# Fulcrum Therapeutics

Nasdaq FULC

November 2024

# Disclaimer and Notice

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including express of implied statements regarding the development status of Fulcrum's product candidates, the potential advantages and therapeutic potential of Fulcrum's product candidates planned meetings with regulatory agencies and availability of clinical trial data. All statements, other than statements of historical facts, contained in this press release, including statements regarding Fulcrum's strategy, future operations, future financial position, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, risks associated with Fulcrum’s ability to obtain and maintain necessary approvals from the FDA and other regulatory authorities; continue to advance its product candidates in clinical trials; initiate and enroll clinical trials on the timeline expected or at all; correctly estimate the potential patient population and/or market for Fulcrum's product candidates; replicate in clinical trials positive results found in preclinical studies and/or earlier-stage clinical trials pociredir and any other product candidates; obtain, maintain or protect intellectual property rights related to its product candidates; manage expenses; and raise the substantial additional capital needed to achieve its business objectives. For a discussion of other risks and uncertainties, and other important factors, any of which could cause Fulcrum's actual results to differ from those contained in the forward-looking statements, see the “Risk Factors” section, as well as discussions of potential risks, uncertainties and other important factors, in Fulcrum's most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent Fulcrum's views as of the date hereof and should not be relied upon as representing Fulcrum's views as of any date subsequent to the date hereof. The Fulcrum anticipates that subsequent events and developments will cause Fulcrum's views to change. However, while  Fulcrum may elect to update these forward-looking statements at some point in the future, the Fulcrum specifically disclaims any obligation to do so.

# Unlocking the Power of Small Molecules to Change the Course of Genetically Defined Rare Diseases

Diversified biotech developing oral small molecules designed to **modify gene expression** in rare disease

**Pociredir**: potential **best-in class** oral small molecule HbF inducer for sickle cell disease (SCD); granted **Fast Track and Orphan Designations**

Discovery efforts validated by advancement of clinical programs

Strong cash position of $257.3M as of 9/30 with **runway into at least 2027**

Founded in 2015

IPO in 2019

Ticker: FULC

# Small Molecule Pipeline Across Multiple Rare Diseases

| Indication | Asset / MOA | Preclinical | Phase 1 | Phase 2 | Phase 3 | Collaborator |
|---|---|---|---|---|---|---|
| **Clinical Programs** | | | | | | |
| FSHD | **Losmapimod** (DUX4 Reduction) | *Future Losmapimod Development Suspended** | | | | sanofi (Ex-U.S.) |
| SCD | **Pociredir** (HbF Induction) | | | | | |
| **Discovery Programs** | | | | | | |
| Blood Disorders | | | | | | |
| Muscle Disorders | | | | | | |
| Cardiomyopathies | | | | | | Bristol Myers Squibb™ |

FSHD: Facioscapulohumeral muscular dystrophy; HbF: Fetal hemoglobin; SCD: Sickle cell disease
* Fulcrum suspended future losmapimod development upon announcement of topline results from the Phase 3 REACH Clinical Trial on September 12, 2024. Losmapimod failed to achieve its primary endpoint of change from baseline in relative surface area (RSA), a measure of reachable workspace (RWS), compared to placebo in the Phase 3 REACH Clinical Trial.

# Pociredir

for Sickle Cell Disease

**Fast Track Designation**

**Orphan Drug Designation**

Fulcrum Therapeutics

# Sickle Cell Disease: Debilitating Disease with High Unmet Need

## The Disease

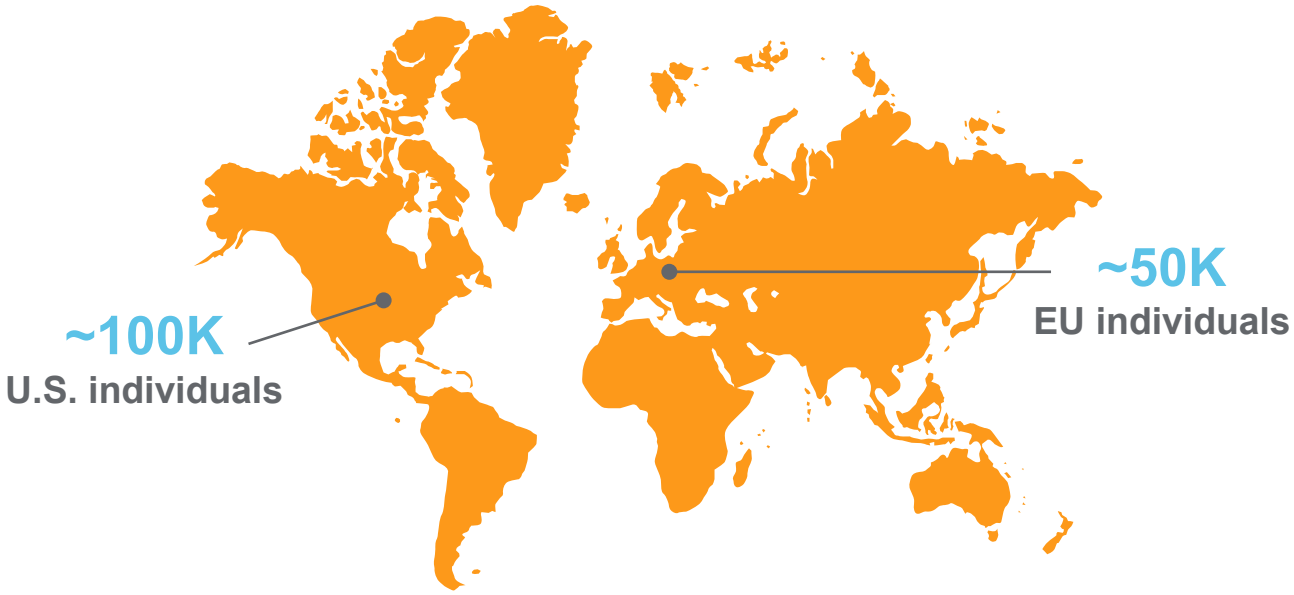
Genetic disorder caused by mutation in Hemoglobin-Beta (*HBB*) gene

