POCIREDR, A NOVEL ORAL ONCE-DAILY FETAL HEMOGLOBIN INDUCER: RESULTS FROM THE PHASE 1B PIONEER STUDY IN ADULT PARTICIPANTS WITH SEVERE SICKLE CELL DISEASE AND HYDROXYUREA INTOLERANCE OR UNRESPONSIVENESS

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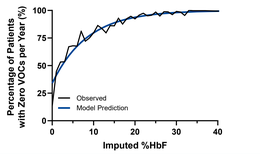
NCT05169580

INTRODUCTION

Higher fetal hemoglobin (HbF) levels improve morbidity and mortality and decrease vaso-occlusive crises (VOCs) in people living with sickle cell disease (SCD).[1-4] Real-world data analyses linking HbF levels to clinical outcomes indicate that incremental increases in HbF expression of as low as 1% are associated with a 4%–8% reduction in VOCs.[5-6]

Probability of Observing Zero VOCs/Year by %HbF[5]



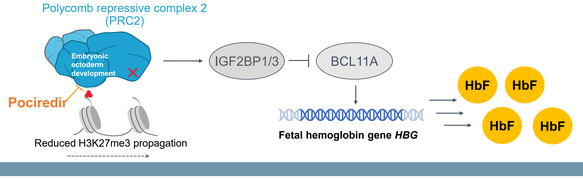
HbF Level	% of Patients Reporting Zero VOCs (Model Prediction)
15%	89%
20%	94%
25%	97%

Pociredir (formerly FTX 6058) is an oral once-daily HbF inducer being evaluated in the PIONEER Phase 1b dose-escalation study in adult patients with severe SCD.

We report safety and efficacy results for cohort 3b (12 mg dose) and cohort 4 (20 mg dose) from the ongoing PIONEER study, with cohort 4 data as of the November 11, 2025, data cut.[a]

[a] Cohort 4 (20 mg) is fully enrolled; N=6 patients had completed the 12-week treatment period as of the November 11, 2025, data cut.

Pociredir Mechanism of Action (MOA)[7-11]



METHOD

PIONEER: A Phase 1B Study in Adult Patients with Severe SCD[a]

Study Design (Open Label, Dose Escalation)

4-Week Screening Period

Cohort 1 (6 mg; N=10)[b]; **Cohort 2** (2 mg; N=2)[b]; **Cohort 3a** (12 mg; N=4)[b] — Completed

Cohort 3b (12 mg; N=16) — Completed

Cohort 4 (20 mg; N=13)[c] — Ongoing

4-Week Follow-Up Period

Select Inclusion Criteria[d]

- Patients with SCD aged 18–65 years
- Discontinued HU for ≥60 days
- Severe SCD 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

Additional criteria apply. For more information, please see https://www.clinicaltrials.gov/study/NCT05169580

[a] Adapted from Alan S, et al. J Sick Cell Dis. 2025;2(suppl 1):yoaf013.001.[11]
[b] Data for cohorts 1, 2, and 3a (12 mg) conducted prior to U.S. FDA full clinical hold for pociredir on February 23, 2023, which was lifted August 23, 2023, have been presented.[12]
[c] Cohort 4 (20 mg) is fully enrolled; N=6 patients had completed the 12-week treatment period as of the Nov 11, 2025, data cut.
[d] U.S. FDA placed a full clinical hold on pociredir on February 23, 2023, which was lifted on August 23, 2023. Inclusion criteria prior to the hold allowed enrollment of patients on concomitant HU (n=5) and those with VOC frequency of ≥2 per year.
F-cells, cells expressing fetal hemoglobin; HU, hydroxyurea; PK, pharmacokinetics; QD, once daily.

CONTACT INFORMATION

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ACKNOWLEDGEMENTS

Thank you to the people living with SCD and their caregivers for participating in this trial as well as the study teams for their contributions.

