
EHA2024
JUNE 13 - 16 | MADRID
IN-PERSON AND LIVE STREAMED

Interim Results of a Phase 1b Study (PIONEER) of an Oral HbF Inducer, Pociredir, in Sickle Cell Disease

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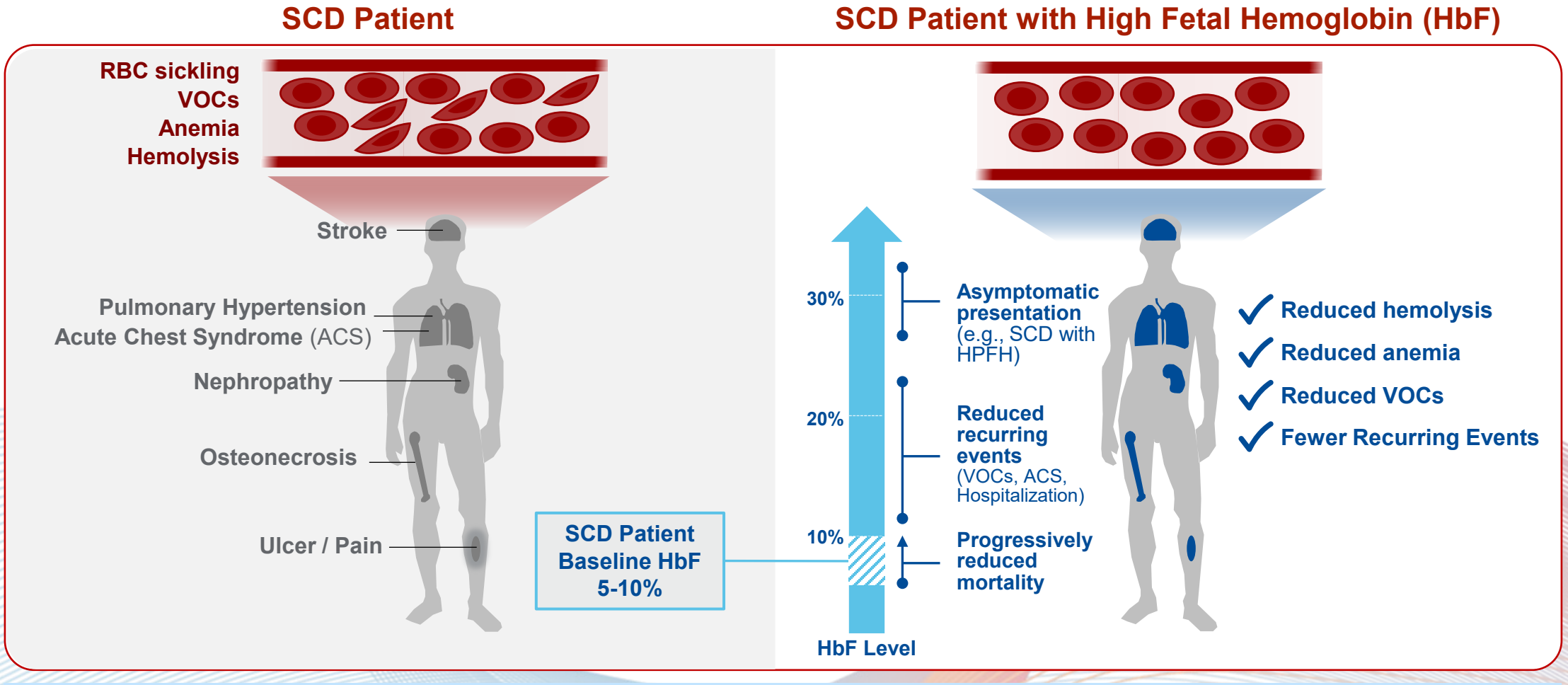
Increasing Fetal Hemoglobin (HbF) is an Established Mechanism to Broadly Improve Outcomes in SCD

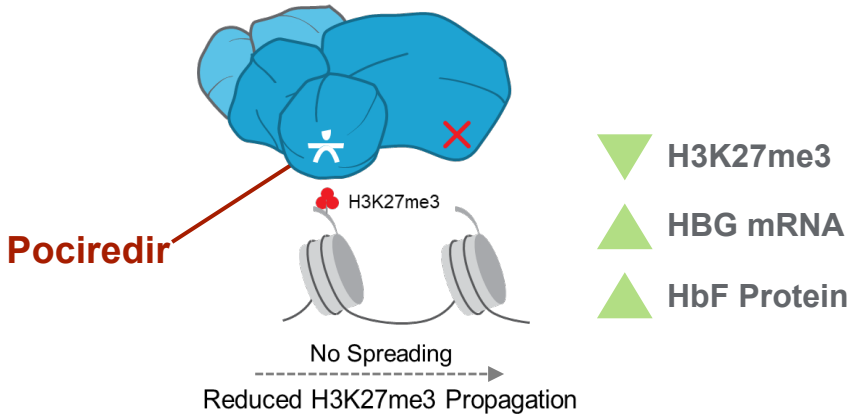


SCD individuals can have additional mutations that cause a condition known as hereditary persistence of fetal hemoglobin (HPFH), which leads to reduced or no symptoms in patients with SCD and β-thalassemia

VOCs: Vaso-occlusive crisis; *Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011; Steinberg M J Clin Med. 2020.*

