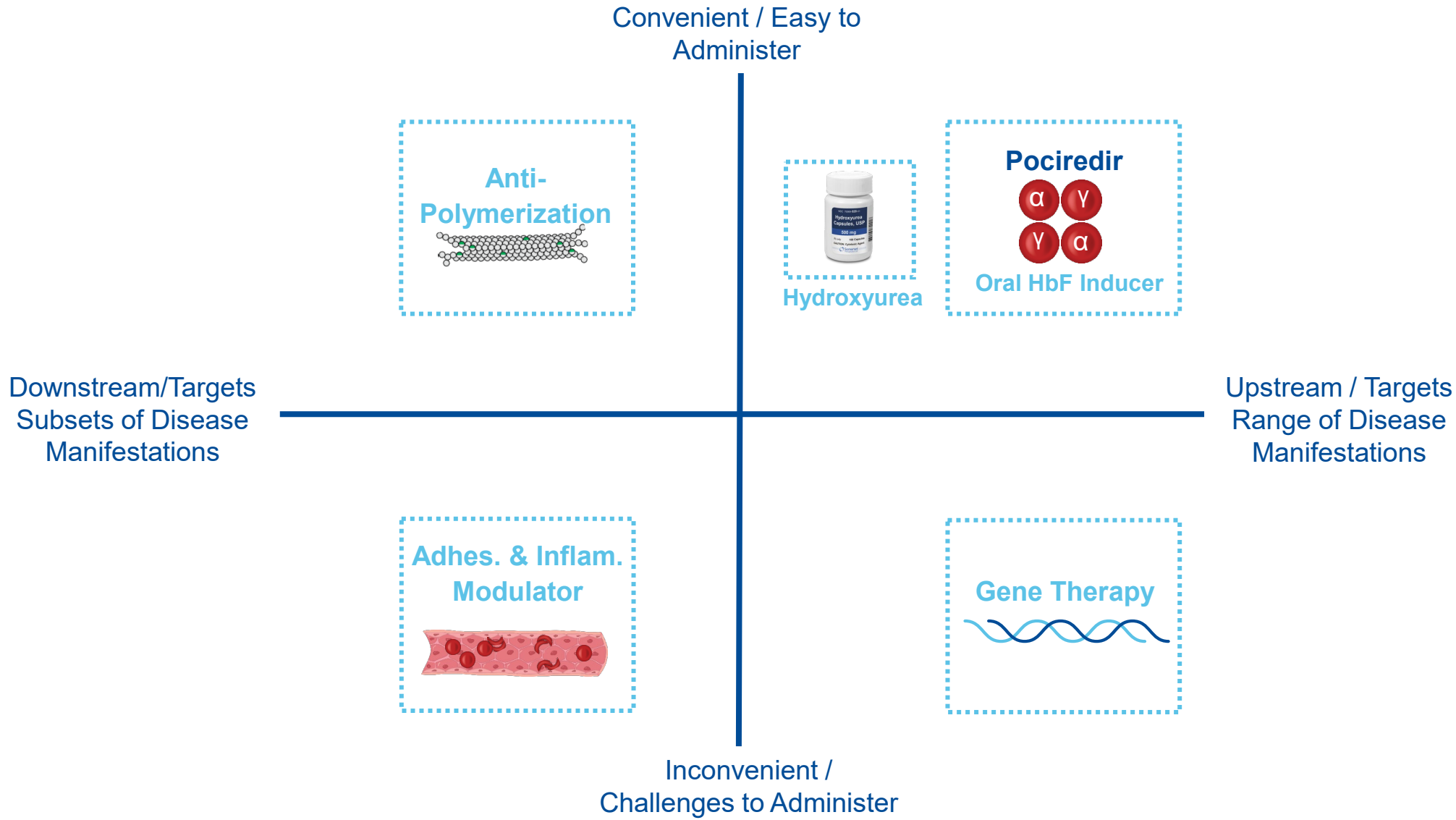
Pociredir has the Potential to Fill a Significant Treatment Gap for SCD



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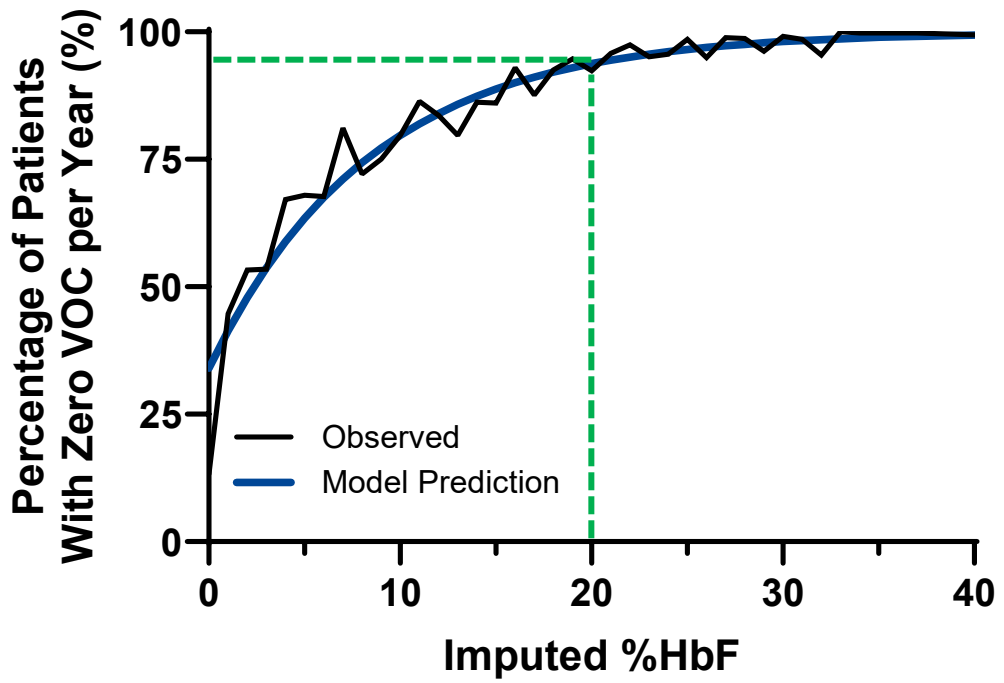
Higher HbF Levels Result in Reduced Symptomology in People Living With SCD