Results in abnormal sickle-shaped red blood cells that rupture or block blood vessels

## Debilitating Symptoms

- Vaso-occlusive crises (VOCs)
- Other complications, including stroke, neuropathy, and acute chest syndrome
- Anemia / hemolysis
- Morbidity and mortality

## Global Impact




**4.4 million worldwide**

SOC: Standard of Care; VOC: Vaso-occlusive crisis; CDC; WHO; UpToDate.

# Despite Therapeutic Options, Significant Unmet Need Remains for People Living With SCD

## Hydroxyurea

*Current Standard of Care*

- \+ Potential to ameliorate disease pathology
- − Non-responders
- − Waning efficacy
- − Safety and tolerability issues

## HbS Polymerization Inhibitors

*Increasing Total Hemoglobin*

- \+ Addresses anemia
- − Does not address broad disease pathology
- − Does not improve outcomes
- − Safety and tolerability issues

## Selectin Inhibitors

*Leukocyte Binding to Selectin*

- \+ Reduces VOCs
- − Does not address broad disease pathology
- − IV administration

## Ex Vivo Genetic Therapies

*BCL11A Editing & Beta-globin Gene Delivery*

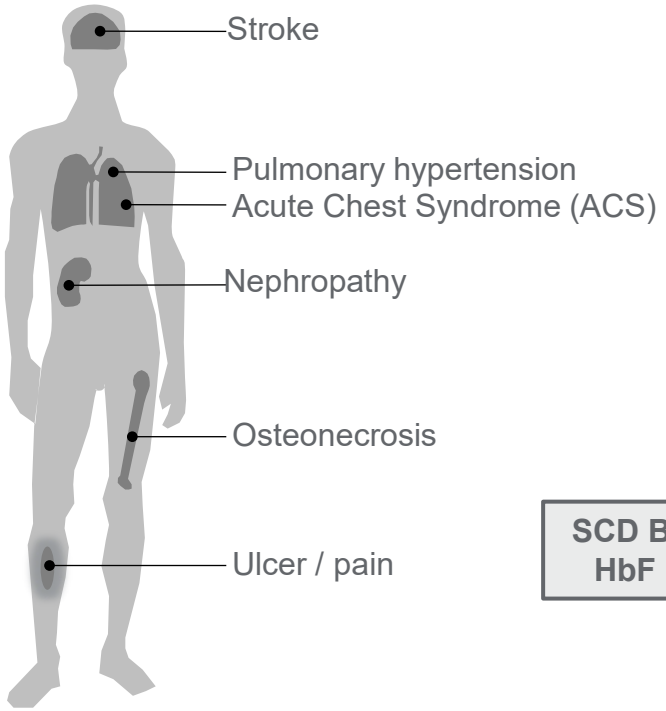
- \+ Potential for a cure
- − Highly invasive (risks associated with myeloablation)
- − Unknown durability
- − Significant barriers to access

SCD: Sickle cell disease; VOC: Vaso-occlusive crisis

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

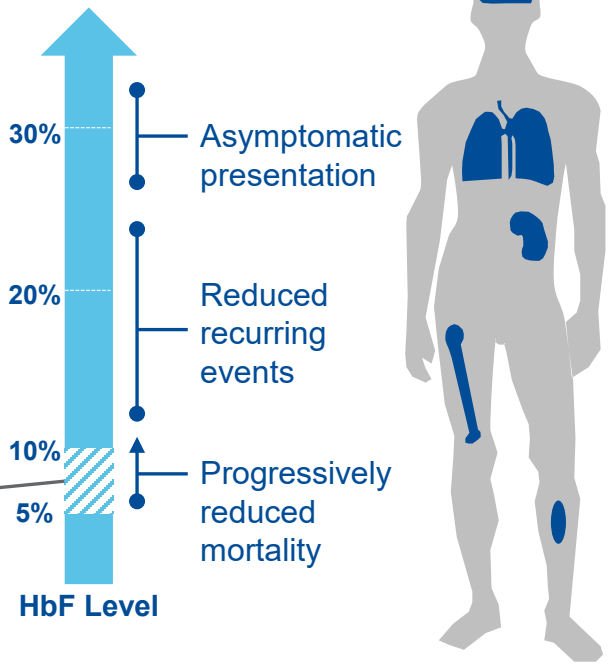
## Even incremental increases in HbF can lead to meaningful improvement in disease severity

**Typical SCD Subject**




SCD Baseline HbF 5-10%

**SCD Subject with High HbF Levels**




- Reduced hemolysis
- Reduced anemia
- Reduced VOCs
- Fewer recurring events

***By Raising HbF Levels, Pociredir Provides the Potential to Ameliorate Disease Pathology through Convenient Oral Dosing***

HbF: Fetal hemoglobin; VOC: Vaso-occlusive crisis; Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.