Targeting the EED subunit of PRC2 Increases HbF

Pociredir Inhibits the PRC2 Complex and Induces HbF expression



Pociredir

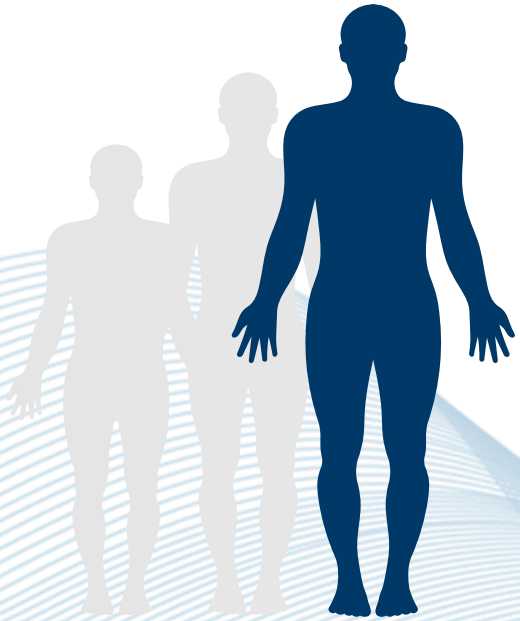
- **Highly Selective**
- **Clean Off-target Profile**
- **Residual H3K27me3 remains (20 – 30%)**

HbF: Fetal hemoglobin protein; HBG: Gamma globin gene (component of fetal hemoglobin); PRC2: polycomb repressive complex 2; EED: embryonic ectoderm development

Phase 1b Clinical Trial in SCD Participants

Study Population

- Participants with SCD
- Aged 18 – 65 yr (inclusive)
- Open Label
- d/c'ed HU ≥60 days



Study Design (dose escalation with 10 patients per cohort)

Screening Period
4 Weeks
(Day -28 to D -1)

Treatment Period (once daily capsule)
12 Weeks
(Day 1 to Day 84)

Follow-up Period
4 Weeks
(Day 85 to Day 112)*
**+3-day visit window*

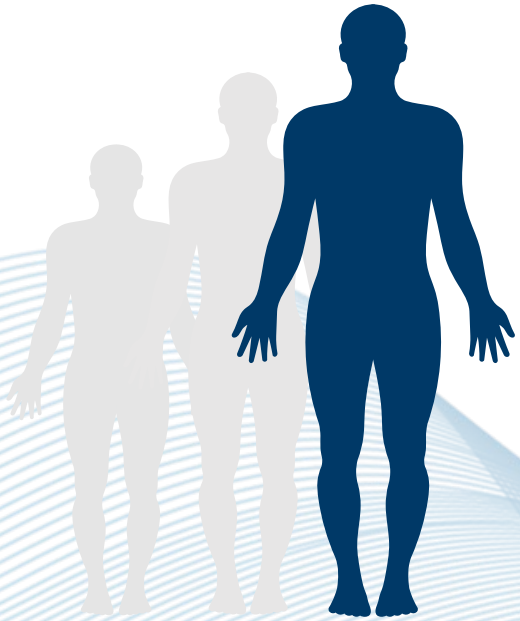
Cohort Dose	Enrolled	Status
6 mg	10	Completed
2 mg	2	Completed
12 mg (a)	4	Completed*
12 mg (b)	Up to 10	Enrolling
20 mg	Up to 10	Planned

* Stopped due to clinical hold; no participant finished

U.S. FDA full clinical hold for Pociredir on February 23, 2023, was lifted on August 18, 2023

Pioneer

Phase 1b Clinical Trial in SCD Participants



Study Endpoints

Primary Endpoints

- Safety and tolerability assessments
- PK parameters

Secondary Endpoints

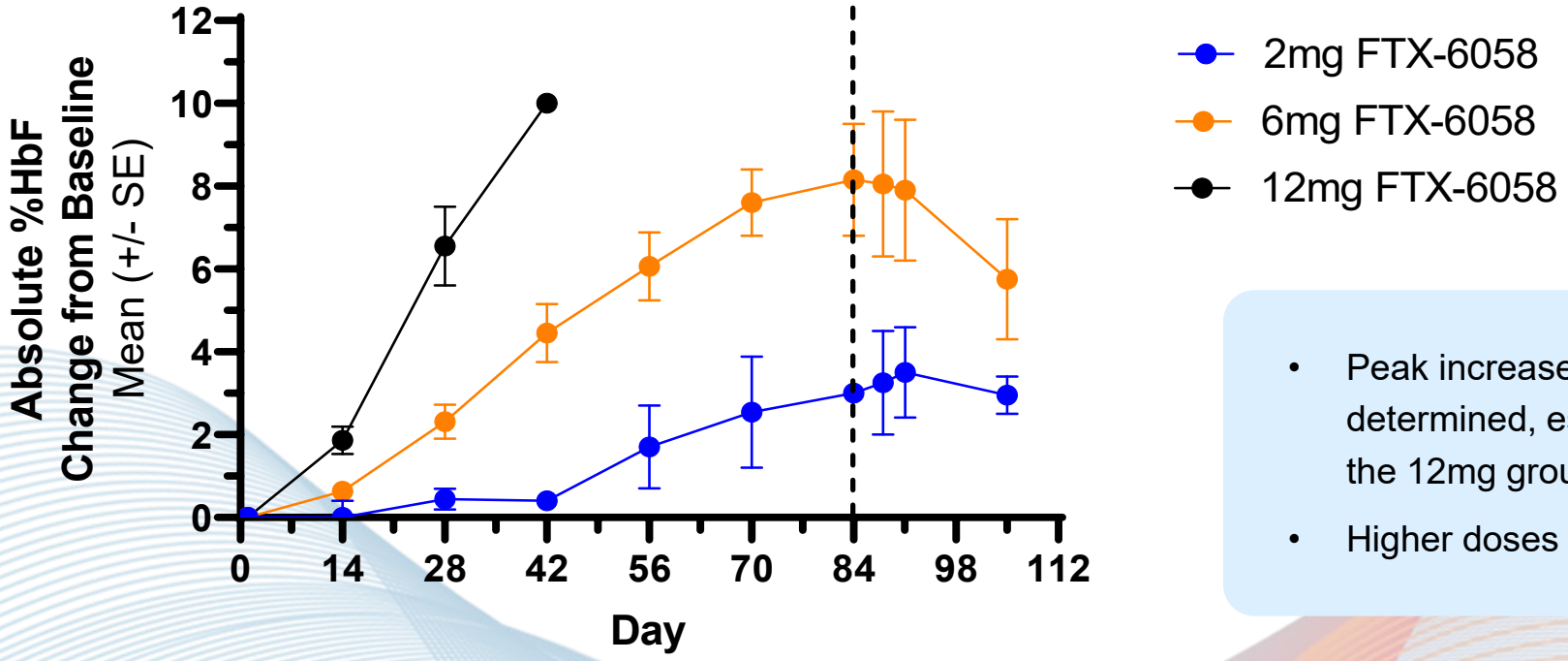
- Measurement of the effect of increased fetal hemoglobin on hemolysis and anemia biomarkers:
  - % HbF (HPLC)
  - Absolute reticulocyte count
  - Total hemoglobin
  - Unconjugated bilirubin