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]

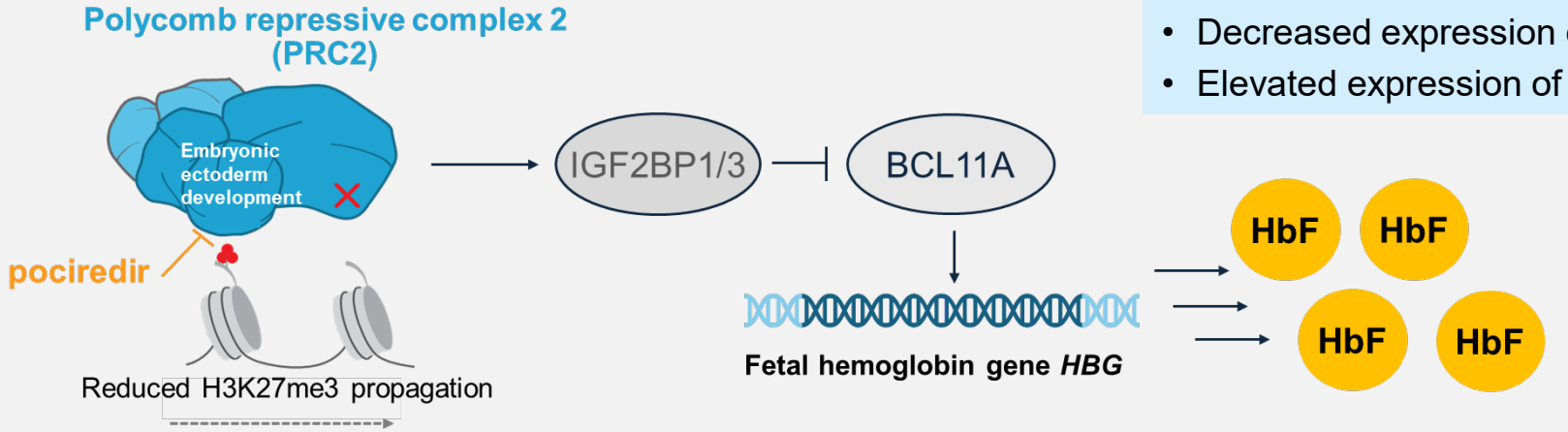
Raising HbF levels also results in:

- Reduced hemolysis
- Reduced anemia
- Fewer recurring events

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).

Targeting EED Results in HbF Increases

Pociredir Is a Potent and Selective EED Binder



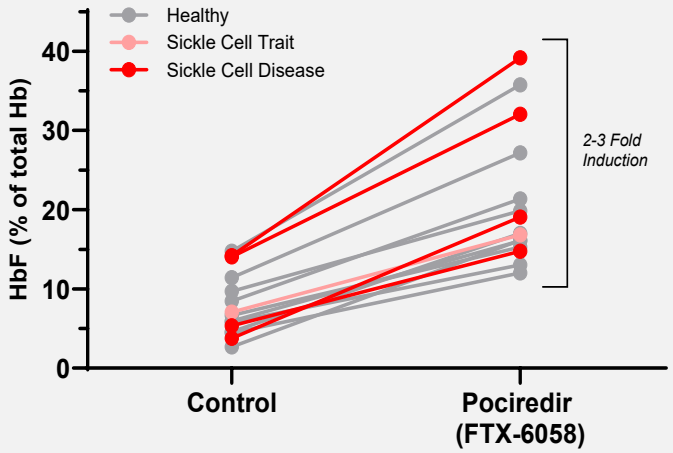
- Decreased expression of HbF repressors and regulators
- Elevated expression of HbF mRNA and protein

- 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

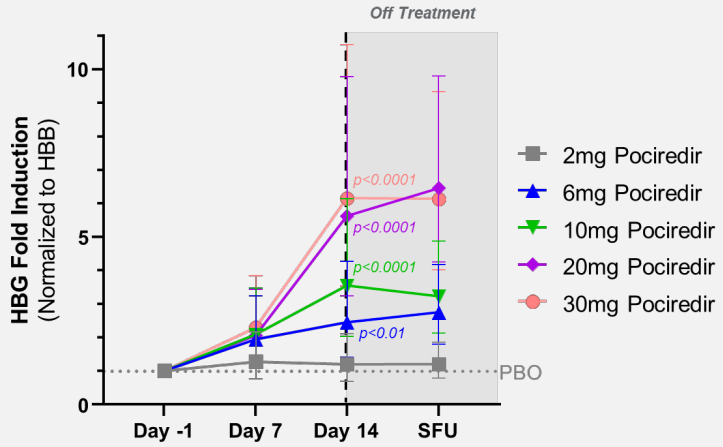
Pociredir Translates Consistently from Preclinical Models to Healthy Volunteers to Patients