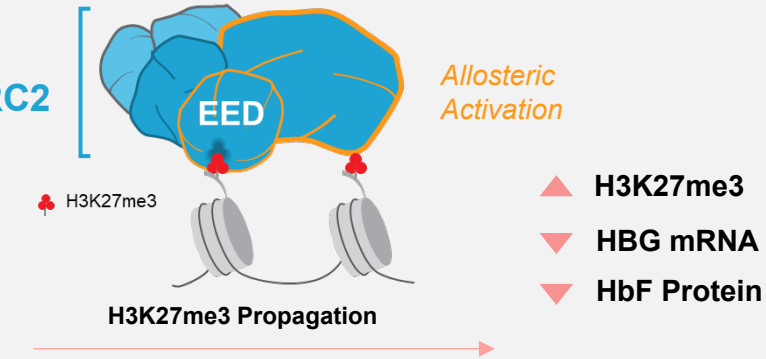
# Targeting EED Results in HbF Increases

**CRISPR + Compound Screening Engine**
*Experimentally screened candidate targets*

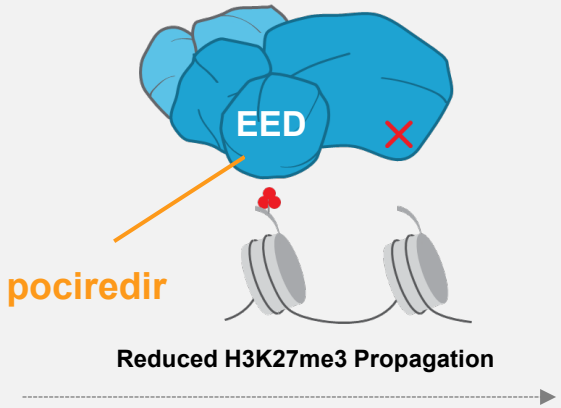
**Computational Data Mining**
*Computationally mined candidate targets*

**Identified Targets that Regulate HbF**

**Identified EED as a Novel Drug Target of Polycomb Repressor Complex 2**




## Pociredir is a Potent and Selective EED Binder




- H3K27me3 ▼
- HBG mRNA ▲
- HbF Protein ▲

**pociredir**

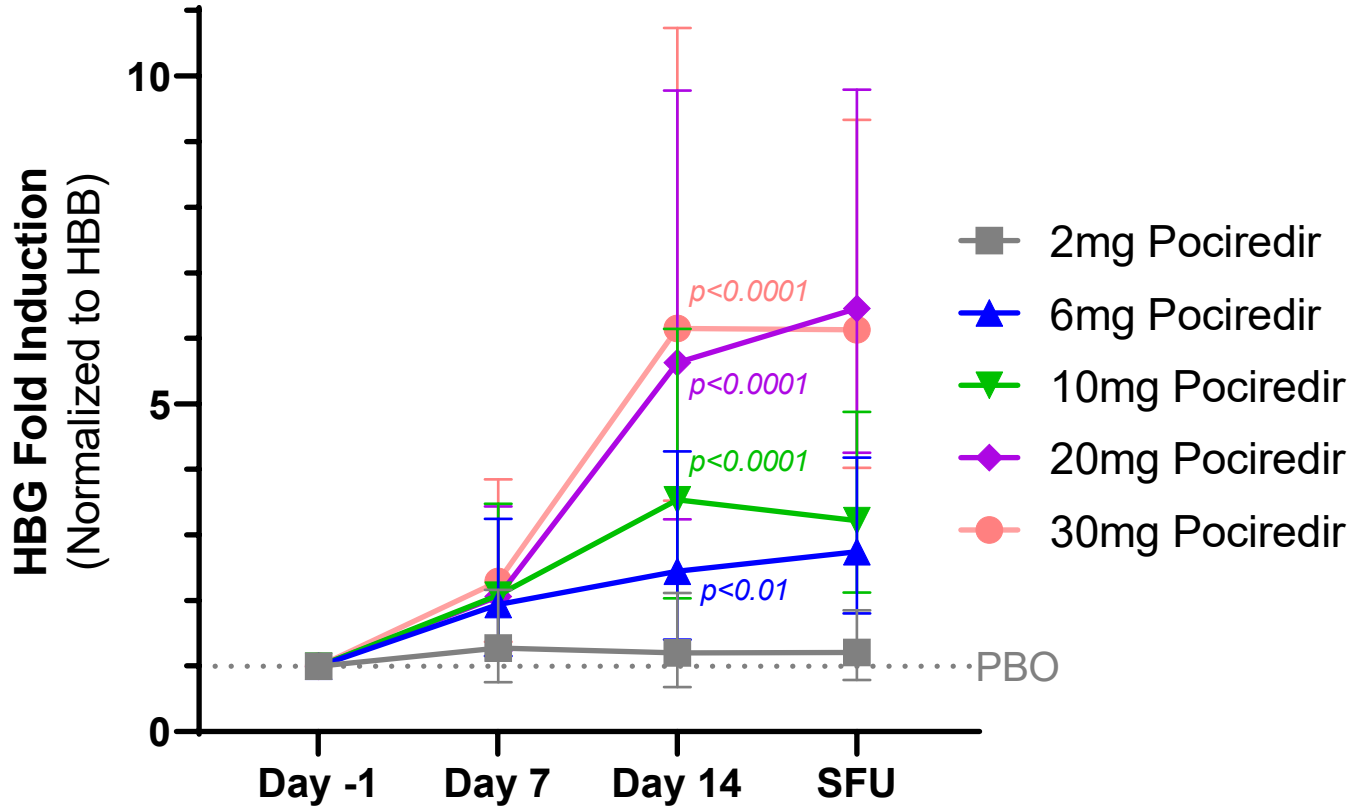
- **Highly Selective**
- **Clean Off-target Profile**
- **Composition of Matter Patent Expires 2040**