Exploratory Endpoints

- Globin gene expression by droplet digital polymerase chain reaction (ddPCR)
- % F-cells by flow cytometry
- Other biomarkers of hemolysis
- Incidence of VOCs
- PK/PD correlation

Initial Pociredir Data Demonstrates Dose-dependent Increases in HbF in SCD Participants

Absolute %HbF Change from Baseline

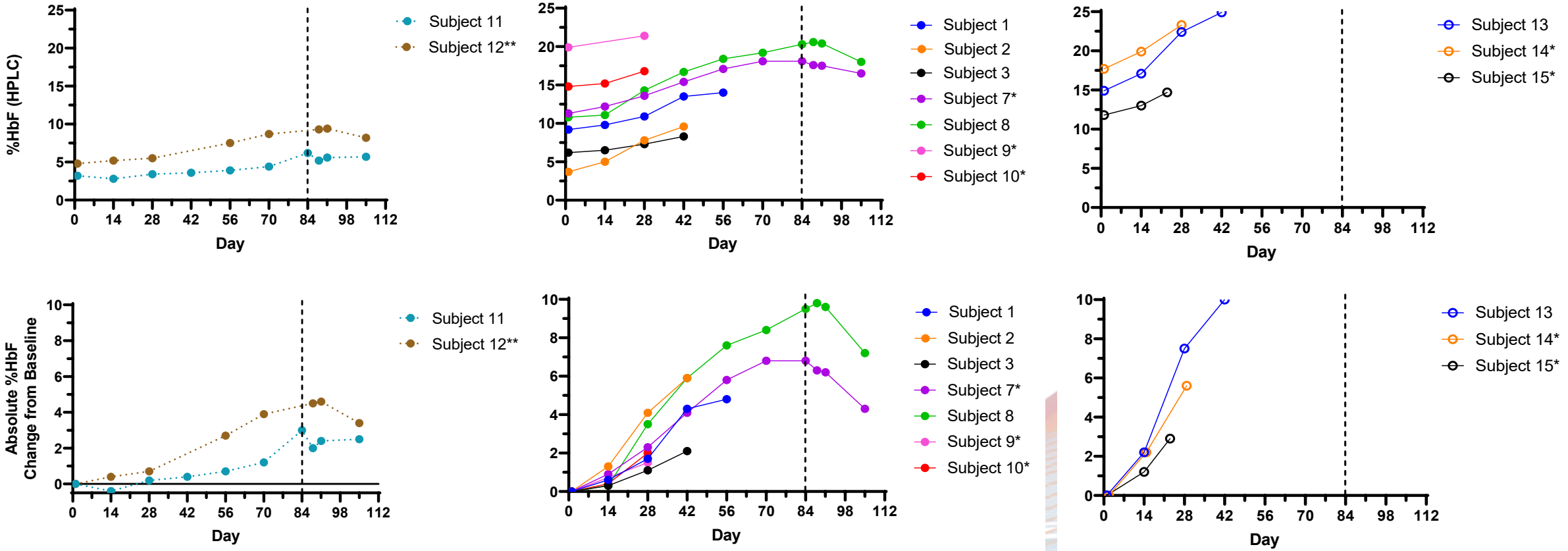


- Peak increases in HbF have yet to be determined, especially the peak increase in the 12mg group.
- Higher doses remain to be studied.

Note: Summary data includes both participants on and off hydroxyurea; Subject 15 ceased dosing on Day 22 and therefore, was only included in the analysis up to Day 14

Pociredir Appears to Have a Dose Dependent, Clinically Relevant and Consistent Increase in HbF

2mg | **6mg** | **12mg**



U.S. FDA issued a full clinical hold for Pociredir on February 23; was lifted on August 18, 2023. Safety data collection continued with data cutoff of March 3, 2023.