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



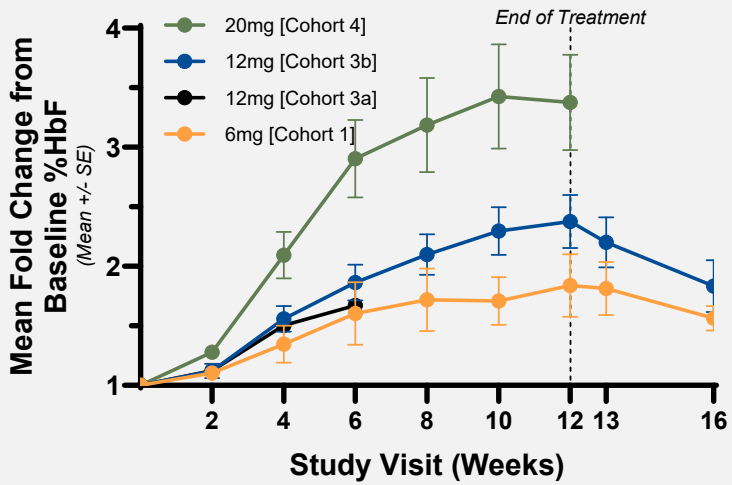
- 8 – 25% absolute increase in %HbF
- Consistent 2-3 fold induction across both healthy subject and SCD CD34+ donor-derived cells

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



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

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



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

1. n=6 per cohort
2. 20 mg cohort PD Analysis Set n=12. 12mg cohort 3b 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 cut of March 3, 2023. 12mg cohort 3a n=1 at Day 42, 6mg cohort n=5 at Day 84, 2 mg cohort n=1 at Day 84.

PIONEER: A Phase 1b Study in Patients With SCD

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

4-Week Screening Period

12-Week Treatment Period (QD Capsule)

- Cohort 1 6 mg (n=10)
- Cohort 2 2 mg (n=2)
- Cohort 3a 12 mg (n=4)
- Cohort 3b 12 mg (n=16)[1]
- Cohort 4 20 mg (n=13)

Completed under previous protocol with a less severe, all-comer SCD patient population

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[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.
1 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
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

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

1. n=12 PD Analysis Set

Dose-Dependent Pociredir PK Exposure in Sickle Cell Disease Patients

Plasma PK Comparison between cohorts in PIONEER Study

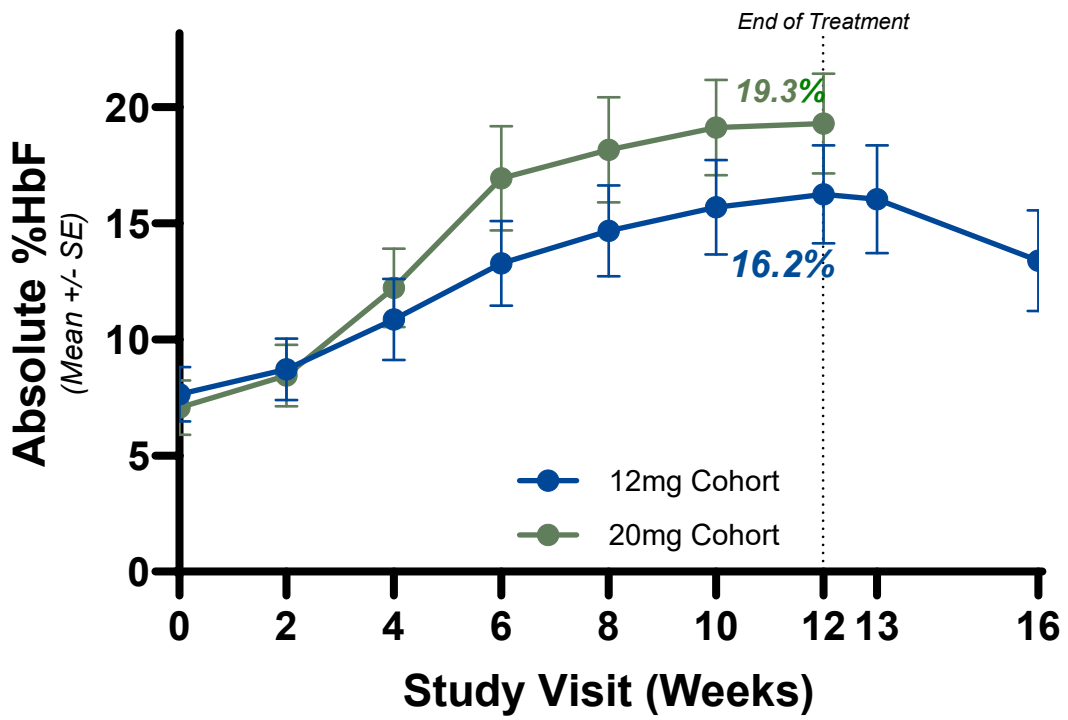
Dose (PIONEER Study)	Number of Patients	Mean C_{max} ng/mL (%CV)	Median T_{max} hrs (range)	Mean AUC_{0-4h} ng·hr/mL (%CV)
6 mg (Day 1)	9	18.1 (20.9)	2.0 (2.0-4.0)	45.2 (24.7)
12 mg (Day 1)	16	38.5 (38.9)	3.0 (2.0-4.0)	94.8 (45.4)
20 mg (Day 1)	12	69.4 (54.7)	3.0 (1.0-4.0)	168.0 (58.0)