EED: Embryonic Ectoderm; HbF: Fetal hemoglobin; HBG: hemoglobin gene

# Dose-dependent HBG mRNA Induction in Healthy Volunteers

## Gamma Globin (HBG) mRNA Induction is both Time- and Dose-dependent in MAD Cohorts

### HBG Fold Induction in Healthy Volunteers




Safety follow-up (SFU) samples were collected 7 – 10 days post 14-day treatment period; PBO: placebo; Data presented as geometric LS mean ratio (to placebo) with 95% confidence interval; mixed-effects model for repeated measures (MMRM) analysis performed for Day 7 and Day 14; analysis of covariance (ANCOVA) utilized for SFU data;. HBG: hemoglobin gene; HBB: hemoglobin subunit beta gene

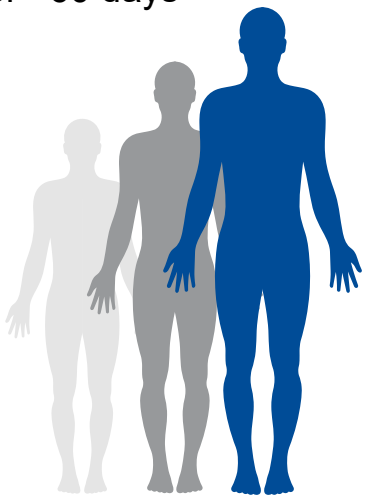
# Pioneer Phase 1b Pociredir Clinical Trial in SCD Subjects

## Study Population

Males and females with SCD, ages 18 – 65 years

Approximately 10 subjects per cohort

Discontinued hydroxyurea for ≥60 days



## Study Design – Open-label


## Study Endpoints

### Primary

Safety and tolerability assessments

PK parameters

### Secondary

HbF induction, hemolysis and anemia:

- % HbF (HPLC)
- Absolute reticulocyte count
- Total hemoglobin
- Unconjugated bilirubin

### Exploratory

Globin gene expression

% F-cells

Biomarkers of hemolysis

Incidence of VOCs

PK/PD correlation

U.S. FDA lifted the clinical hold for pociredir on August 18, 2023. *Reinitiated trial at the 12mg dose, to be followed by the 20mg dose.

HbF, fetal hemoglobin; HPLC, high-performance liquid chromatography; PD, pharmacodynamics; PK, pharmacokinetics; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

# 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 prior to first dose of 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

TEAE: Treatment-emergent Adverse Event; SAE: Serious adverse event; VOC: Vaso-occlusive crisis;

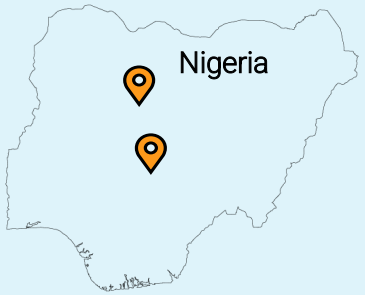
# Pioneer Phase 1b Clinical Trial Sites

**Active Sites:**

- **US Sites**
  - University of Miami (PI: Alvarez)
  - University of North Carolina, Chapel Hill (PI: Little)
  - Jacobi Medical Center (Bronx, NY) (PI: Rivlin)
  - Lynn Health Sciences Institute (PI: Griffin)
  - Virginia Commonwealth University (PI: Smith)
  - Boston Medical Center (PI: Ribeil)
  - University of California Los Angeles (PI: Sehl)
  - Mississippi Center for Advanced Medicine (PI: Pennington)
  - University of Arkansas, Little Rock (PI: Birrer)
  - Lady of the Lake Hospital (Louisiana) (PI: Stagg)
  - Inova Cancer Center (Fairfax, VA) (PI: Alan)
- **South Africa Site**
  - Wits Health Consortium (Johannesburg) (PI: Mahlangu)

