Initial Data from First SCD Subjects in FTX-6058 Phase 1b Study

June 10th, 2022

Fulcrum Therapeutics

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Agenda

- **Introduction**
  Bryan Stuart
- **Overview of FTX-6058**
  Judith Dunn, PhD
- **EHA Presentation of Initial Data from Phase 1b Trial of FTX-6058**
  Julie Kanter, MD
- **Conclusion**
  Bryan Stuart
- **Q&A Session**

Fulcrum Therapeutics

Bryan Stuart

President and Chief Executive Officer

Our Mission is to Treat the Root Cause of Rare Genetic Diseases

We aim to

Deliver disease-modifying therapies that improve the lives of people with rare genetic diseases

Three Clinical-Stage Programs

FSHD: Phase 3; positioned to be first-to-market with a disease-modifying therapy

Sickle cell disease (SCD): Phase 1b patient study; potential first oral functional cure

Non-SCD hemoglobinopathies: Phase 1b ready

FulcrumSeek™

Product engine to systematically identify high-value, de-risked targets at speed and scale for rare genetic diseases

FSHD: Facioscapulohumeral Muscular Dystrophy

Key Takeaways From Today's Update

Proof-of-concept data support FTX-6058 as a novel oral HbF inducer

FTX-6058 has already achieved levels of HbF induction associated with broad clinical benefit for people with SCD

Based on these data, we plan to complete enrollment of the Phase 1b dose-ranging study in 2022, and align with regulators on the design of the registrational study initiating in 2023

Fulcrum Therapeutics

Judith Dunn, PhD

President, Research & Development

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

Millions more worldwide

Treatment Options

Current therapies are highly invasive and/or do not address broad symptomatology

- Current SOC offers limited benefit and is only effective in a subset of patients
- Newly approved therapies address only a subset of SCD symptomatology (i.e., anemia or VOCs)

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

Significant Unmet Need Remains

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 VOCs

P-Selectin Inhibitors

Leukocyte Binding to P-selectin

- \+ Reduces VOCs
- − Does not address hemolysis
- − IV administration

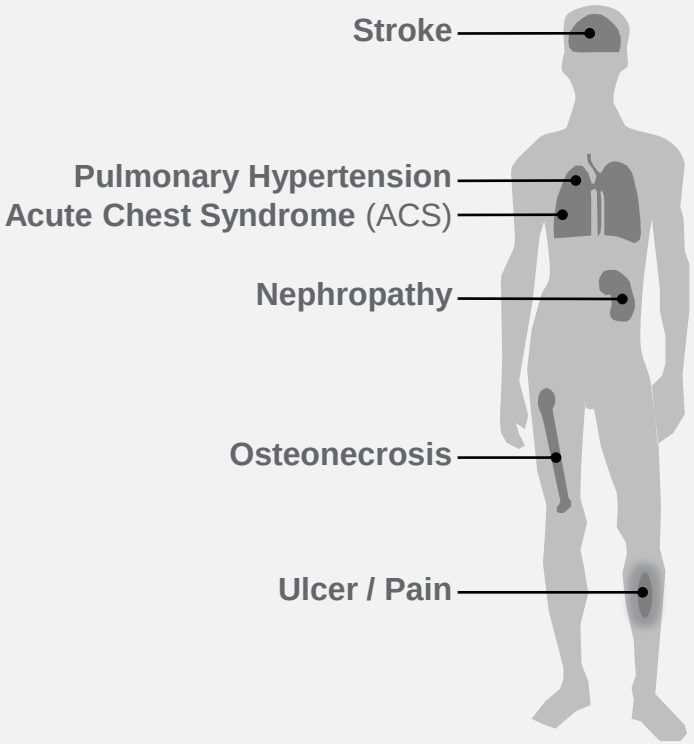
BCL11A Gene Editing

Increasing HbF

- \+ Potential for a cure
- − Highly invasive
- − Unknown durability
- − Barriers to access