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

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

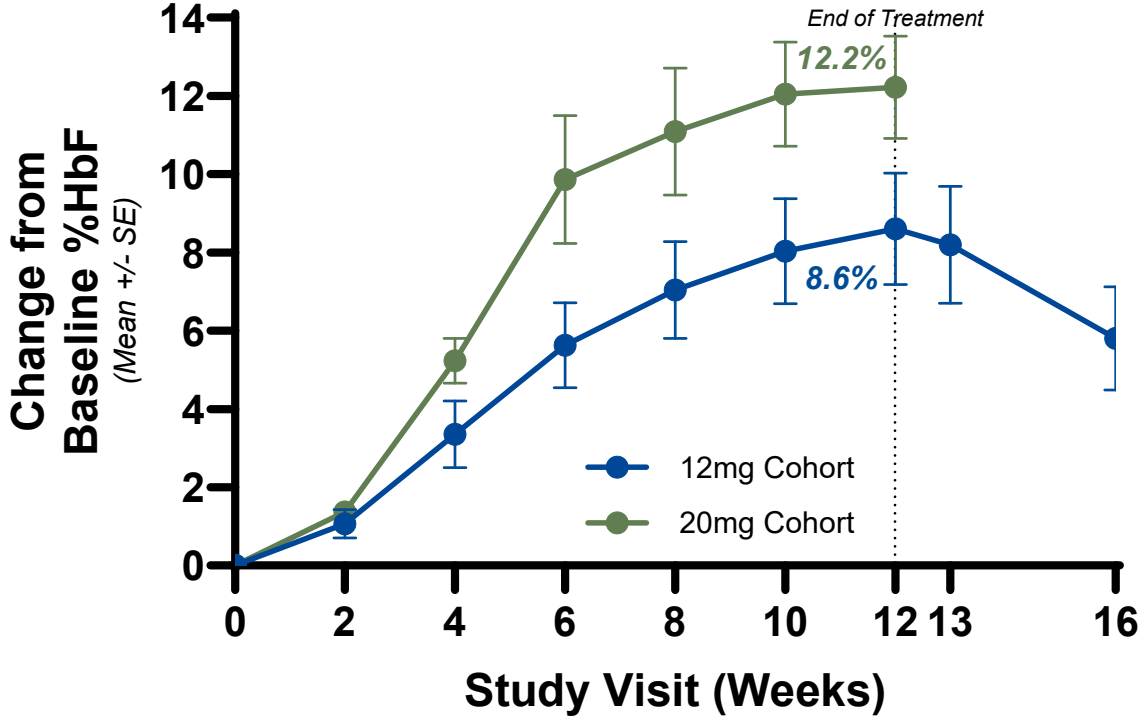
Data as of Dec 23, 2025 Data Cut

Mean Absolute %HbF



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

Mean Absolute %HbF Change from Baseline



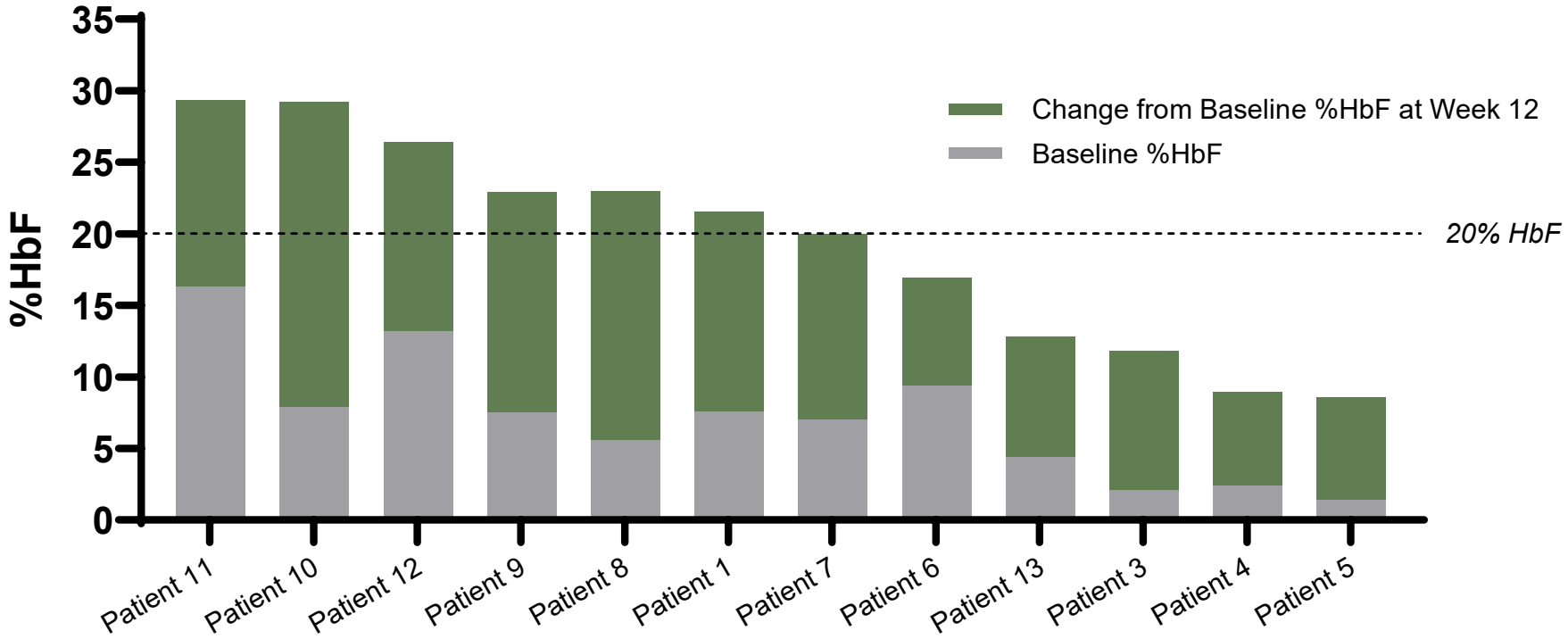
20 mg Pociredir increased %HbF by 12.2% at Week 12