Participants on stable dose of hydroxyurea; Note: Subject 15 ceased dosing on Day 22

*** Day 42 and day 84 data not available for subject 12; samples were received by the lab outside of stability window*

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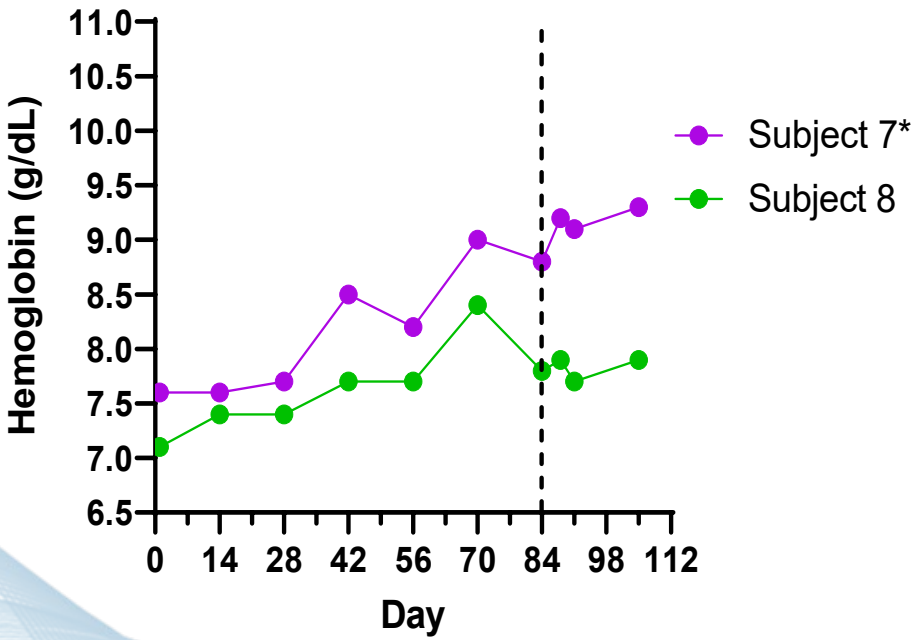
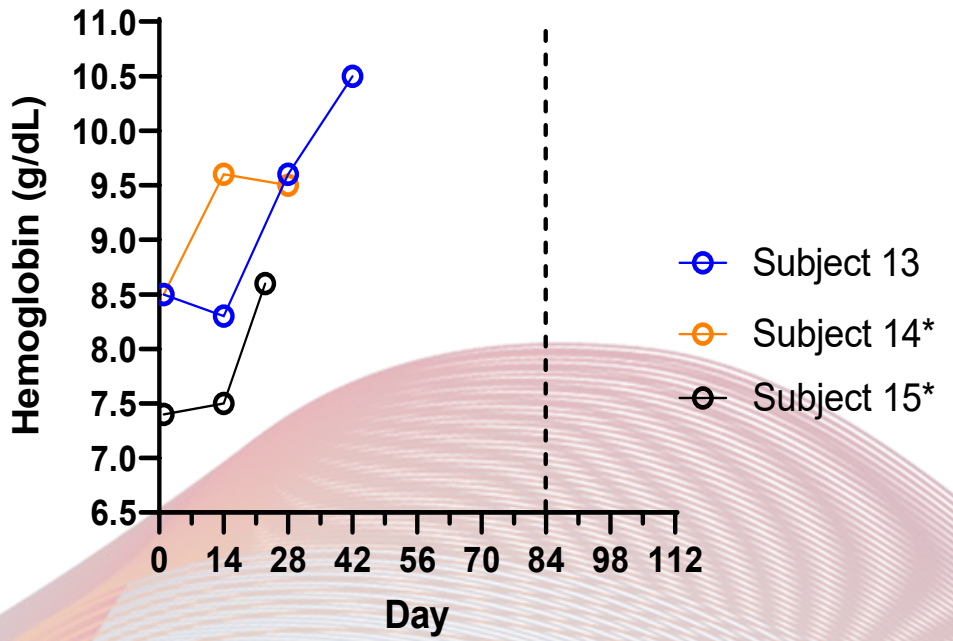
Pociredir Appears to Have a Dose Dependent, Clinically Relevant and Consistent Increase in Total Hemoglobin

