Fulcrum Therapeutics

Nasdaq FULC

January 13, 2025

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 or implied statements regarding the development status of Fulcrum's product candidates, the potential advantages and therapeutic potential of Fulcrum's product candidates, filings with regulatory agencies and availability of clinical trial data, effects of using AiCure, and Fulcrum’s preliminary unaudited cash position and cash runway. All statements, other than statements of historical facts, contained in this presentation, including express or implied 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; and complete the audit of its 2024 financials. 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 presentation 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. While Fulcrum may elect to update these forward-looking statements at some point in the future, Fulcrum specifically disclaims any obligation to do so.

Fulcrum's financial closing procedures for the fourth quarter and year ended December 31, 2024 are not yet complete. It is possible that the final cash position and cash runway guidance may differ from the preliminary unaudited year end cash position and cash runway disclosed herein between now and when results are finalized.

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 diseases with a **focus on benign hematology**

Pociredir

- Potential **best-in class** oral small molecule HbF inducer for sickle cell disease (SCD)
- **Fast Track and Orphan Designations**
- Planned timing for Phase 1b PIONEER data disclosure
  - Cohort 3 (12 mg): **mid-2025**
  - Cohort 4 (20 mg): **YE 2025**

Discovery & Cash Position

- Advancing discovery programs for pipeline sustainability
- IND submission planned in Q4 2025
- Cash position of ~$240M as of 12/31 with **runway into at least 2027**

HbF: Fetal hemoglobin

Small Molecule Pipeline Across Multiple Rare Diseases

Indication	Asset / MOA	Preclinical	Phase 1	Phase 2	Phase 3	Collaborator
Clinical Programs						
Sickle Cell Disease	**Pociredir** (HbF Induction)					
Discovery Programs						
DBA & Inherited Aplastic Anemias						
Novel HbF Inducers						
Fibrotic Disorders						
Cardiomyopathies						Bristol Myers Squibb™

DBA: Diamond-Blackfan anemia

Fulcrum Therapeutics

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 the 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
- Reduced life expectancy >20 years; mortality rate up to 9x higher than general population

Global Impact

4.4 million worldwide

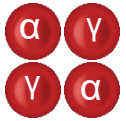
VOC: Vaso-occlusive crisis; CDC; WHO; UpToDate.

Competitive Landscape in SCD

Hydroxyurea

Current Standard of Care

HbF Inducers



Pociredir – Fulcrum Therapeutics

BMS-986470 – Bristol Myers Squibb

ITU-512 – Novartis

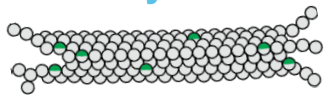
Ndec (decitabine + tetrahydrouridine) – Novo Nordisk / EpiDestiny

Adakveo® – Novartis

Inclacumab – Pfizer

Selectin Inhibitors

Anti-Polymerization



Gene Therapy

Lyfgenia® – Bluebird Bio

Casgevy® – Vertex Pharmaceuticals

BEAM-101 – Beam Therapeutics

EDIT-301 – Editas Medicine (ceased development)

HbS Polymerization Inhibitors

Oxbryta® – Pfizer (withdrawn)

Osivelotor (GBT-601) – Pfizer

PK Activators

Mitapivat (AG-348) – Agios

Etavopivat (FT-4202) – Novo Nordisk

Tebapivat (AG-946) – Agios

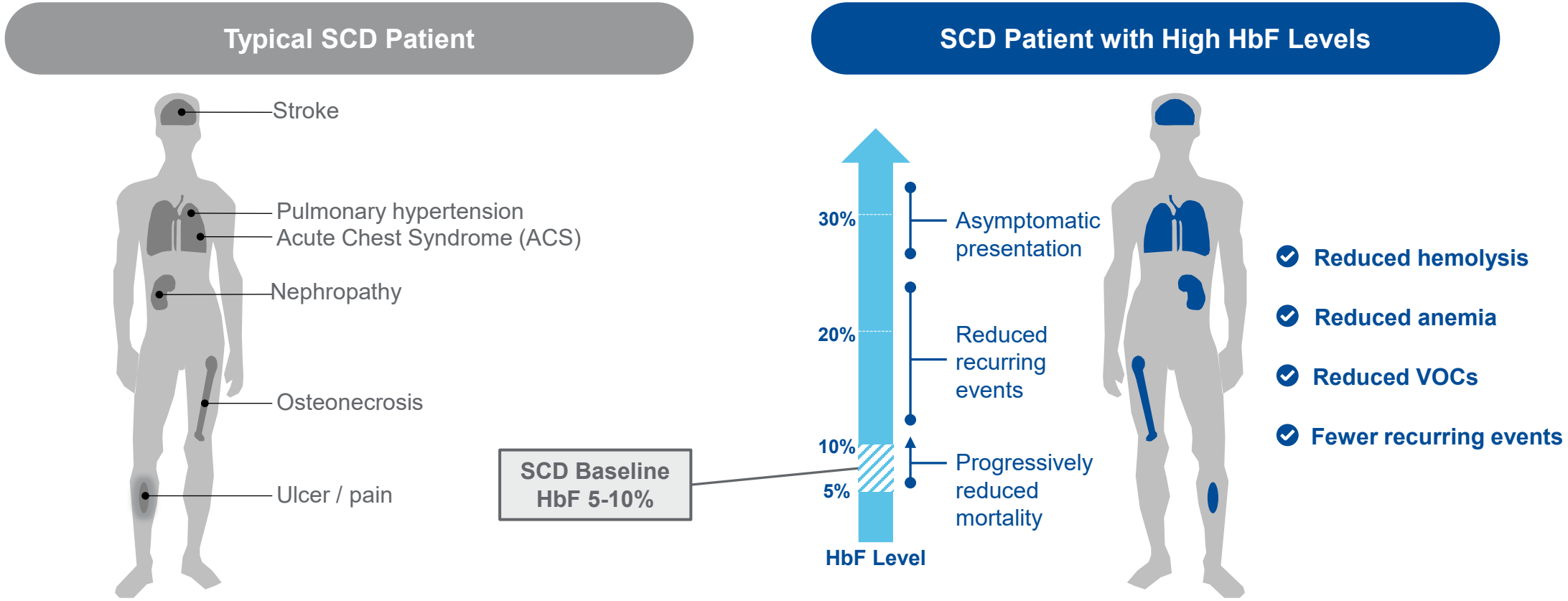
HbS: Sickle hemoglobin. PK: Pyruvate kinase.