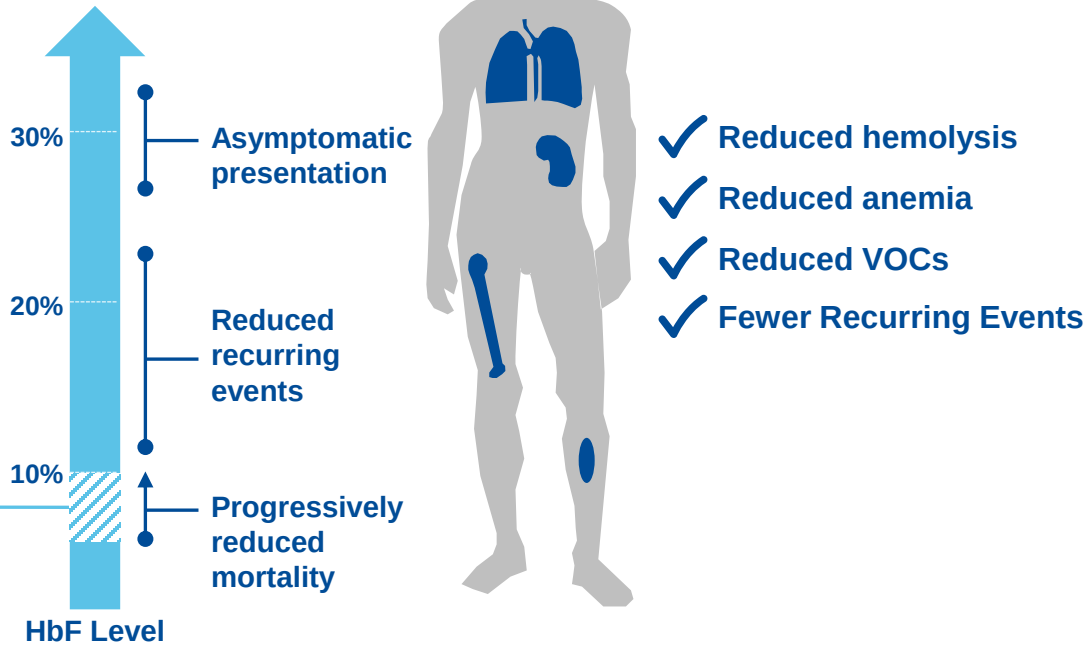
HbF Increases of 5-10% Above Baseline Have Been Shown to Broadly Improve Outcomes in SCD