Demonstrates Improvement in Anemia

6mg



12mg



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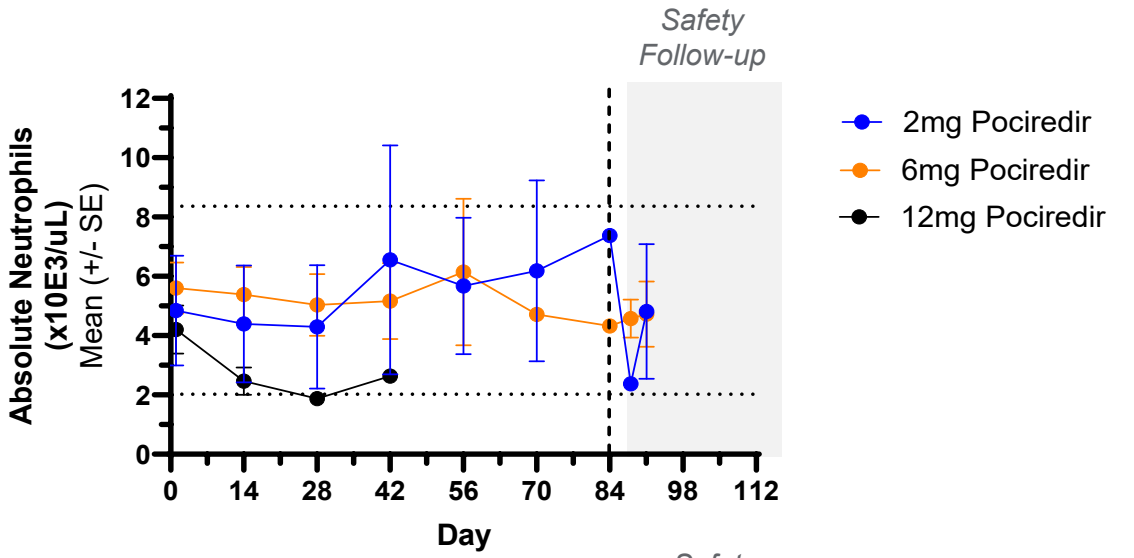
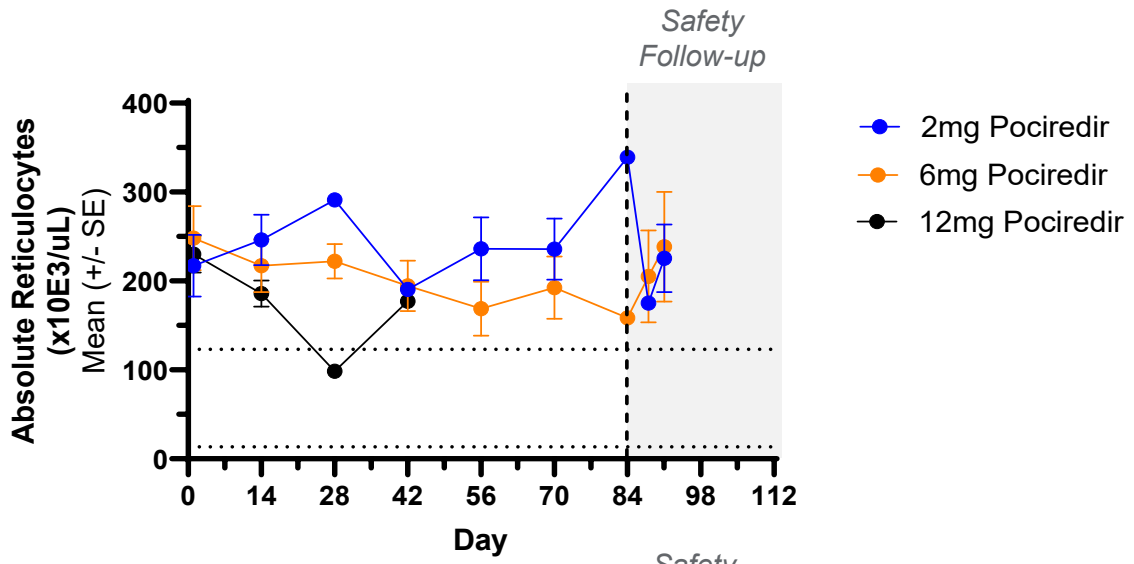
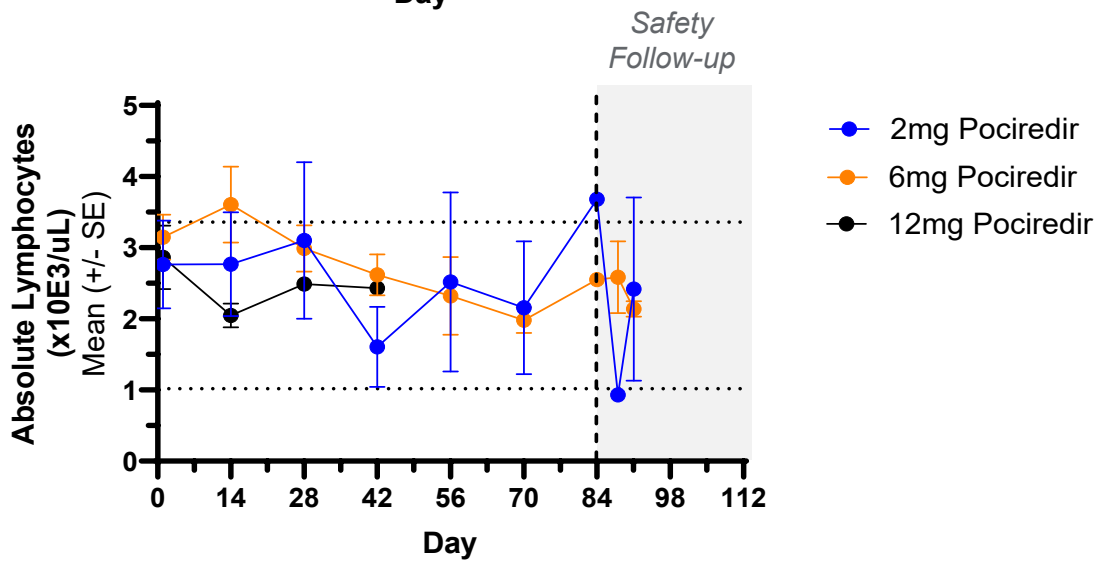
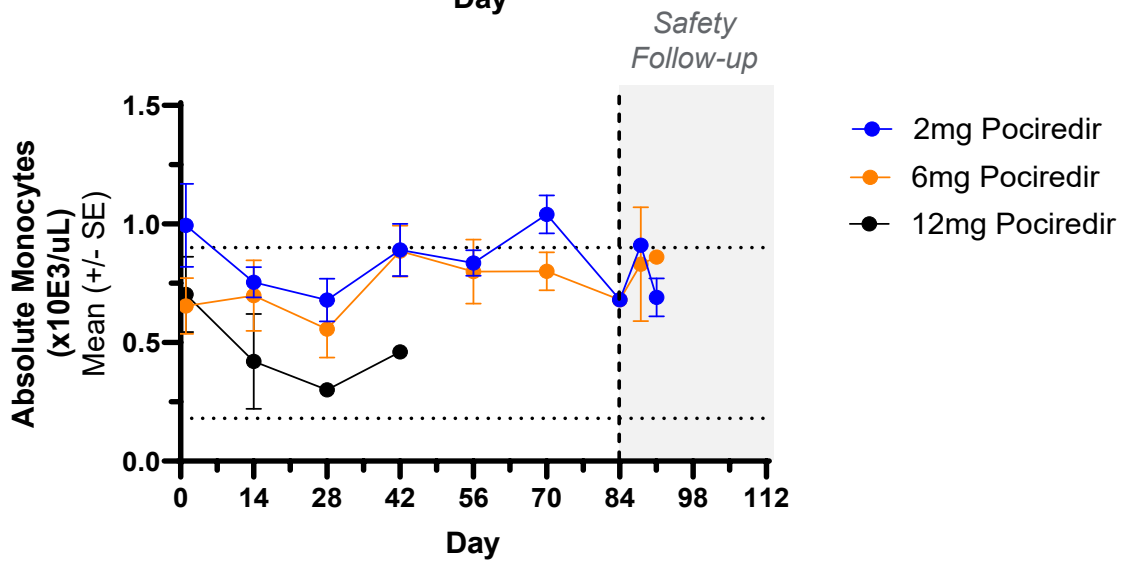
Hematological Effects of Pociredir