Fulcrum Therapeutics

Best-in-class Potential of Pociredir to Address Significant Unmet Need for People Living With SCD

	Addresses underlying disease pathology	Ability to reduce VOC / impact survival	Safety & Tolerability	Ability to be administered orally
HbF Inducers				
PK Activators				
HbS Polymerization Inhibitors				
Selectin Inhibitors				

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



By Raising HbF Levels, Pociredir Provides the Potential to Ameliorate Disease Pathology

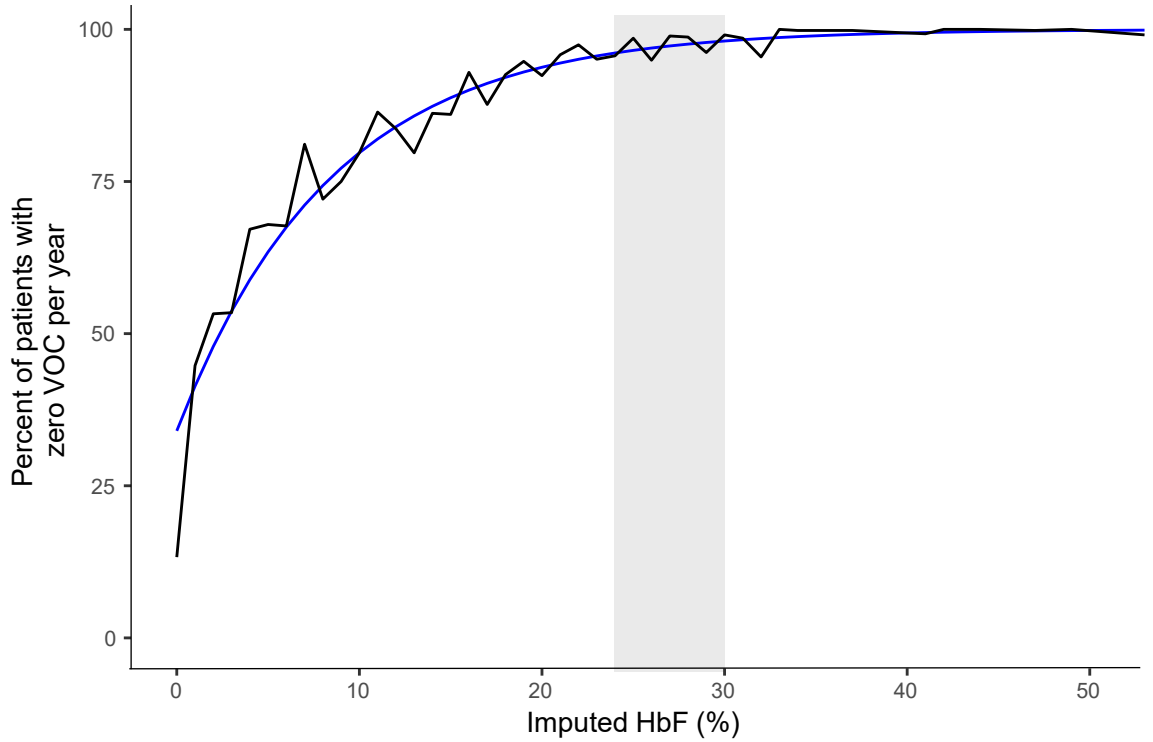
VOC: Vaso-occlusive crisis; Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.

Even Modest Increases in HbF Reduce Mortality and Symptom Severity

Each 1% increase in HbF is associated with a 4%-8% reduction in VOCs[1]

Analysis	IRR (95% CI)	Interpretation
Cooperative Study of SCD (CSSCD)		
Analysis 1: Baseline HbF Approach N=1395 N=1395	0.94 (0.92 – 0.97)	1% increase in HbF is associated with **6% reduction in VOC rate**
Analysis 2: Equal observation time approach N=1367 N=3056	0.96 (0.94 – 0.98)	1% increase in HbF is associated with **4% reduction in VOC rate**
Analysis 3: All observation approach N=1367 N=3056	0.95 (0.94 – 0.97)	1% increase in HbF is associated with **5% reduction in VOC rate**
Multicenter Study on Hydroxyurea (MSH) (N= 299)		
HbF analysis: Post-randomization VOC	0.92 (0.89 – 0.96)	1% increase in HbF is associated with **8% reduction in VOC rate**