Typical SCD Patient



SCD Patient Baseline HbF 5-10%

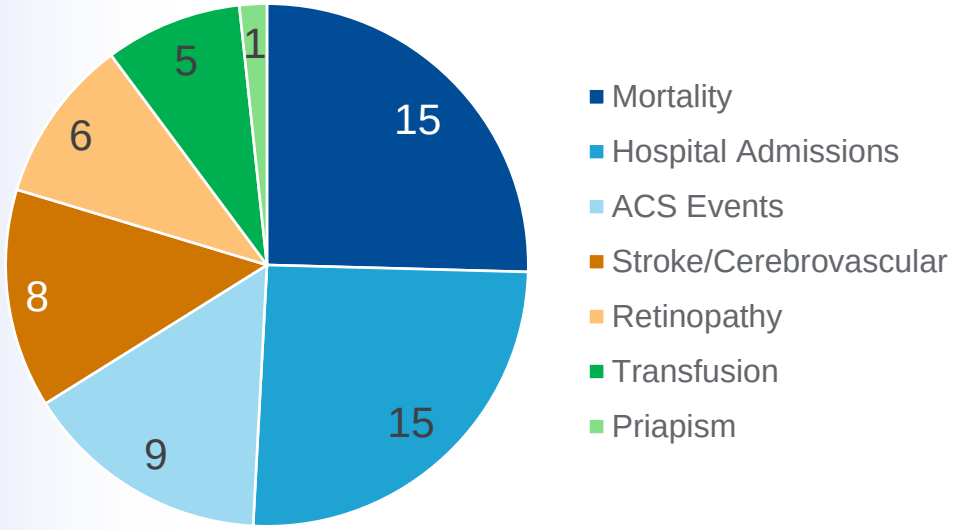
SCD Patient with HPFH



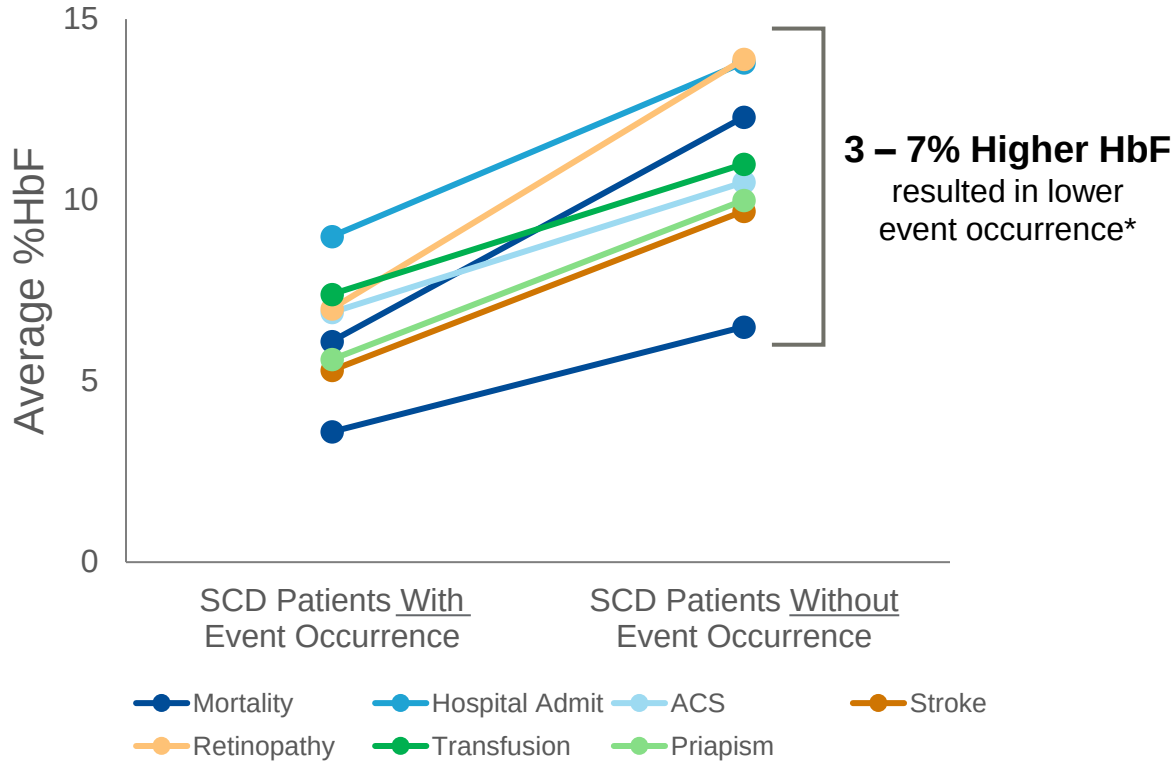
VOCs: Vaso-occlusive crisis; HPFH: Hereditary Persistence of Fetal Hemoglobin; *Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.*

Higher Levels of HbF Protein Provide Broad Clinical Benefit

Numerous Published Analyses Demonstrate the Clinical Benefit of Higher Levels of HbF



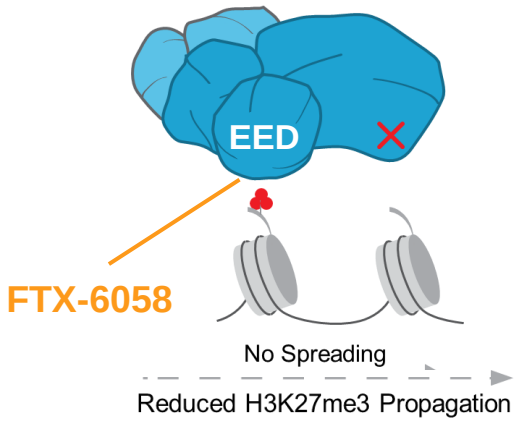
Higher HbF Levels are Associated with Improved Clinical Outcomes



Sources: Systematic Literature Review of publications from 1980 to 2021. Adeodu, et al. *Mediterr J Hematol Infect Dis.* 2017; Duan, et al. *Am J Ophthalmol.* 2019; Curtis, et al. *PLoS One.* 2016; Odenheimer, et al. *Am J Hum Genet*. 1987; Shurafa, et al. *Am J Hematol.* 1982. * Data represents observational studies of SCD patients, each line represents a separate analysis over the study duration.