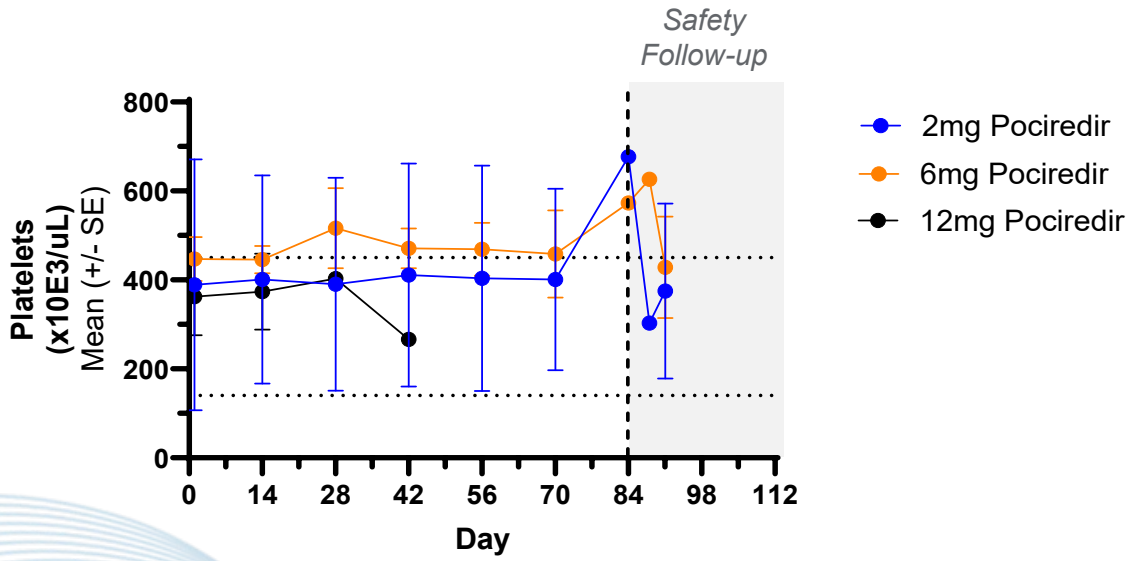


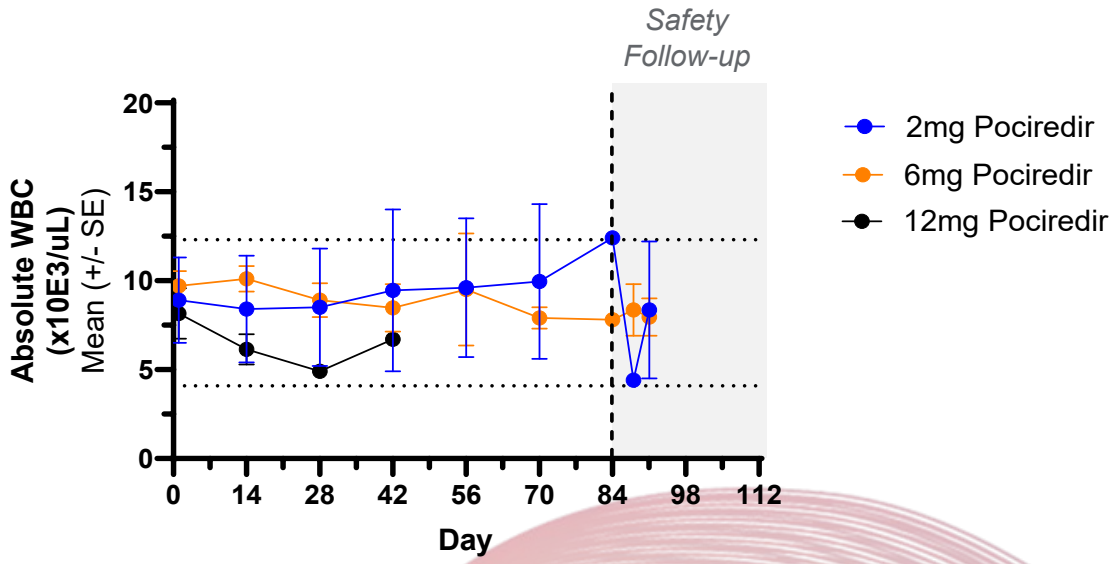






Hematological Effects of Pociredir





Pociredir Was Generally Well-tolerated with No Serious Treatment-related Adverse Events (Pioneer Ph1b – Open Label)

Number of Patients with:	Pociredir (n=16) n (%)
Any TEAE	10 (62.5)
Any treatment-related TEAE	5 (31.3)
Any serious adverse event (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 after signing consent but prior to starting study drug

23 Treatment Emergent Adverse Events (TEAEs) in 10/16 (62.5%) patients

- 8/23 treatment-related TEAEs in 5/16 (31.3%) patients: (headache [x2], lip numbness, diarrhea, fatigue, somnolence, nausea, tinnitus)
  - All mild in severity, non-serious and resolved while patient remained on study drug