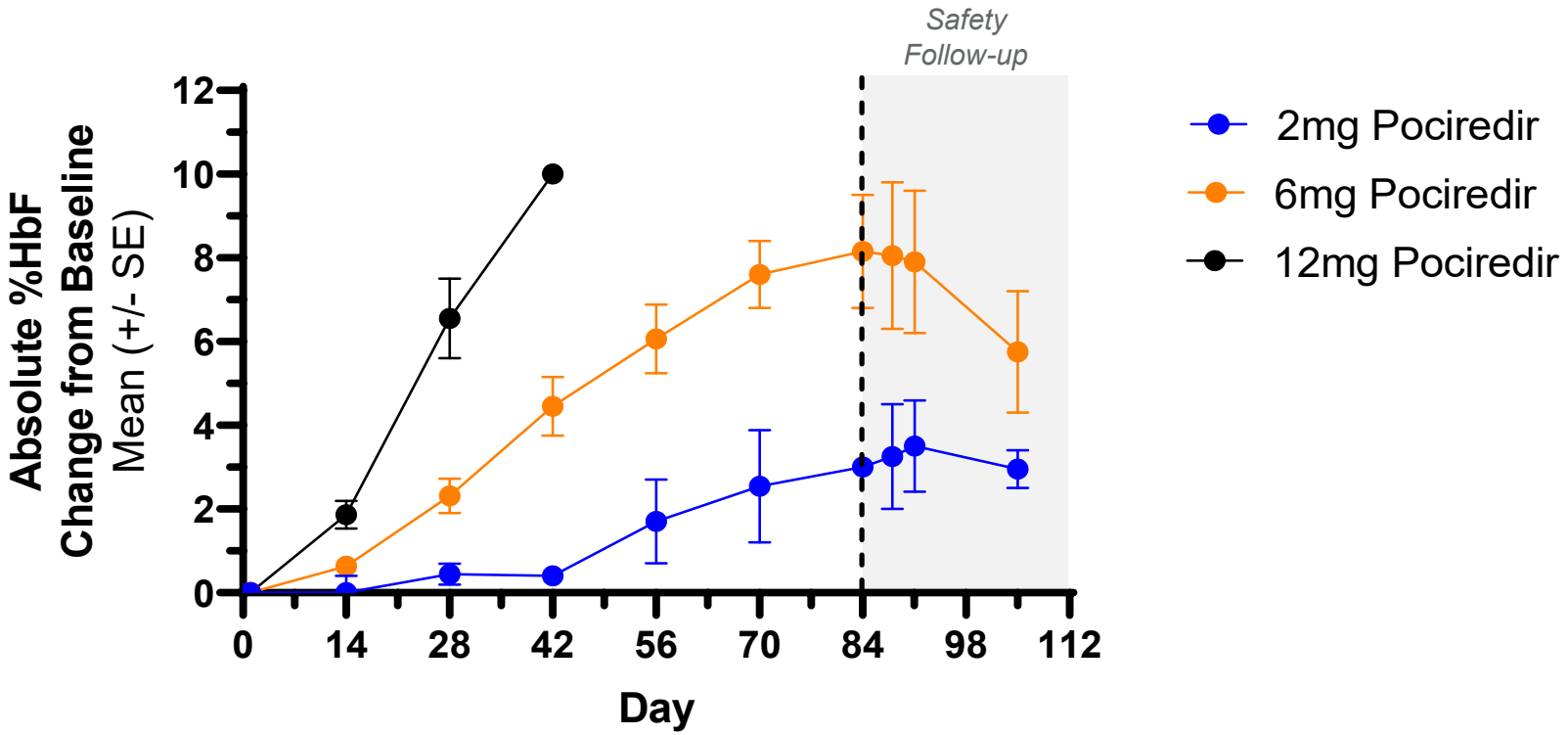
**On-boarding Sites:**

- **US Sites**
  - UT Houston (PI: Idowu)
  - University of Illinois Chicago (PI: Molokie)
  - Queens Hospital Cancer Center (Jamaica, NY) (PI: Ferman)
  - Massachusetts General Hospital (PI: Azar)
  - East Carolina University (PI: Liles)
- **Nigeria Sites**
  - National Hospital, Abuja (PI: Ojika)
  - Barau Dikko Teaching Hospital (PI: Dogara)

# Initial Pioneer Data Demonstrates Dose-dependent Increases in HbF

## Absolute %HbF Change from Baseline




U.S. FDA issued a full clinical hold for pociredir on February 23, 2023. Safety data collection continued with data cutoff of March 3, 2023.

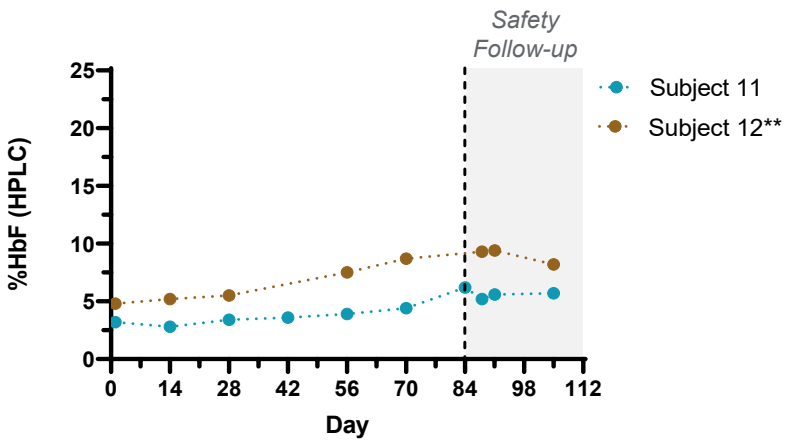
Note: Summary data includes both subjects on and off hydroxyurea; Subject 15 ceased dosing on Day 22 and therefore, was only included in the analysis up to Day 14