FTX-6058: Oral HbF Inducer with Potential to Provide Broad Clinical Benefit

FulcrumSeek™ identified EED as a therapeutic target for SCD



Internal Medicinal Chemistry Led to FTX-6058, a Potent and Selective EED Inhibitor

- Once-daily treatment
- Potent and highly selective
- Clean off-target profile
- Composition of matter patent expires 2040
- Induced HBG mRNA and HbF protein preclinically

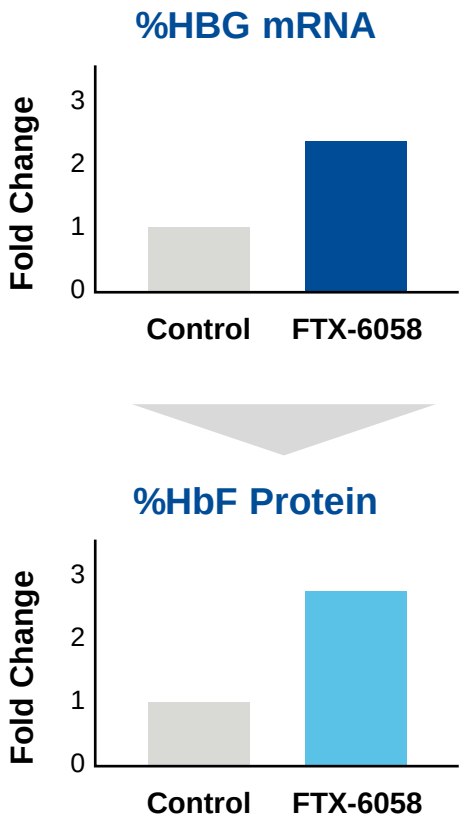
EED: Embryonic Ectoderm Development

Consistent 2 – 3 Fold HbF Induction with Strong Correlation Between mRNA and Protein in Preclinical Studies

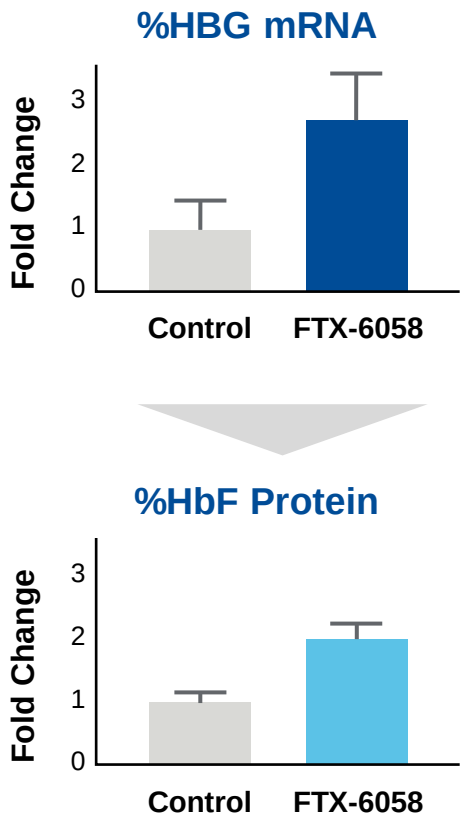
Extensive Preclinical Validation

- ✓ **HUDEP-2 Cells** (Human)
- ✓ **Healthy CD34+ Cells** (Human)
- ✓ **SCD CD34+ Cells** (Human)
- ✓ **Wild-type Mouse***
- ✓ **SCD Townes Mouse**

Healthy CD34+ Cells



SCD Townes Mouse



*Assessment based on embryonic ortholog in wild-type mouse; Note: Representative mRNA and protein data from one healthy CD34+ donor

FTX-6058 Phase 1 Healthy Volunteer Study Demonstrated Proof-of-Mechanism and Proof-of-Biology

Target Engagement

Robust reductions in H3K27me3 demonstrated **proof-of-mechanism**

HBG mRNA Induction

Demonstrated **proof-of-biology** as evidenced by HBG mRNA induction

Increases in F-reticulocytes

Increases in F-reticulocytes provide **earliest indication HbF production is starting**

FTX-6058 has been **generally well-tolerated**, with no SAEs reported to-date, no discontinuation due to TEAEs, and all TEAEs possibly related to FTX-6058 deemed Grade 1 or 2 per CTCAE criteria