HbF levels > mid-to-high 20% results in near abolition of VOCs[2]



Probability of observing zero VOC/year by HbF
Blue line = model prediction; Black line = observed

[1] Table adapted from Peter Bruun-Rasmussen. ASH 2024 (poster #1124).
[2] Unpublished data from Fulcrum analysis of Picnic Health real-world dataset, n = 673; ≥ 2 years old ; Mean HbF = 8.6%

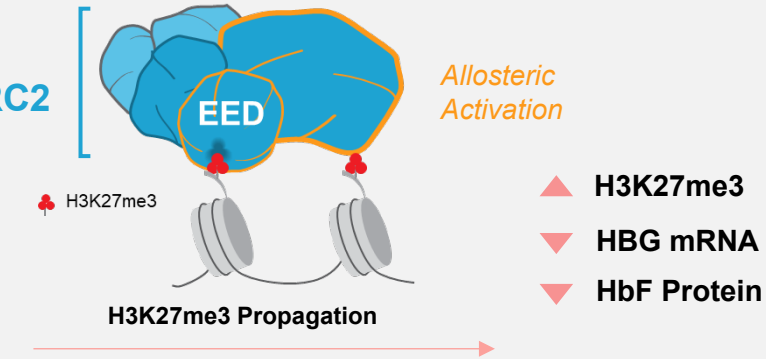
Targeting EED Results in HbF Increases

CRISPR + Compound Screening Engine
Experimentally screened candidate targets

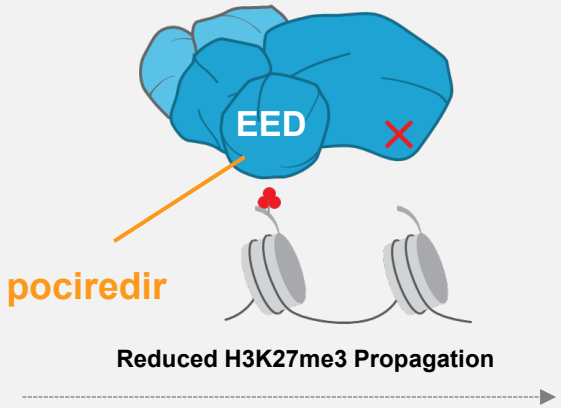
Computational Data Mining
Computationally mined candidate targets