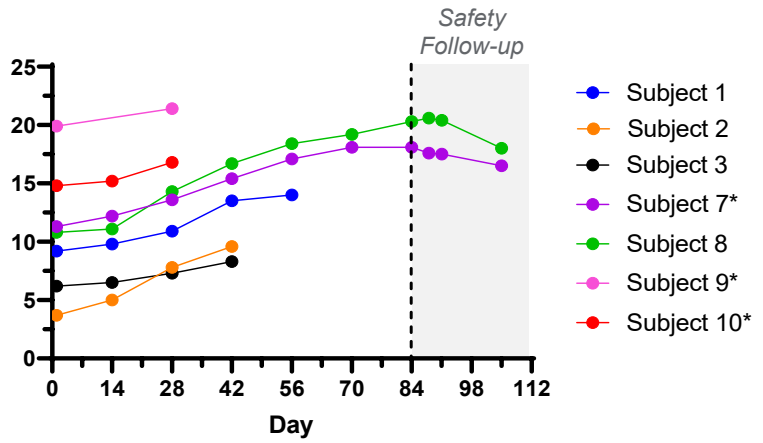


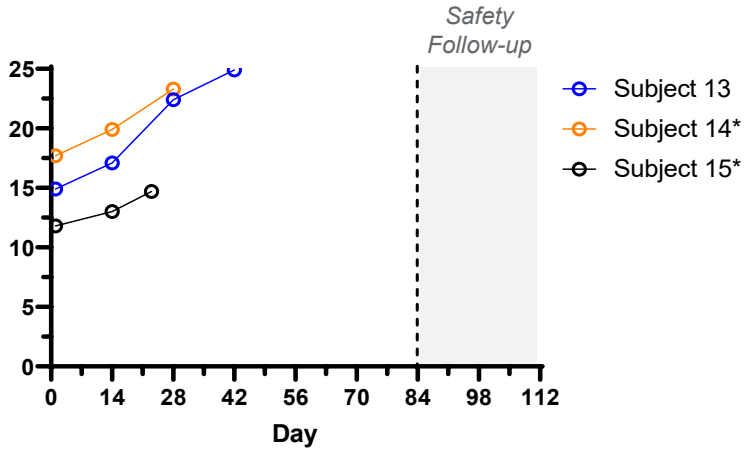
Fulcrum Therapeutics

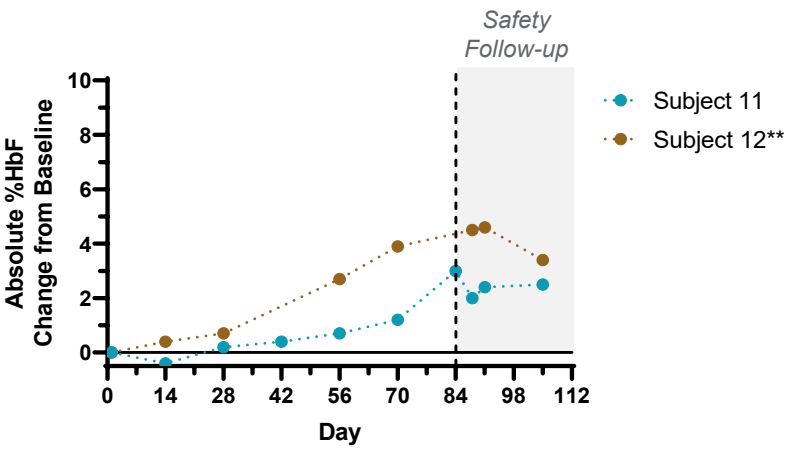
# Dose Dependent, Clinically Relevant and Consistent Increases in HbF

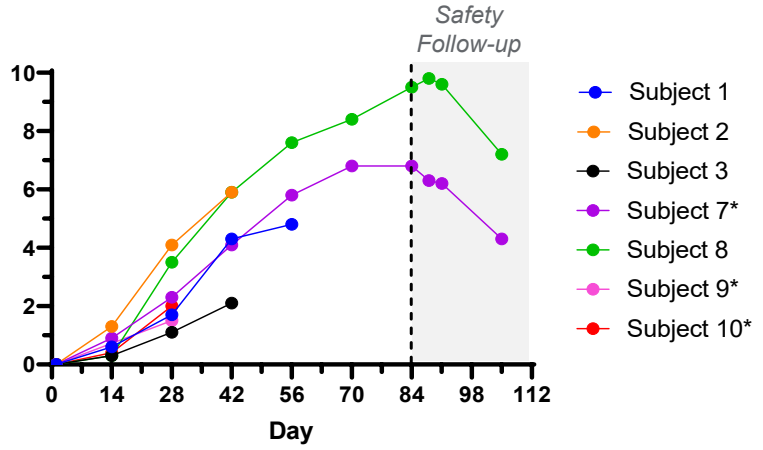
**2mg** | **6mg** | **12mg**

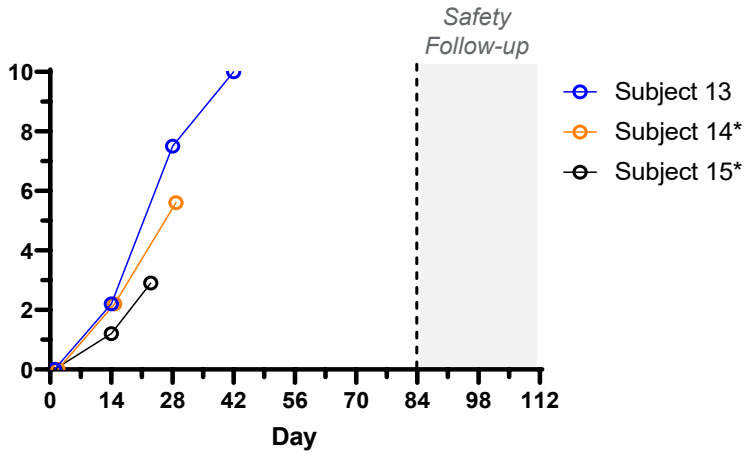


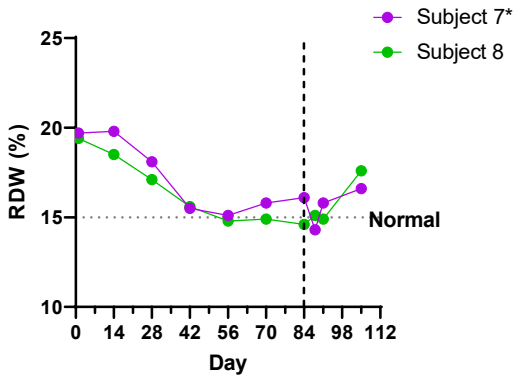



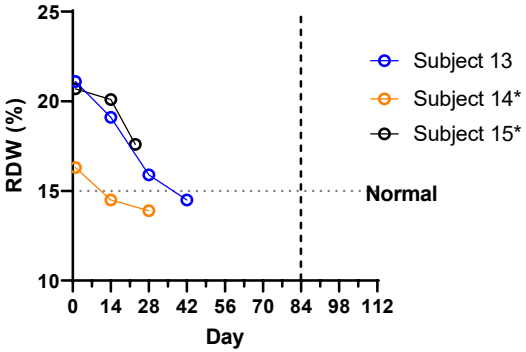

U.S. FDA issued a full clinical hold for pociredir on February 23, 2023. Safety data collection continued with data cutoff of March 3, 2023.