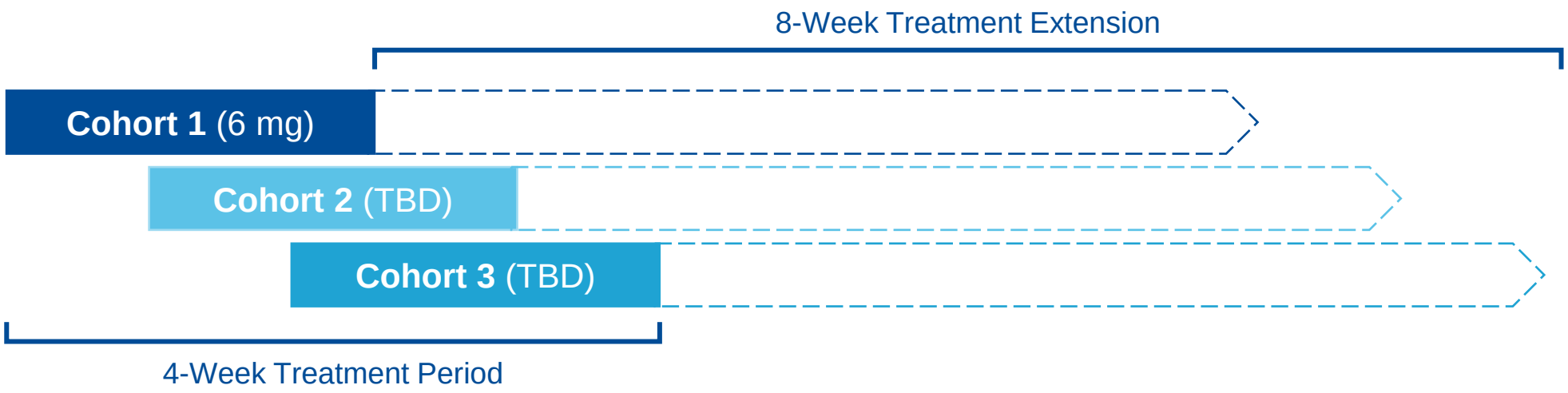
SAE: Serious adverse event; TEAE: Treatment-emergent adverse event; CTCAE: Common criteria for adverse events

Ongoing Phase 1b Clinical Trial in SCD Subjects

Study Population

Subjects with SCD, Age 18 – 65, on or off hydroxyurea

Study Design



Study Endpoints

Primary	Secondary	Exploratory
▪ Safety and tolerability ▪ Pharmacokinetic measurements	▪ %HbF protein by HPLC ▪ %F-cells by flow cytometry	▪ Target engagement ▪ Incidence of VOCs ▪ Biomarkers of hemolysis ▪ QOL measures

HPLC: High-performance Liquid Chromatography; QOL: Quality of Life

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Initial Data from First SCD Subjects in FTX-6058 Phase 1b Study

Data analysis cutoff as of May 25th, 2022

Dr. Julie Kanter, MD, Associate professor of Hematology and Oncology and Director of the Adult Sickle Cell Clinic at the University of Alabama at Birmingham.

SCD Phase 1b Demographics

	Phase 1b Study (6mg Cohort)
Number of subjects enrolled, n	6
Average age, years (range)	31 (25, 48)
Gender, Male (%)	1 (16%)
Mean baseline HbF (range)	5.7% (3.7, 9.2)
Genotype, n (%)	
HbSS	6 (100%)
HbSβ^0	0 (0%)
HbSβ$^+$	0 (0%)
Hydroxyurea Utilization, n (%)	0 (0%)

- Mean baseline HbF of 5.7% is consistent with recent SCD clinical studies and published data
- No hydroxyurea utilization among enrolled subjects
- All subjects enrolled to date have the HbSS genotype

Data analysis cutoff as of May 25th, 2022; One subject was omitted from PD analysis due to protocol deviation