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 ▲

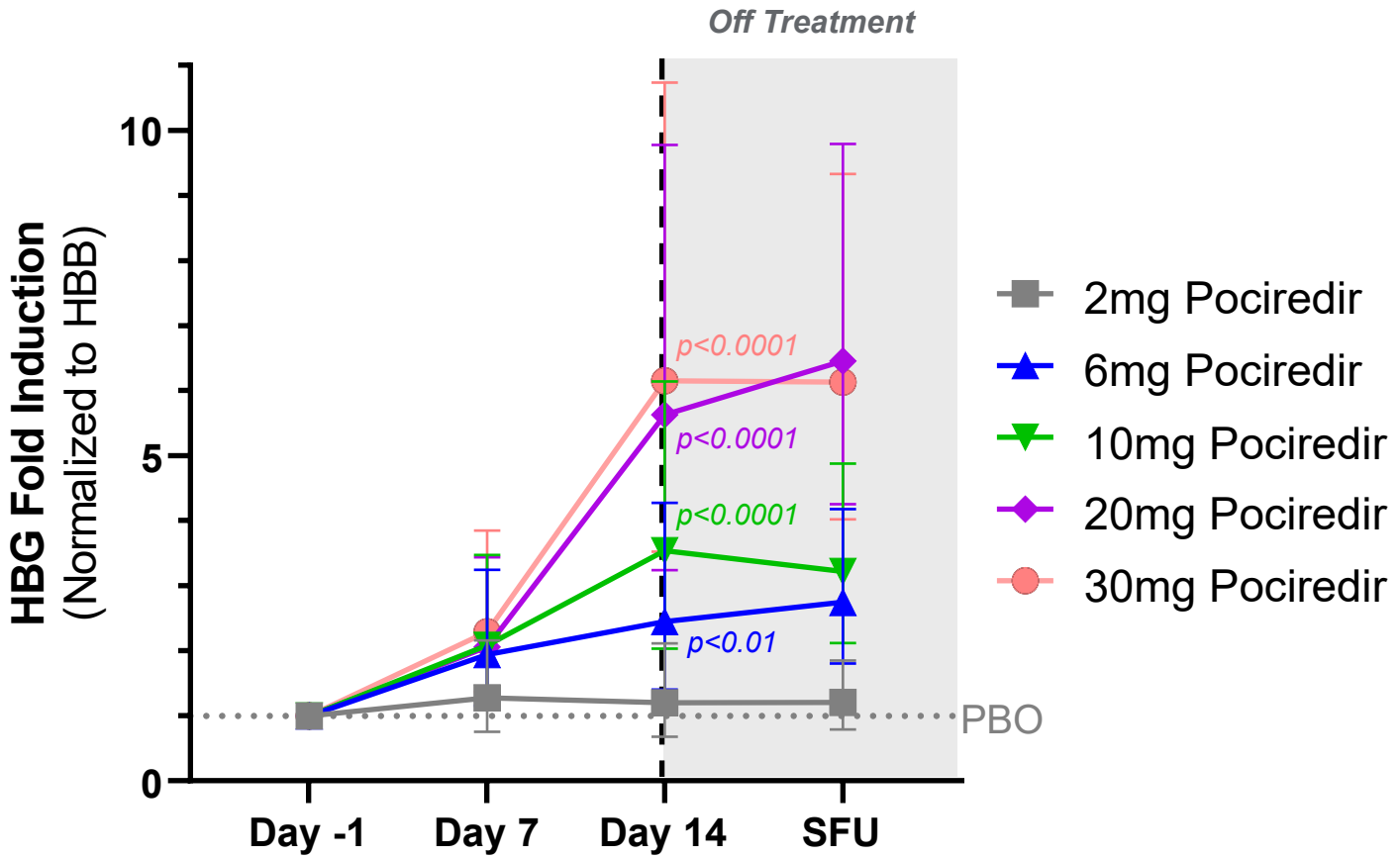
pociredir

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

EED: Embryonic Ectoderm; HbF: Fetal hemoglobin; HBG: Gamma globin gene (encodes mRNA for fetal hemoglobin)

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

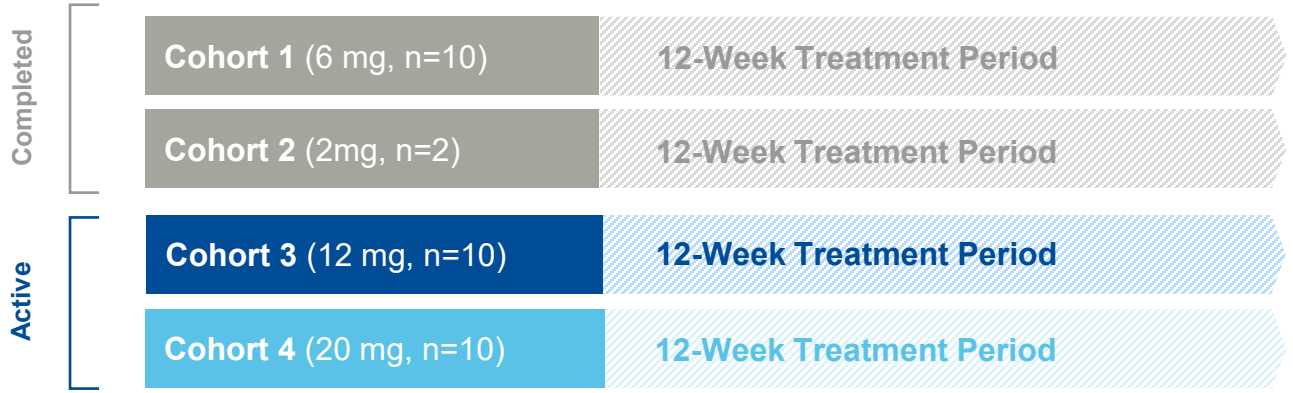
Patient Severity

- ≥4 VOCs over 12 months or ≥2 VOCs over 6 months *or*
- ≥2 VOCs + at least 1 non-VOC severe acute event (ACS, sequestration, priapism) over 12 months *or*
- ≥2 non-VOC severe acute events (ACS, sequestration, priapism) over 12 months *or*
- SCD end-organ disease severity (CKD or PAH)

Concomitant Medications

- Prior experience with hydroxyurea / Current hydroxyurea use excluded
- Other disease modifying therapies (crizanlizumab, L-glutamine) allowed

Study Design – Open-label**



Key Study Endpoints

Primary

- Safety and tolerability assessments
- PK parameters

Secondary/Exploratory

HbF induction, hemolysis, and anemia:

- % HbF (CE/HPLC) and % F-cells (flow cytometry)
- Absolute reticulocyte count
- Total hemoglobin
- Unconjugated bilirubin

**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.

CE, capillary electropherisis ; CKD, chronic kidney disease ; HbF, fetal hemoglobin; HPLC, high-performance liquid chromatography ; PAH, pulmonary arterial hypertension ; 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 data through 2023)

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 were treatment-related TEAEs in 5/16 (31.3%) patients: (headache [x2], lip numbness, diarrhea, fatigue, somnolence, nausea, tinnitus)#
- 4/23 TEAEs (in 4 patients) were 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

All mild in severity, non-serious and resolved while patient remained on study drug

Pioneer Phase 1b Clinical Trial Sites

Active Sites

United States

- UT Houston (PI: Idowu)
- Queens Hospital Cancer Center (PI: Ferman)
- University of Miami (PI: Alvarez)
- University of North Carolina (PI: Little)
- Jacobi Medical Center (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 (PI: Birrer)
- Lady of the Lake Hospital (PI: Stagg)
- Inova Cancer Center (PI: Alan)

South Africa

- Wits Health Consortium (PI: Mahlangu)