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

Data as of Dec 23, 2025 Data Cut

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

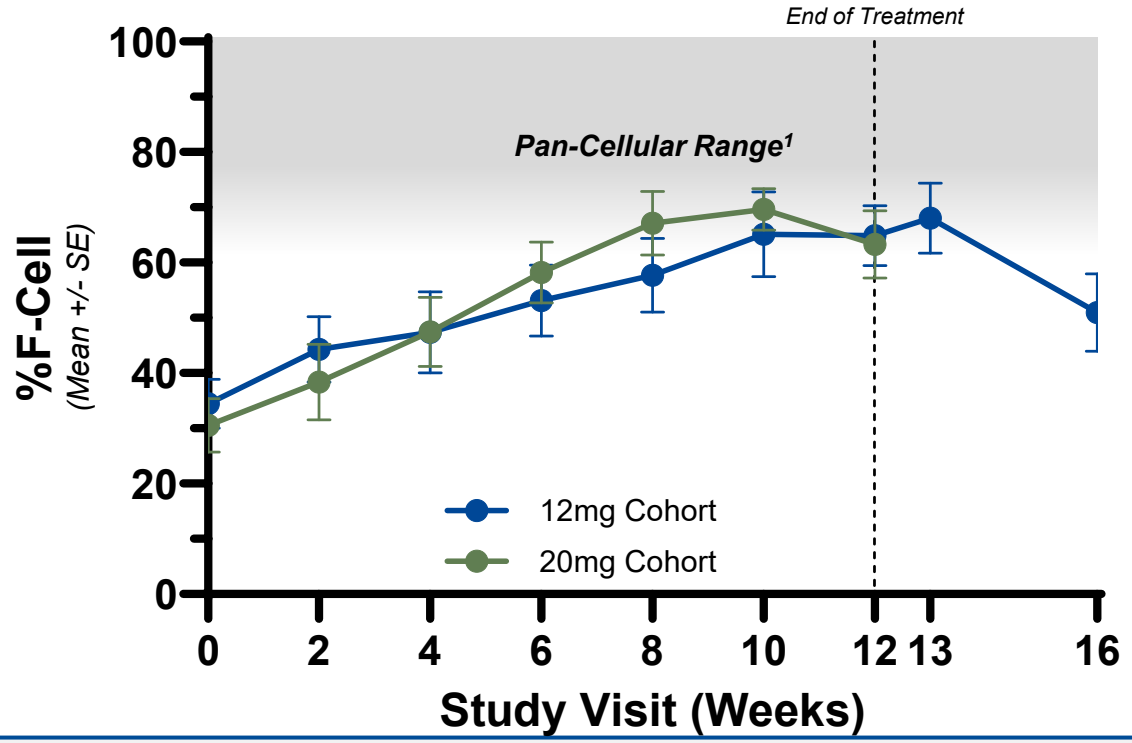


- **7 of 12 patients (58%) achieved a ≥20% absolute level of %HbF at their latest study visit**
- **All patients in the 20 mg cohort achieved at least a 6.5% absolute increase in HbF (or greater)[1]**

1. No patients received transfusions during the treatment period.

Progression Toward Pan-Cellular Induction of HbF

Mean %F-Cells



Data as of Dec 23, 2025 Data Cut

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

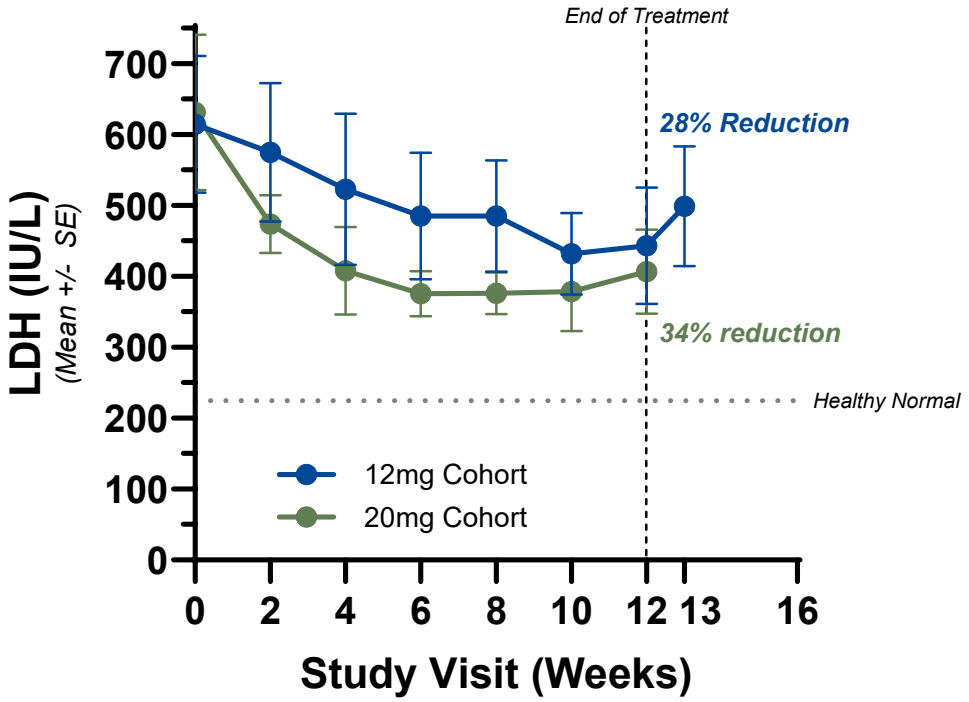
F-Cells are red blood cells that contain HbF, which increases their resistance to sickling and hemolysis. A higher proportion of F-cells is associated with improved red blood cell health.[1]