Day 1 Pharmacokinetic Parameters for FTX-6058 6mg Dose

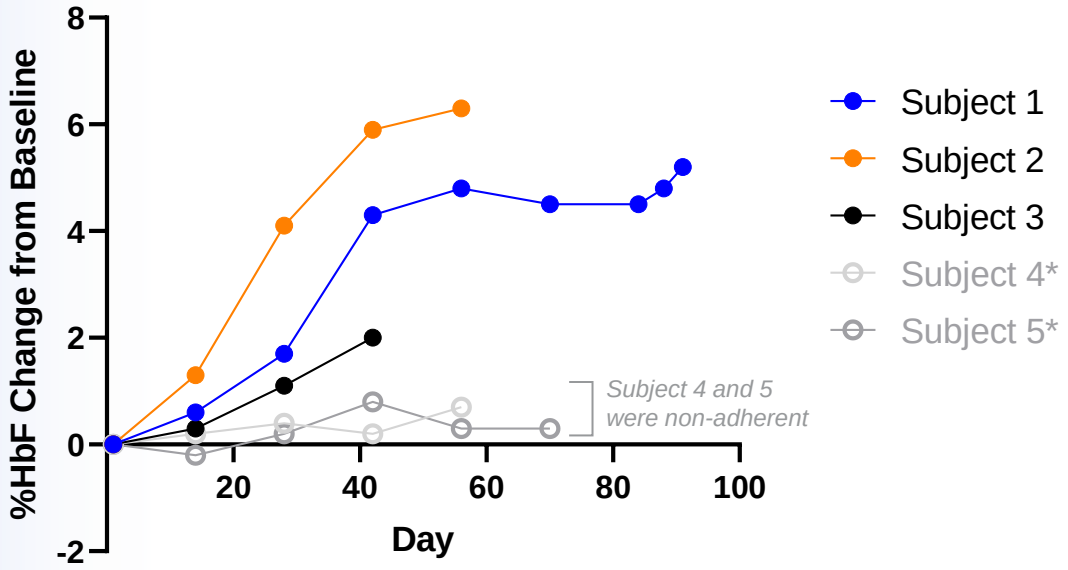
	Phase 1 HV Values (SD)	Phase 1b SCD Values (SD)
Cmax (ng/mL)	**24.9** (9.3)	**16.9** (3.5)
Tmax (hr)	**4.08** (0.80)	**2.50** (0.84)
T1/2 (hr)	**5.60** (0.36)	**5.47** (0.72)
AUC 0-last (hr*ng/mL)	**192.5** (57.02)	**134** (45.4)

- **Potentially lower exposure (25 – 30%) observed in SCD subjects versus healthy volunteers (HVs)**
  - Preliminary observations suggest differences in absorption (vs metabolism)

- **In SCD subjects, exposure (AUC 0-last) from 6mg dose appears similar to ~4mg dose in HVs**

Data analysis cutoff as of May 25th, 2022

FTX-6058 Achieved Up To 6.3% Absolute Increase in HbF



Subject	Baseline %HbF	%HbF at Data Cutoff	Δ%HbF
Subject 1	9.2	14.4	5.2
Subject 2	3.7	10	6.3
Subject 3	6.2	8.3	2.1
Subject 4*	4.8	5.3	0.7
Subject 5*	7.0	7.3	0.3

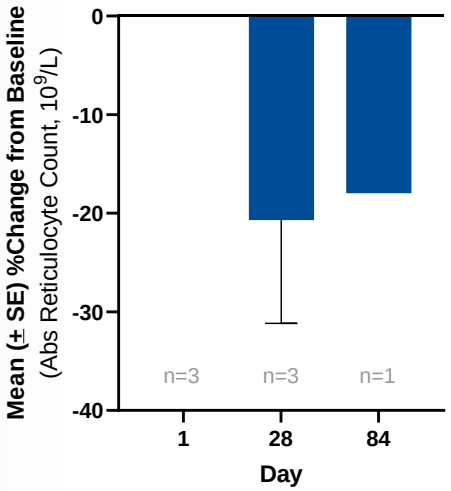
- Two subjects achieved absolute HbF increases within the 5 – 10% range that have been shown to provide transformational benefit to people living with SCD
- Observed measurable increases in HbF protein as early as 14 days after treatment initiation
- Exposure appears to correlate with efficacy
- HBG mRNA and HbF protein fold induction correlation (approximately 1:1) is consistent across preclinical and clinical data