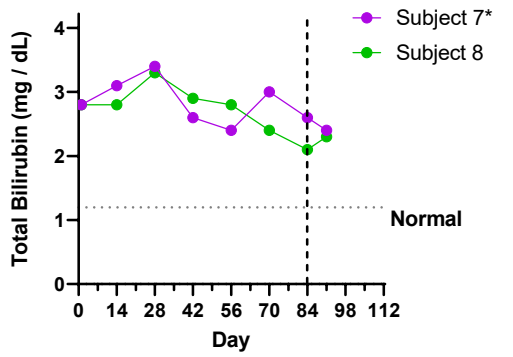
*Subjects on stable dose of hydroxyurea; Note: Subject 15 ceased dosing on Day 22
** Day 42 and day 84 data not available for subject 12; samples were received by the lab outside of stability window

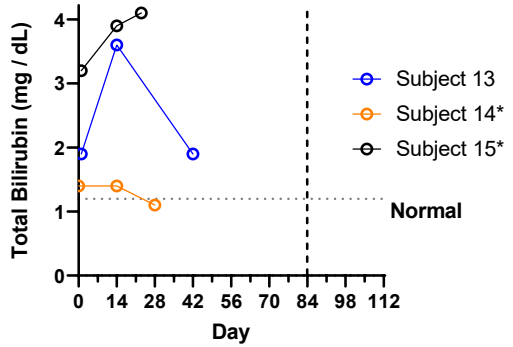
# Improvements in Biomarkers of Hemolysis and Anemia from initial 6mg and 12mg Pioneer data

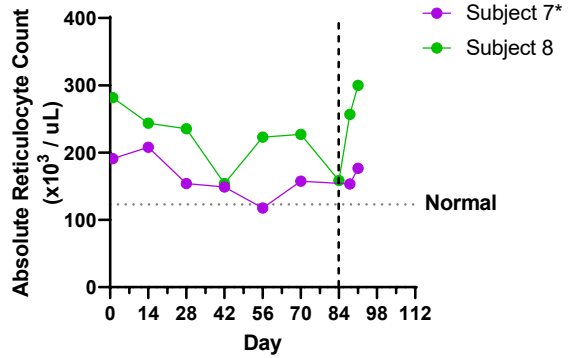
**Red Cell Distribution Width (RDW)** | **Total Bilirubin** | Absolute Reticulocyte Count | Total Hemoglobin

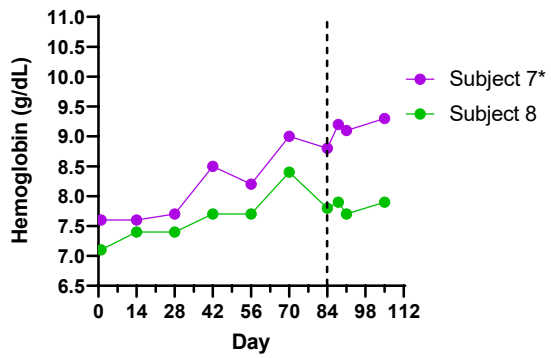


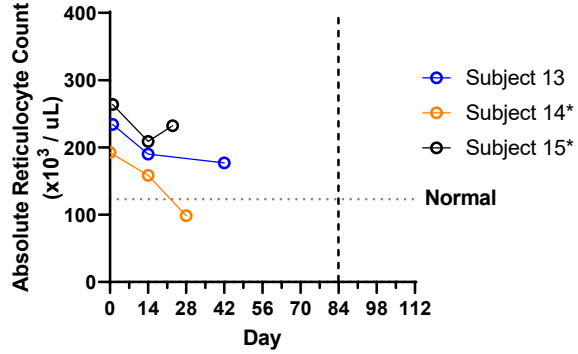



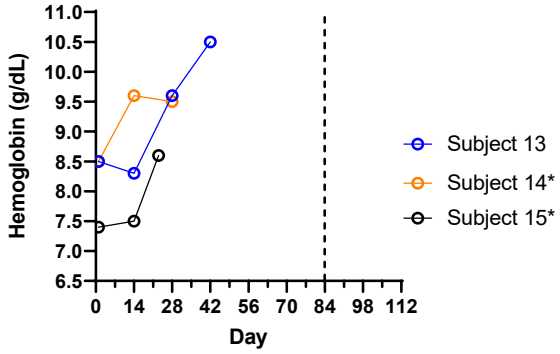




6 mg

12 mg

Reductions in RDW indicate RBCs are becoming more uniform in shape

Bilirubin decreases indicate less hemolysis

Reductions in reticulocytes and increases in total hemoglobin indicate less anemia and healthier bone marrow function

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



FULCRUM THERAPEUTICS

Fulcrum Therapeutics

# Robust Process Implemented to Ensure Study Drug Adherence – AiCure

Smartphone application is utilized to ensure:

- Study drug adherence
  - Reminders provided to participants
  - Interactive dosing steps with guided assistance
- Robust data collection
  - Record of date, time and results of dosing
  - Close to real-time data for oversight
  - Visual recognition of participant
  - Visual confirmation of non-dosing (e.g., cheeking, spitting, removing, or wrong study drug) or wrong person