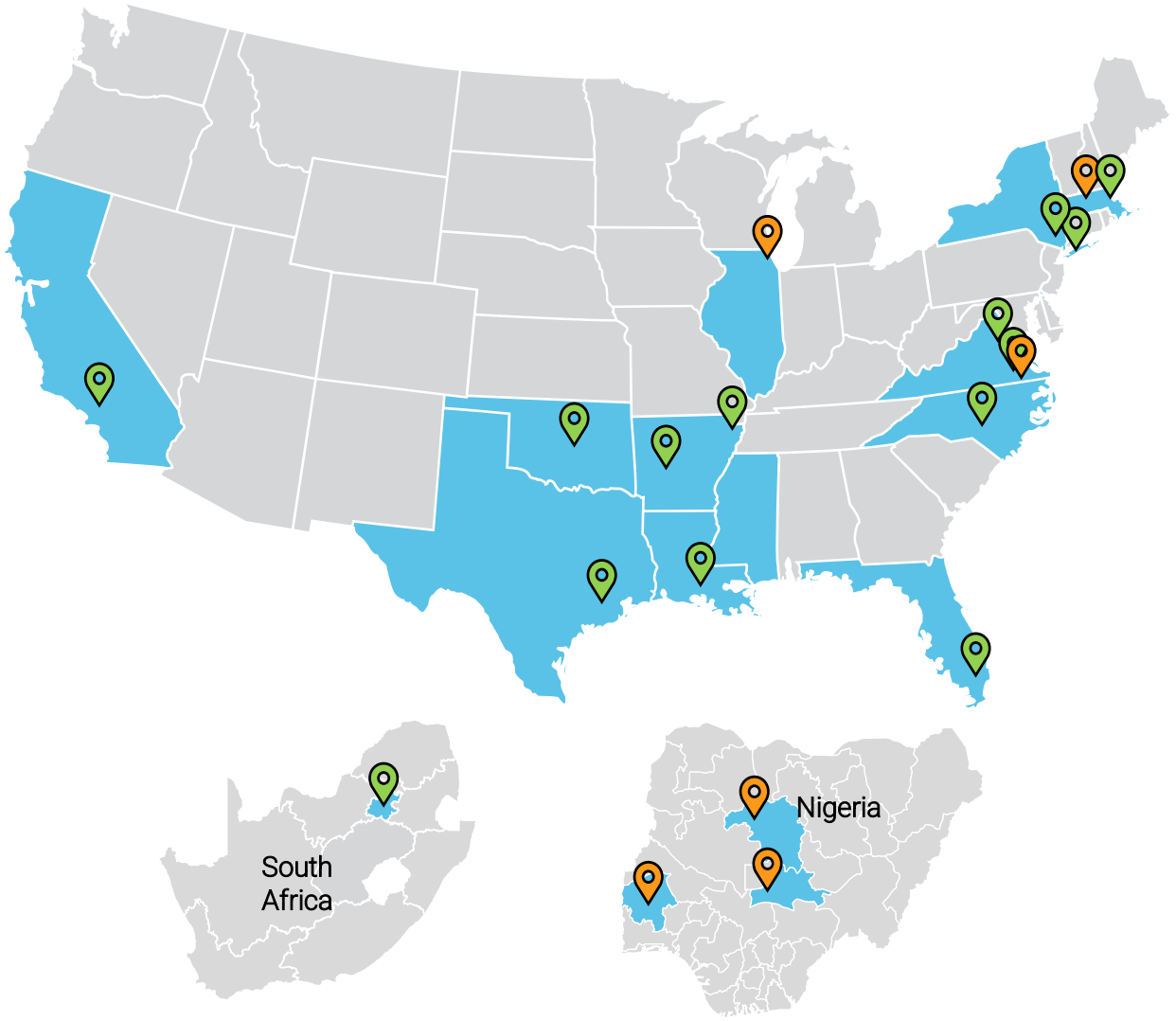
Onboarding Sites

United States

- University of Illinois Chicago (PI: Molokie)
- Massachusetts General Hospital (PI: Azar)
- East Carolina University (PI: Liles)