RESULTS

Cohort 3b (12 mg) and Cohort 4 (20 mg) Baseline Demographics and Characteristics

	Cohort 3b (12 mg); n=16 % or Mean (SD)	Cohort 4 (20 mg); n=12[a] % or Mean (SD)
Sex, % male	44%	17%
Age, years	34.3 (12.25)	32.3 (6.98)
Country		
United States	62.5%	58.3%
South Africa	37.5%	8.3%
Nigeria	0%	33.3%
Genotype		
Hb SS	87.5%	83.3%
Hb Sβ[0]	12.5%	8.3%
Hb Sβ[+]		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)

[a] n=12 pharmacodynamic (PD) analysis set, which excludes the one patient who discontinued on day 1 of study.

Generally Well Tolerated, with No Serious Treatment-Related Adverse Events

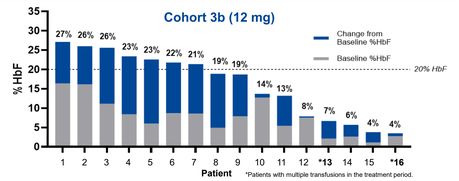
Event[a]	Cohort 3b, n=16 (%)[b]	Cohort 4, n=13 (%)[b]
Patients with adverse events (AEs) regardless of causality	15 (94)	11 (85)
Treatment-related AEs	3 (19)	3 (23)
Grade ≥3 AEs	8 (50)	4 (31)
Grade ≥3 treatment-related AEs	0 (0)	1 (8)
Serious adverse events (SAEs)	5 (31)	4 (31)
SAEs consistent with VOC/SCD complications	5 (31)	4 (31)
Treatment-related SAEs	0 (0)	0 (0)
AEs with treatment interruption	1 (6)	1 (8)
AEs with treatment discontinuation	0 (0)	1 (8)[c]

AEs >10% of Patients (n) with Event[d]					Treatment-Related AEs[e]				
AE, Preferred Term	n (%)	Highest Grade	n (%)	Highest Grade	AE, Preferred Term	n	Grade	n	Grade
VOC	8 (50)	3	5 (38)	3	Headache	1	1		
Pain (back, extremity)	5 (31)	2	2 (15)	2	Nausea	1	1		
Fatigue	4 (25)	2	3 (23)	2	Paresthesia (face)	1	1		
Arthralgia	4 (25)	2	2 (15)	1	Diarrhea	1	1		
Diarrhea	3 (19)	2	0 (0)	NA	Rhinorrhea	1	1		
Constipation	3 (19)	2	0 (0)	NA	Reticulocytopenia (ARC)			1	3
Vomiting	2 (13)	1	0 (0)	NA	Insomnia			1	1
Headache	3 (19)	2	2 (15)	1	Iron overload			1	1
Nausea	2 (13)	2	0 (0)	NA					
Urinary tract infection	2 (13)	3	2 (15)	2					
Cough	2 (13)	1	0 (0)	NA					
Dyspnea	2 (13)	2	0 (0)	NA					
Rash	2 (13)	2	0 (0)	NA					
Acne	2 (13)	2	0 (0)	NA					
Edema peripheral	2 (13)	2	0 (0)	NA					
Bone pain	0 (0)	NA	2 (15)	2					
Malaria	0 (0)	NA	3 (23)	2					
Muscle spasm	2(13)	2	0 (0)	NA					

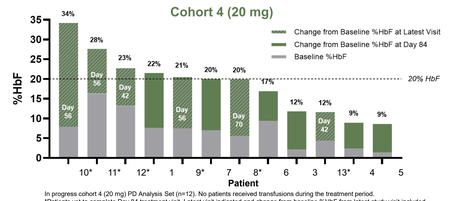
[a] AEs in table are treatment-emergent AEs
[b] Safety Analysis Sets
[c] One discontinuation occurred due to death (grade 5 SAE). Death was determined by the investigator to be unrelated to treatment following complications from VOC reported on day 1 of study. Participant had previously undisclosed hospital admissions for VOC on days -7 and -1 prior to treatment.
[d] AEs could be reported multiple times as individual symptoms during an event such as a VOC.
[e] Includes AEs deemed possibly related, probably related, or definitely related.