4/23 TEAEs (in 4 patients) 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

SAE: Serious adverse event; VOC: Vaso-occlusive crisis;

Background on Resolved Clinical Hold

- Clinical hold initiated on 23-Feb-2023 to allow for further evaluation of a potential safety signal observed in preclinical studies.
- FDA requested an updated study population in which the potential benefit balances the potential risk.
  - Previous experience with HU and at least one of the newly approved drugs (Voxelotor, Crizanlizumab, L-Glutamine) but has shown non-response or intolerance
  - Severe SCD based on VOCs and/or End Organ disease
  - Concomitant HU and any other disease modifying therapy is an exclusion criteria
- As of 18-Aug-2023 FDA has lifted clinical hold for Pociredir.

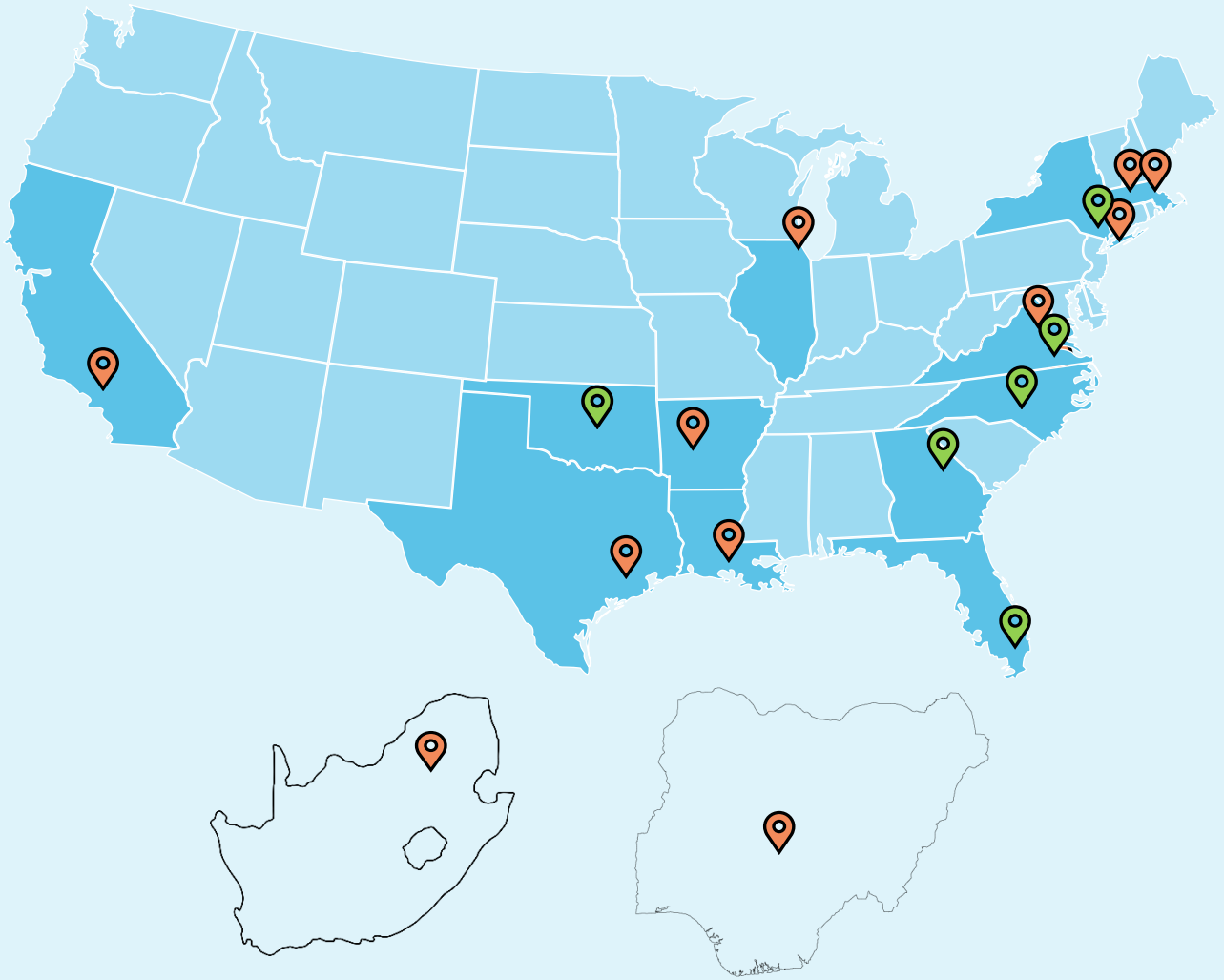
Site Activation Status

Active Sites:

- University of Miami
- Augusta University
- University of North Carolina, Chapel Hill
- Jacobi Medical Center (Bronx, NY)
- Lynn Health Sciences Institute
- Virginia Commonwealth University

On-boarding Sites:

- **US Sites**
  - University of California Los Angeles
  - UT Houston
  - University of Arkansas, Little Rock
  - Lady of the Lake Hospital (Louisiana)
  - University of Illinois Chicago
  - Inova Cancer Center (Fairfax, Virginia)
  - Queens Hospital Cancer Center (Jamaica, NY)
  - Massachusetts General Hospital
  - Boston Medical Center
  - East Carolina University
  - Wake Forest University
- **South Africa Site**
  - Wits Health Consortium (Johannesburg)
- **Nigeria Site**
  - National Hospital Abuja

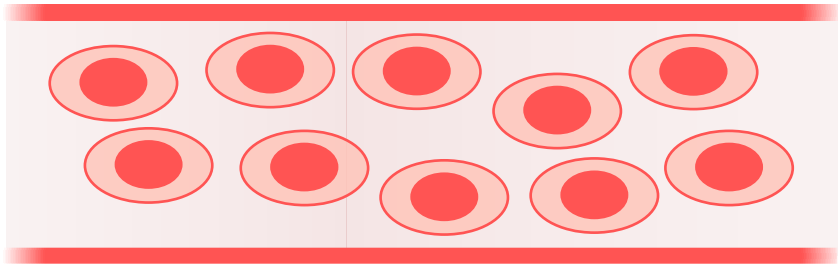


Study Conclusions

Preliminary data from the PIONEER study shows that pociredir:

- Has the potential to increase HbF to levels associated with significant clinical benefits in patients with SCD
- Short term data reveal no safety signal
- Additional data will be generated to further define the benefits and risks associated with pociredir in patients with SCD

Pioneer



Thank You

Advocacy Information

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www.clinicaltrials.gov

NCT05169580

Clinical Trial Information

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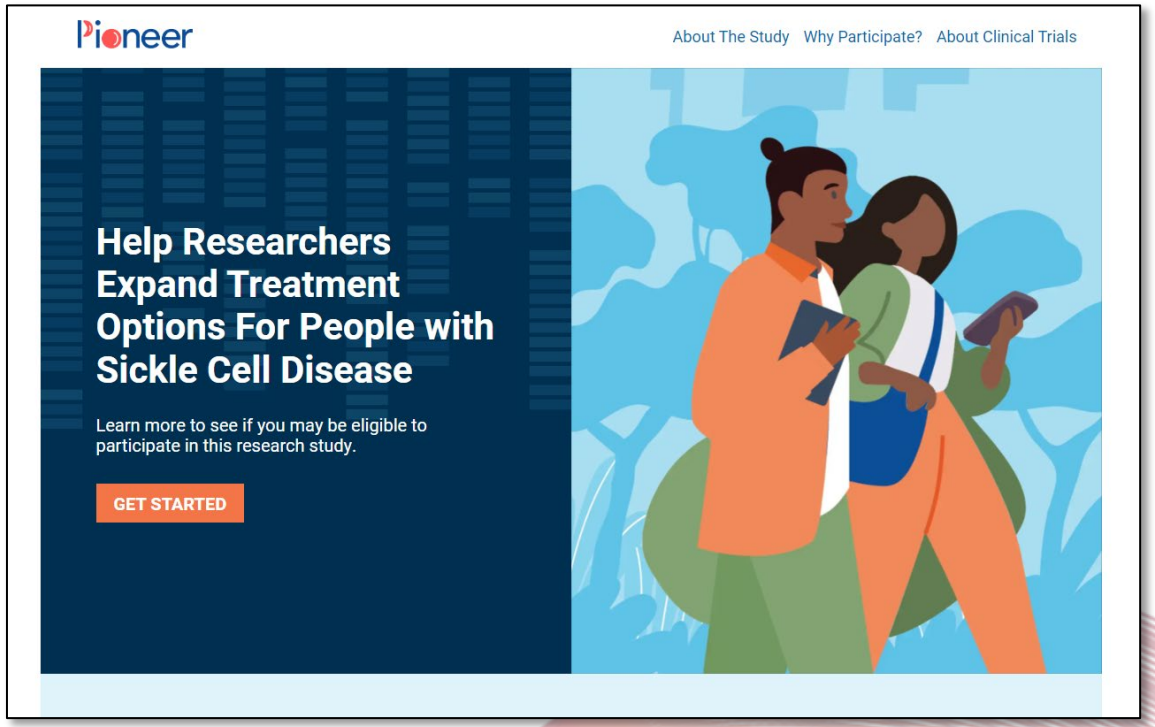

https://www.pioneerscdstudy.com/