Nigeria

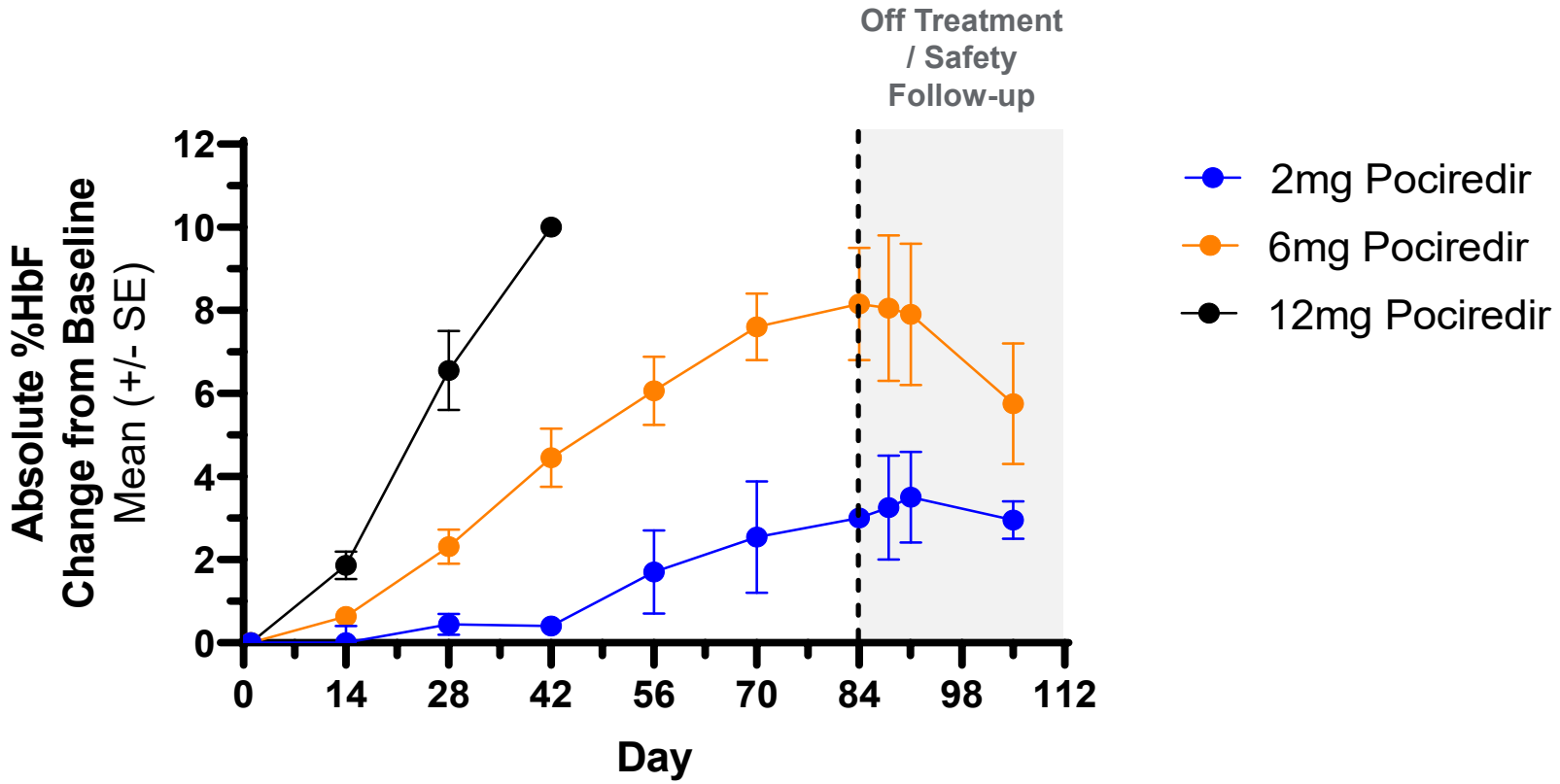
- National Hospital, Abuja (PI: Ojika)
- Barau Dikko Teaching Hospital (PI: Dogara)
- University of Ibadan (PI: Fasola)



Clinical trial site status as of January 6, 2025

Initial Pioneer Data Demonstrated Dose-dependent Increases in HbF

Absolute %HbF Change from Baseline

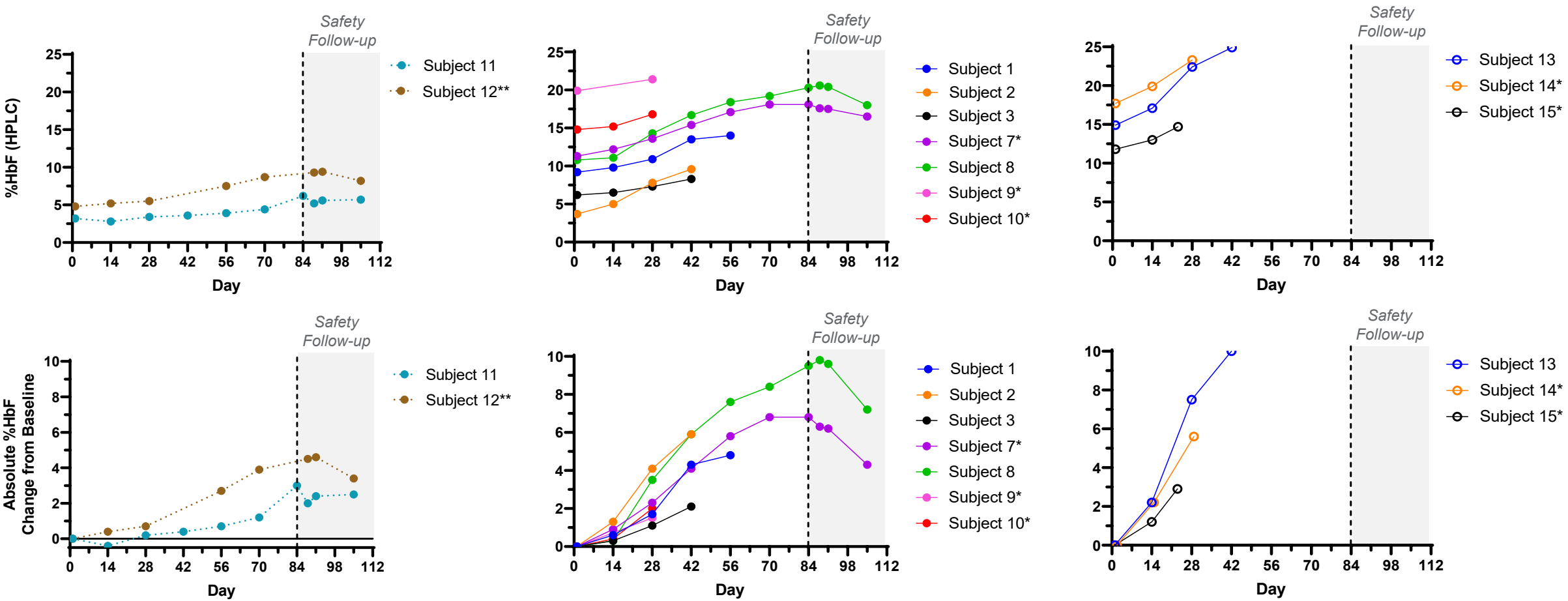


U.S. FDA issued a full clinical hold for pociredir on February 23, 2023 which was lifted August 23, 2023. Safety data collection continued with data cutoff of March 3, 2023.