- There were no dose-limiting toxicities or dose discontinuations due to treatment-related AEs
- Cohort 3b (12 mg)
  - 3 patients reported treatment-related AEs; all were grade 1 in severity
    - All related AEs resolved during the treatment period
  - A total of 12 VOCs were reported on study
    - 3 of the 12 VOCs occurred off drug during the study follow-up period
- Cohort 4 (20 mg)
  - 3 patients reported treatment-related AEs
    - All related AEs resolved during the treatment period
    - Grade 3 reticulocytopenia alongside broader complete blood count (CBC) reductions in the context of a viral infection (presumed parvovirus B19) and amoxicillin treatment. Treatment was interrupted for 14 days. CBC values continued to normalize following re-exposure to pociredir
  - A total of 6 VOCs were reported on study at data cut
    - 1 of 6 VOCs occurred in the safety follow-up
- AE profile consistent with severe sickle cell disease
- Following this cohort 4 (20 mg), pociredir has been dosed in 148 adults to date
  - 103 healthy adults
  - 45 patients with SCD

Baseline %HbF and Change from Baseline %HbF at Latest Time Point



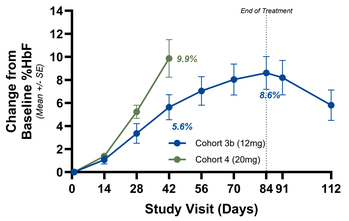
- HbF increased in all 16 patients at day 84
- 7 of 16 patients (44%) achieved a ≥20% absolute level of %HbF at day 84



In progress cohort 4 (20 mg) PD Analysis Set (n=12). No patients received transfusions during the treatment period.
*Patients yet to complete Day 84 treatment visit. Latest visit indicated and change from baseline %HbF from latest study visit included.

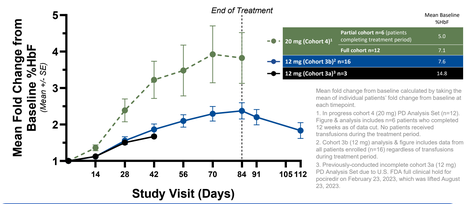
- As of data cut, 7 of 12 patients (58%) achieved a ≥20% absolute level of %HbF at their latest study visit
- All patients in cohort 4 (20 mg) achieved a ≥6.5% absolute HbF increase from baseline

Mean Absolute %HbF Change from Baseline



- 12 mg pociredir increased %HbF by 8.6% (p<0.0001) through week 12
- 20 mg pociredir increased %HbF by 9.9% through week 6

Demonstration of Dose Response; Cohort 4 (20 mg)[1] Preliminary Results Show Improvement Over Cohorts 3a, 3b (12 mg)



Mean fold change from baseline calculated by taking the mean of individual patients' fold change from baseline at each timepoint.
1. In progress cohort 4 (20 mg) PD Analysis Set (n=12). Figure & analysis includes n=6 patients who completed 12 weeks as of data cut. No patients received transfusions during the treatment period.
2. Cohort 3b (12 mg) analysis & figure includes data from all patients enrolled (n=16) regardless of transfusions during treatment period.
3. Previously-conducted incomplete cohort 3a (12 mg) PD Analysis Set due to U.S. FDA full clinical hold for pociredir on February 23, 2023, which was lifted August 23, 2023.

- Mean fold change from baseline accounts for variability across cohort baselines to evaluate dose response
- Patients with complete 12-week data (n=6) in cohort 4 (20 mg) achieved >3.75-fold induction of HbF, demonstrating a clear dose-response vs. prior cohorts 3a, 3b (12 mg)

Percentage of F-Cells (Exploratory Endpoint):
Erythroid cells containing HbF increased in both cohort 3b and cohort 4 (as of data cut), as evidenced by %F-cells reaching 53% at day 42 in cohort 3b (12 mg) and 58% at day 42 in cohort 4 (20 mg). Cohort 3b (12 mg) approached pan-cellular ranges of %F-cells, 65% after 12-weeks of treatment.