# Overview of Key Inclusion Criteria: Previous Use of Hydroxyurea AND One Other Approved Therapy

**Hydroxyurea**

- Continued VOC or episodes of acute chest syndrome for at least 6 months at the maximum tolerated dose
- Inability to tolerate the adverse effects of the therapy
- Unmanageable drug-drug interactions
- Patient refusal

***And***

**Voxelotor or crizanlizumab or L-glutamine**

- Continued pain crises and other VOCs while on stable dose for at least 6 months
- Failure to increase Hb by 1 g/dL (for vox.) or continued VOC episodes (for criz. or L-glutamine)
- Inability to tolerate the adverse effects of the therapy
- Unmanageable drug-drug interactions
- Patient refusal

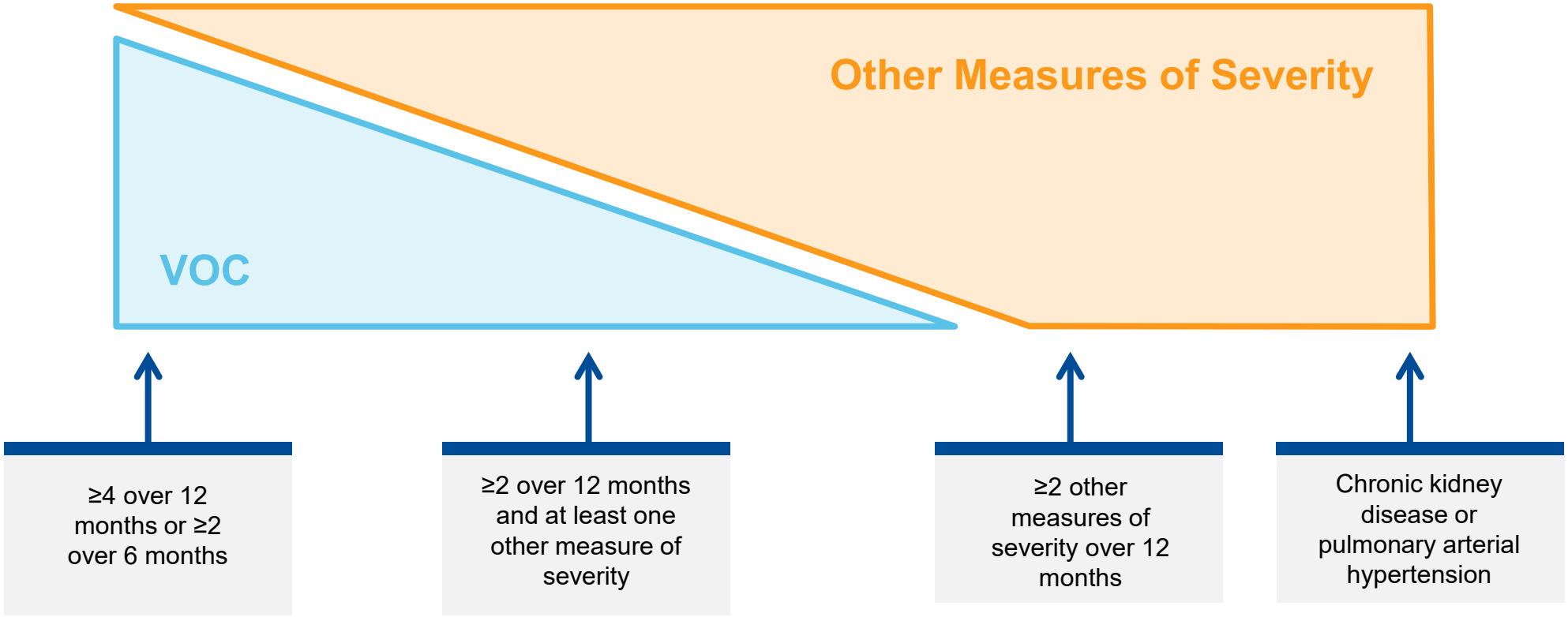
***Or***

**Lack of access to advanced therapies**

- Lack of availability
- Lack of insurance coverage

**We estimate that there are approximately 7,500 to 10,000 patients in the U.S. that meet the inclusion and exclusion criteria of the amended protocol**

# Overview of Key Inclusion Criteria: Patient Severity



# Demonstrates Best-in-Class Potential

## Healthy volunteer mRNA data indicate higher levels of HbF induction are possible

- To date, all patients on treatment have responded
- Levels of HbF increase are clinically relevant among patients both on HU and off HU
- Consistency of response demonstrated across patients, independent of baseline HbF
- Dose response at 2 mg, 6 mg, and 12 mg
- Overall pociredir was generally well-tolerated

HbF: fetal hemoglobin; HU: hydroxyurea

# Pociredir: Differentiated HbF Inducer with Best-in-Class Potential

**Persistent unmet need**

SCD is a severe disorder (estimated US SCD population is ~100,000)

Approximately 200,000 annual emergency department visits related to SCD

**Best-in-class potential**

Oral small molecule HbF inducer

Potential to be broadly protective of SCD symptomology

**Demonstrated proof-of-concept**

Dose responsive target engagement and HbF increase

Robust HbF increases in adherent patients, on and off hydroxyurea*

**Development path forward**

FDA Fast Track Designation

Phase 1b study actively enrolling patients

Composition of matter patent into 2040

Sedrak and Kondamudi, StatPearls, last update August 29, 2022; Hussain et al, Am J Prev Med, 2010

Fulcrum Therapeutics

# THANK YOU