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.

Consistent Reductions in Markers of Hemolysis

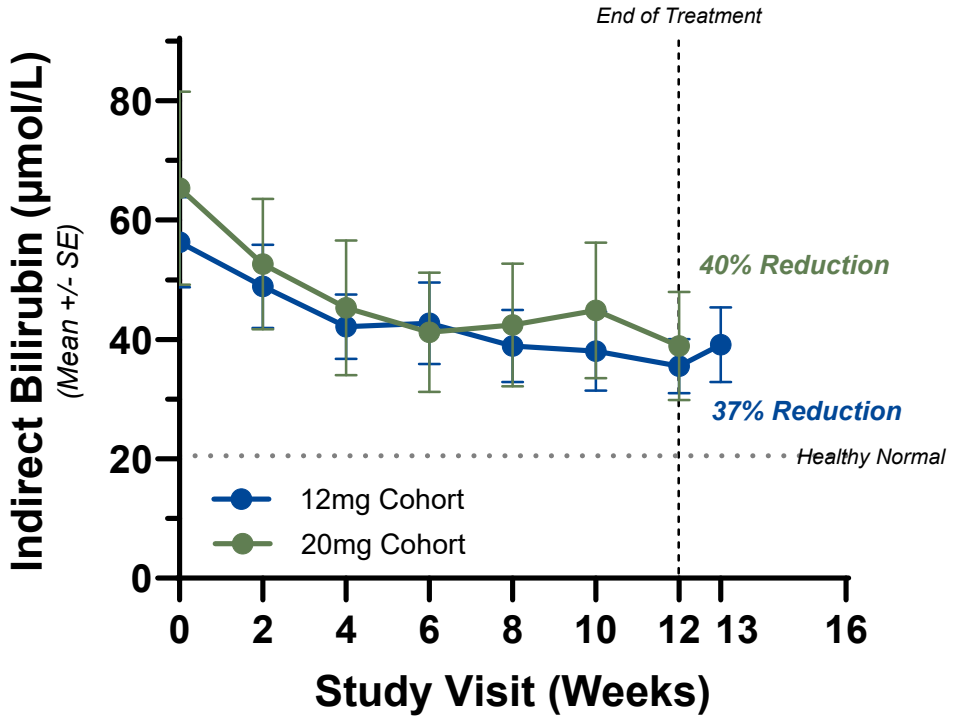
Data as of Dec 23, 2025 Data Cut

Mean Lactate Dehydrogenase (LDH)



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

Mean Indirect Bilirubin



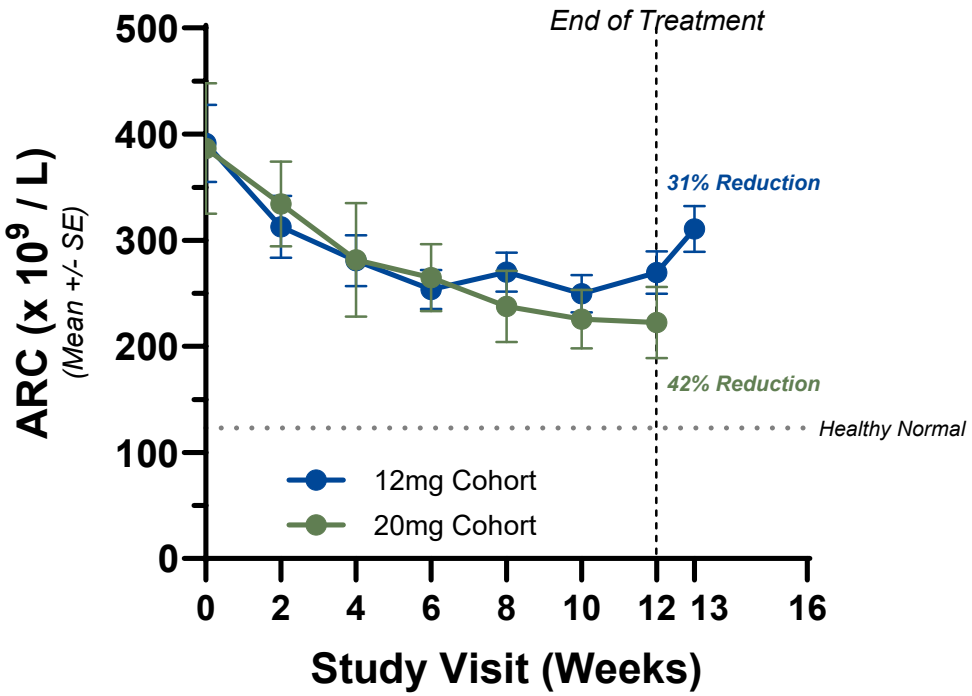
Indirect bilirubin increases with red blood cell destruction

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.