Changes in Markers of Hemolysis and Erythropoiesis

		Baseline (SD)	Mean Change from Baseline (SD)		
			Treatment Period		Safety Follow-Up (Off Drug)
			Day 42	Day 84	Last Data Collection
Mean indirect bilirubin (μmol/L)	Cohort 3b (12 mg)	56.3 (30.3)	-13.6 (20.1) P=0.0161	-20.9 (19.0) P=0.0005	-17.9 (15.1) P=0.0004 [a]
	Cohort 4 (20 mg)	65.3 (55.9)	-24.2 (27.4) P=0.0114	-	-
Mean lactate dehydrogenase (IU/L)	Cohort 3b (12 mg)	614.6 (385.9)	-129.4 (146.9) P=0.0031	-171.5 (135.6) P=0.0001	-133.3 (163.2) P=0.0069 [a]
	Cohort 4 (20 mg)	609.7 (377.2)	-238.2 (301.6) P=0.0256	-	-
Mean absolute reticulocyte count (103 cells/μL	Cohort 3b (12 mg)	391.4 (146.3)	-147.8 (155.3) P=0.0024	-121.8 (133.6) P=0.0024	-59.1 (128.8) P=0.0972 [a]
	Cohort 4 (20 mg)	386.6 (204.8)	-127.9 (164.7) P=0.0276	-	-
Mean red cell distribution width (%)	Cohort 3b (12 mg)	21.1 (3.5)	-5.0 (2.8) P<0.0001	-5.6 (2.6) P<0.0001	-5.0 (3.1) P<0.0001 [b]
	Cohort 4 (20 mg)	21.1 (3.2)	-4.7 (2.6) P=0.0001	-	-
Mean hemoglobin (g/dL)	Cohort 3b (12 mg)	7.8 (1.8)	1.0 (0.6) P<0.0001	0.9 (0.8) P=0.0004	0.7 (0.7) P=0.0023 [b]
	Cohort 4 (20 mg)	7.3 (1.2)	0.7 (0.5) P=0.0005	-	-

Cohort 3b (12 mg) includes data from all patients enrolled (n=16) regardless of transfusions during treatment period.
Cohort 4 (20 mg) in progress. PD Analysis Set (n=12). Analysis includes data through visits with complete laboratory data. No patients received transfusions during the treatment period.

[a] Day 91 last study visit with data collection
[b] Day 112 last study visit with data collection

CONCLUSIONS

- Doses of 12 mg and 20 mg each of pociredir have been generally well tolerated with no dose-limiting toxicities or treatment-related SAEs, consistent with findings from cohort 1 (6 mg), cohort 2 (2 mg), cohort 3a (12 mg)
- As of November 11, 2025 data cut, treatment with 20 mg of pociredir resulted in a more rapid and robust increase in HbF (+9.9% at week 6) compared to treatment with 12 mg pociredir (+8.6% at week 12), with 58% (7/12) of patients in cohort 4 (20 mg) achieving ≥20% HbF at their latest study visit, compared to 44% (7/16) in cohort 3b (12 mg) at week 12.
- Consistent with the MOA of pociredir, patients demonstrated improvements in markers of hemolysis, anemia, and erythropoiesis
- Fewer on-study VOCs were reported in both cohort 3b (12 mg) and cohort 4 (20 mg) than were projected based on the reported annualized rate prior to enrollment. Fifty percent (8/16) of patients in cohort 3b (12 mg) did not experience a VOC during the 16-week study period. As of data cut, five VOCs had been reported in four patients in cohort 4 (20 mg) during the treatment period. Data generation is ongoing.
- Pociredir administered once daily at either 12 mg or 20 mg induces a dose dependent increase in HbF in patients with SCD, reaching ranges where clinically relevant benefit is anticipated.

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