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

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

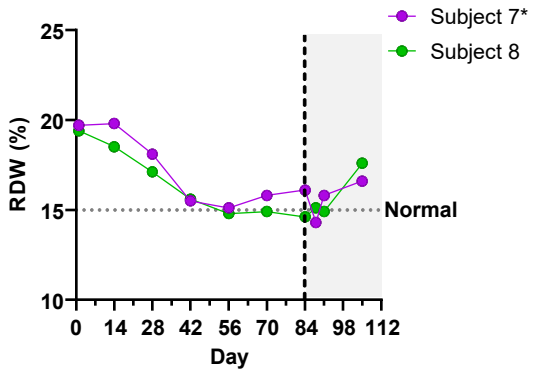
** Day 42 and day 84 data not available for subject 12; samples were received by the lab outside of stability window

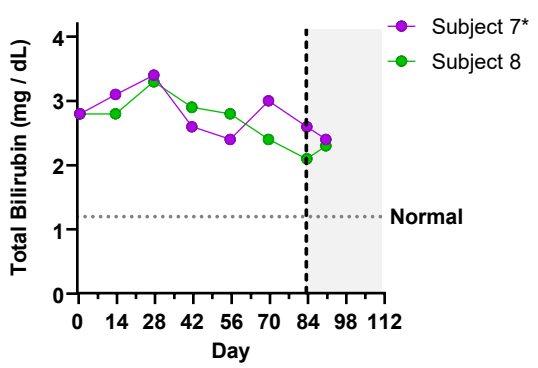
***Data includes subjects with confirmed study drug adherence

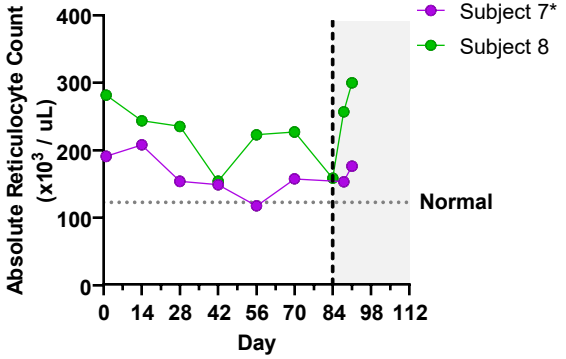
Improvements in Biomarkers of Hemolysis and Anemia from initial 6mg and 12mg Pioneer data

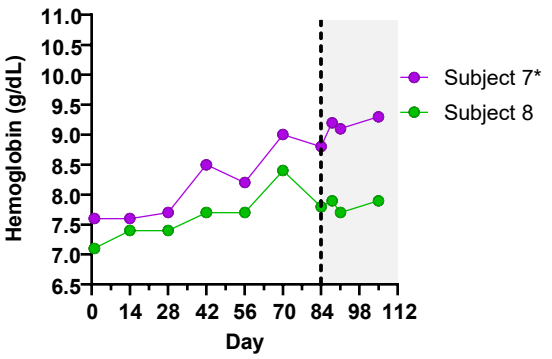
Red Cell Distribution Width (RDW) | **Total Bilirubin** | Absolute Reticulocyte Count | Total Hemoglobin