Improved Erythropoiesis and Normalization of Red Blood Cell Morphology

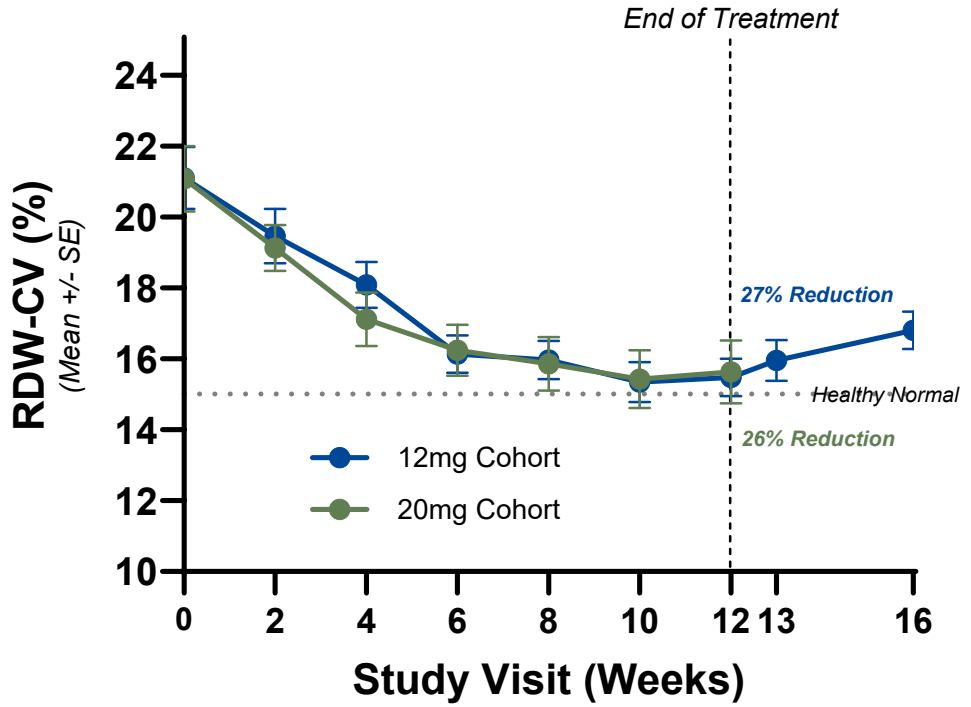
Data as of Dec 23, 2025 Data Cut

Mean Absolute Reticulocyte Count (ARC)



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

Mean Red Cell Distribution Width (RDW-CV)



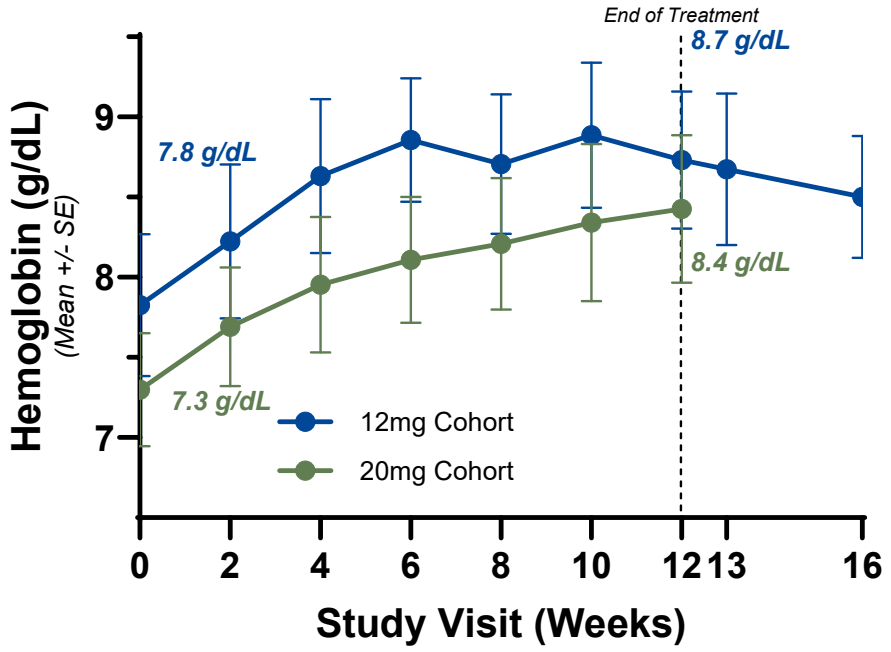
Normalization of RDW-CV indicates a more uniform red blood cell population