*Data analysis cutoff as of May 25th, 2022; Subject 1 was not dispensed drug after Day 56; Subject 3 withdrew from the study; *Per SAP, Subjects 4 and 5 were determined to be non-adherent based on investigator and patient reporting, and/or pill count; Subject 6 was discontinued due to protocol deviation*

FTX-6058 Decreased Hemolysis

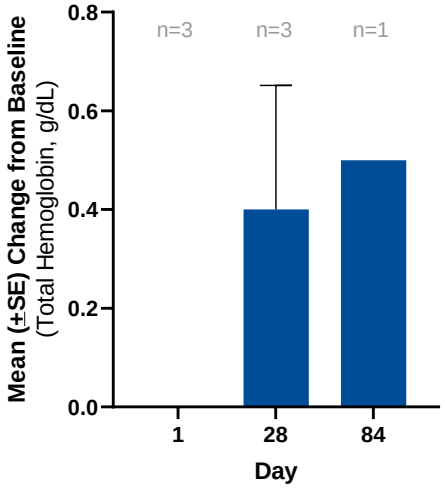
Absolute Reticulocyte Count

Mean baseline level: 330 x 10^9 / L



Total Hemoglobin

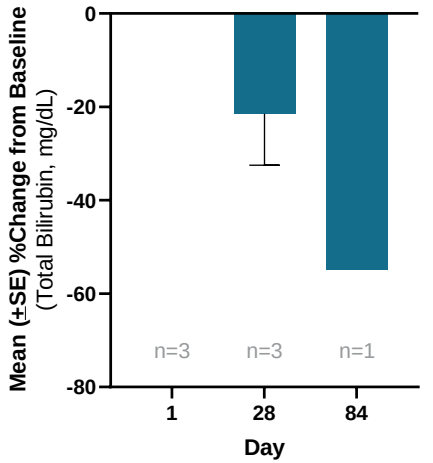
Mean baseline level: 7.5 g/dL



Reductions in reticulocytes and increases in total hemoglobin indicated less anemia and hemolysis

Total Bilirubin

Mean baseline level: 2.5 mg/dL



Bilirubin decreases indicated less hemolysis

Data analysis cutoff as of May 25th, 2022; Data presented are from Subject 1 - 3

FTX-6058 has been Generally Well Tolerated

Summary of All Treatment Emergent Adverse Events (TEAEs)

Subject	TEAE	Severity
Subject 1	Swelling of Legs and Feet	Mild (Grade 1)
	Light Headache	Mild (Grade 1)
	Lower Back Pain	Mild (Grade 1)
	Sore Throat	Mild (Grade 1)
	Abdominal Pain	Moderate (Grade 2)
	UTI	Moderate (Grade 2)
Subject 2	Tonsilitis	Moderate (Grade 2)
Subject 4	VOC (L Lower Leg Pain Crisis)	Moderate (Grade 2)

- **All TEAEs are non-serious, resolved, and were deemed to be unrelated to study drug**
- No treatment emergent SAEs reported, and no discontinuation reported due to TEAEs
- Unlike hydroxyurea, no myelosuppression observed
- VOC observed in non-adherent subject (i.e., Subject 4)

Data analysis as of May 25th, 2022; Subject 1 was not dispensed drug after Day 56

Initial FTX-6058 Data in Subjects with SCD Validates Proof-of-Concept

Conclusions

- **FTX-6058 rapidly and robustly Induces HbF**
  - Initial subjects from first dose cohort achieved up to 6.3% HbF induction over baseline
  - HbF levels increasing at last measured timepoint
  - HBG mRNA and HbF protein fold induction correlation (approximately 1:1) is consistent across preclinical and clinical data
- **FTX-6058 improved biomarkers of hemolysis**
- **FTX-6058 was generally well-tolerated in SCD subjects with up to 3 months exposure**

Initial FTX-6058 Data in Subjects with SCD Validates Proof-of-Concept

Next Steps

- **Complete Phase 1b dose-ranging study**
  - Plan to complete enrollment in 3 cohorts in 2022
    - Gain experience in combination with hydroxyurea
    - Initiate 2mg cohort
      - Facilitate identification of minimally efficacious dose
- **Align with regulators on design of registrational study initiating in 2023**
  - Discuss HbF as a potential biomarker supporting accelerated approval