6 mg

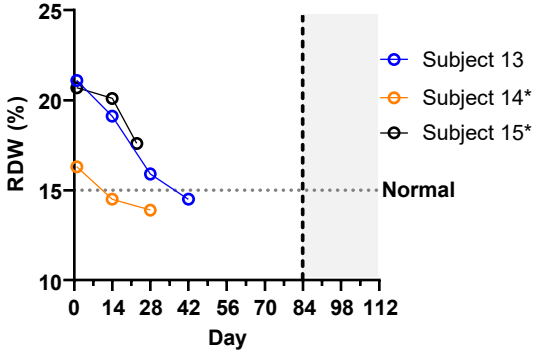


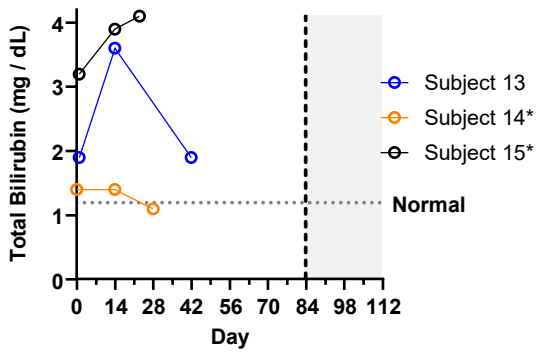


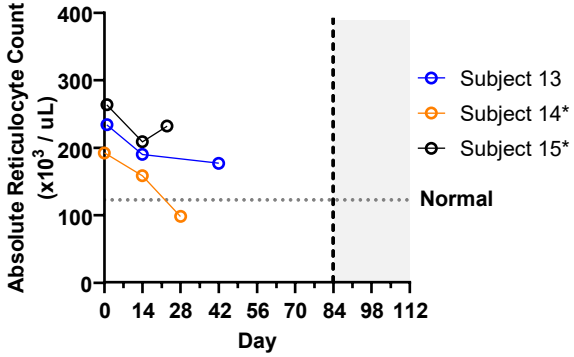


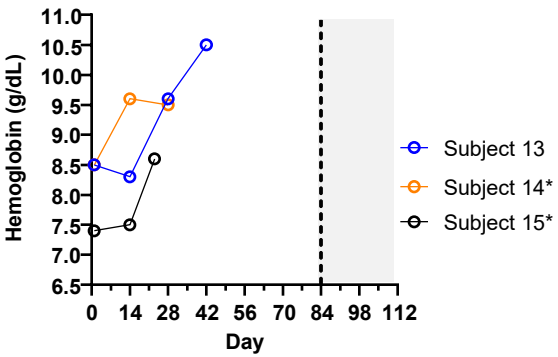


12 mg









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

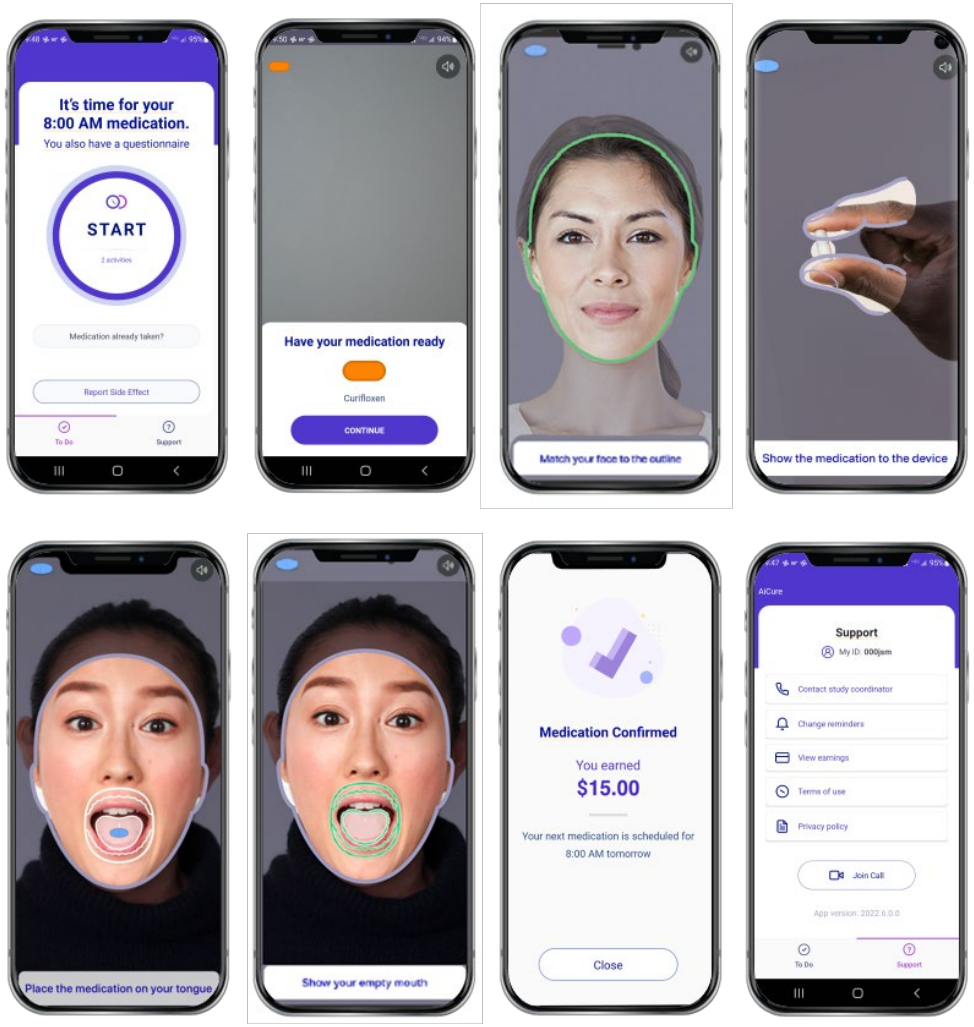
*Subjects on stable dose of hydroxyurea; Note: Subject 15 ceased dosing on Day 22

Utilizing Artificial Intelligence (AI) from AiCure to Increase Drug Adherence

Improves Study Drug Adherence

Robust Data Collection

Real-Time Feedback to Clinical Trial Sites



Fulcrum Therapeutics

Well-Positioned for Transformational Year in 2025

Pociredir: Best-in-class potential

- Oral small molecule HbF inducer with demonstrated proof-of-concept
- Potential to be broadly protective of SCD symptomology
- Planned timing for Phase 1b PIONEER data disclosure
  - cohort 3 (12 mg): mid-2025
  - cohort 4 (20 mg): YE 2025

Preclinical Programs

- Advanced preclinical program for the potential treatment of DBA & inherited aplastic anemias
- Foundation for pipeline sustainability in benign hematology
- IND submission planned in Q4

Cash Position

- ~$240 million as of December 31, 2024
- Estimated 2025 cash burn of $55 - $65 million
- Cash runway until at least 2027

Fulcrum Therapeutics

THANK YOU