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

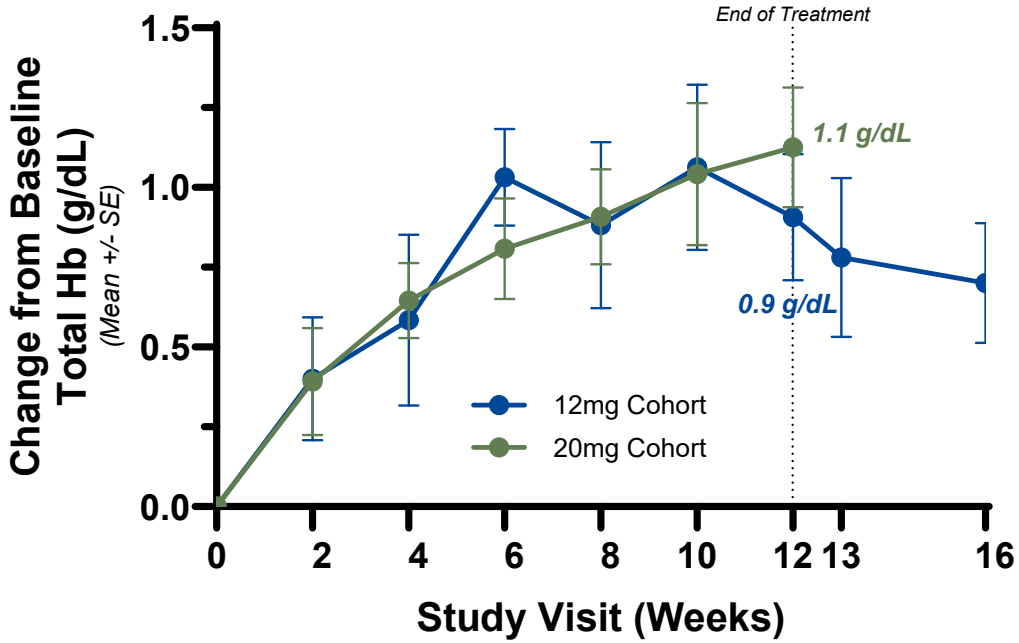
Reduction in Anemia: >1 g/dL Increase in Hemoglobin in 12 Weeks, With no Transfusions

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,

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

Data as of Dec 23, 2025 Data Cut

Baseline

Reported Baseline VOCs

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

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

Study Treatment Period

N=12 PD Analysis Set

Observed VOCs in the Treatment Period

6 VOCs observed in 5 patients[3]

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

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

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

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

Data as of Dec 23, 2025 Data Cut

Adverse Event (AE)*	Cohort 4 (20 mg) n=13 (%)[1]
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)
AE with treatment interruption	1 (8)
AE with treatment discontinuation	1 (8)[b]

AE > 10% of Patients (n) with event*			Treatment-related AEs		
Preferred term	n (%)	Highest Grade	Preferred term	# of AEs	Grade
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			

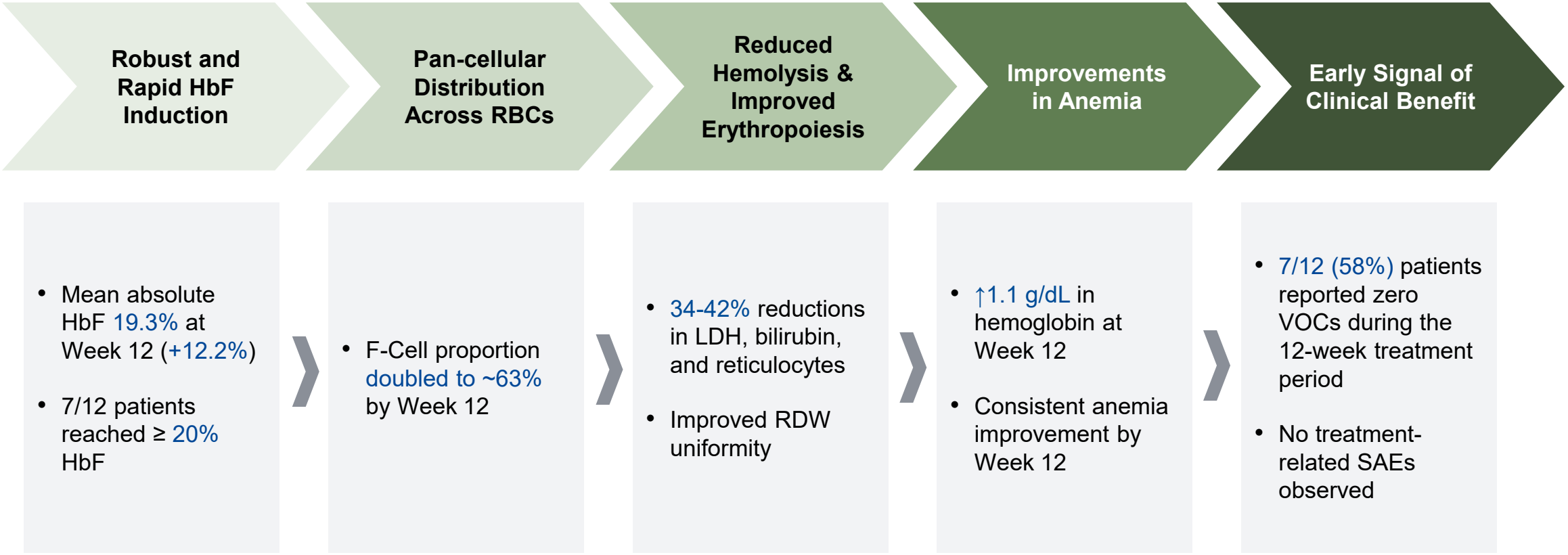
- 3 patients reported treatment-related AEs
  - All treatment-related AEs resolved during treatment period
  - Grade 3 Reticulocytopenia alongside broader CBC reductions in the context of a viral infection (presumed Parvo B19) and amoxicillin treatment. 14-day pociredir treatment interruption. Continued 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 on study 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.

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

Pociredir: Potential to Transform the Treatment of SCD

Connecting the Dots from HbF Induction to Reduced VOCs



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

Q1 2026 PIONEER Data ✓	H1 2026 Regulatory Alignment	H1 2026 Initiate PIONEER Open-Label Extension Study	H2 2026 Registrational 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