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# Initial Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Data from an Ongoing Open-Label Study Investigating FTX-6058 in Adults Living with Sickle Cell Disease

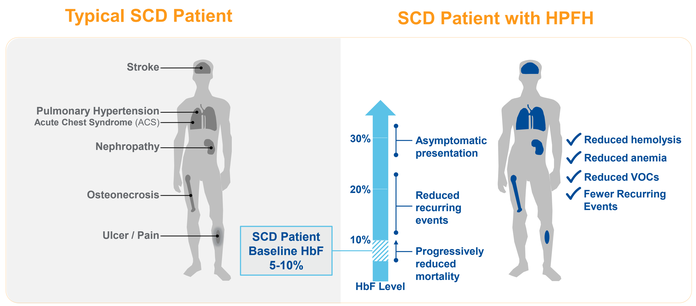
Julie Kanter[1], Jae Ahn[2], Geoff Allen[2], Paul Bruno[2], Judy Dunn[2], Olga Mitelman[2], Chris Morabito[2], Billy Stuart[2], William Tracewell[2], John Ziegler[2]
[1]University of Alabama at Birmingham, Birmingham, Alabama, USA; [2]Fulcrum Therapeutics. 26 Landsdowne Street, Cambridge, Massachusetts, USA

## Background

FTX-6058 is a potent and selective oral small-molecule inhibitor of Embryonic Ectoderm Development (EED) that has demonstrated robust HbF (fetal hemoglobin) protein induction in human primary cell and murine models of sickle cell disease (SCD). SCD is a genetic disorder of the red blood cells caused by a mutation in the hemoglobin beta (HBB) gene, which results in red blood cell sickling, hemolysis, vaso-occlusive crises (VOCs), and other complications. HbF ($\alpha_2\gamma_2$) prevents the pathologic polymerization of sickle hemoglobin (HbS) in deoxygenated environments. Individuals with SCD who also have hereditary persistence of HbF (HPFH) have attenuated pathology. HPFH provides genetic and clinical evidence that increasing HbF has the potential to prevent or reduce disease-related pathophysiology, including hemolysis, pain, and VOCs.

FTX-6058 has demonstrated consistent 2-3 fold HbF induction with strong correlation between HBG mRNA and HbF protein in pre-clinical studies, which has the potential to positively impact important clinical outcomes in SCD. Clinically, multiple ascending dose (MAD) data from a Phase 1, randomized, double-blind, placebo-controlled study of FTX-6058 in healthy volunteers demonstrated robust target engagement (H3K27me3 reduction) and potent induction of HBG (hemoglobin subunit γ) mRNA, translation of which is required for HbF expression.

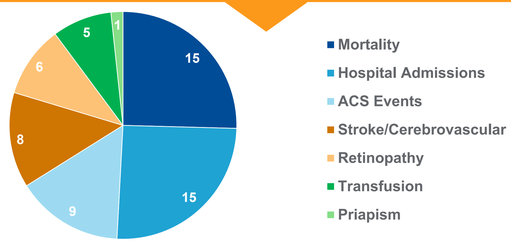
### HbF Increases 5-10% Above Baseline (10-20% Total HbF) Have Been Shown to Broadly Improve Outcomes in SCD



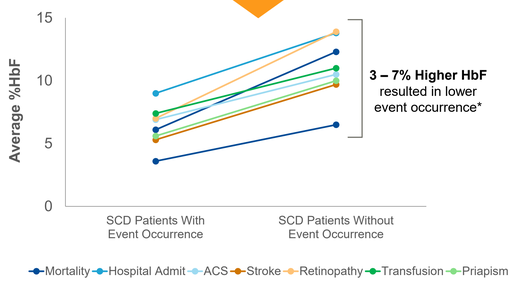

VOCs: Vaso-occlusive crisis; HPFH: Hereditary Persistence of Fetal Hemoglobin

### Increases in HbF Protein can Provide Broad Clinical Benefit

**Numerous Published Analyses Demonstrate the Clinical Benefit of Increased HbF**




**Higher HbF Levels are Associated with Improved Clinical Outcomes**




Sources: Systematic Literature Review of publications from 1980 to 2021.
* Data represents observational studies of SCD patients, each line represents a separate analysis over the study duration.

## Methodology

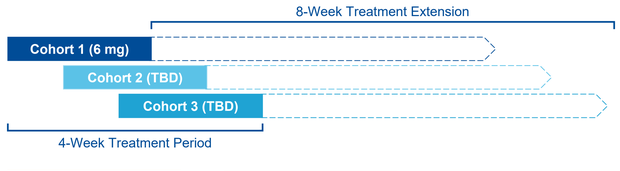
The ongoing Phase 1b open-label dose ranging study investigating FTX-6058 is a multiple cohort trial that is being conducted in adults with SCD on and off hydroxyurea. In the first cohort, up to 10 subjects will receive FTX-6058 6 mg once daily orally for 4 weeks. Eligible subjects may choose to continue dosing for an additional 8 weeks at the same dose via an extension study. Up to two additional cohorts with doses selected between 2 – 20 mg inclusive may be added to the study. The primary endpoints of the study are the safety and tolerability of FTX-6058 as measured by the frequency of adverse events and the pharmacokinetic profile of FTX-6058 in subjects with SCD. Secondary and exploratory endpoints include the effect of FTX-6058 on HbF induction in peripheral blood and other relevant SCD biomarkers and clinical endpoints.

### 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<br>▪ Pharmacokinetic measurements | ▪ %HbF protein by HPLC<br>▪ %F-cells by flow cytometry | ▪ Target engagement<br>▪ Incidence of VOCs<br>▪ Biomarkers of hemolysis<br>▪ QOL measures |

### Demographics

**SCD Phase 1b Demographics**

| | Phase 1b Study (6 mg 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%) |
| *HbSβ⁰* | 0 (0%) |
| *HbSβ⁺* | 0 (0%) |
| **Hydroxyurea Utilization, n (%)** | 0 (0%) |

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

- **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**

## Results

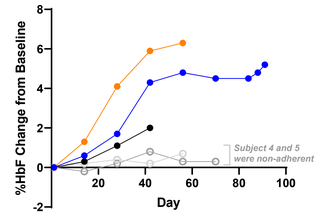
### Day 1 Pharmacokinetic Parameters for FTX-6058 6 mg Dose

| | 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 6 mg dose is similar to ~4 mg dose in HVs**

## Results (continued)

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



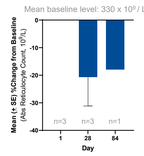

| Subject | Baseline %HbF | %HbF at Data Cutoff | Δ%HbF |
|---|---|---|---|
| Subject 1 | 9.2 | 14.4 | 5.2 |
| Subject 2 | 3.7 | 10 | 6.3 |
| Subject 3 | 6.2 | 8.3 | 2.1 |
| Subject 4* | 4.6 | 5.3 | 0.7 |
| Subject 5* | 7.0 | 7.3 | 0.3 |

- **Achieved absolute HbF increases within the 5 – 10% range which has 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**

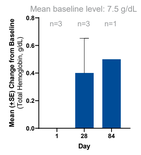
*Data analysis cutoff as of May 25th, 2022; Subject 1 was not dispensed drug after Day 56; Subject 3 withdrew from the study; *Per SAP, Subjects 4 and 5 were determined to be non-adherent based on investigator and patient reporting, and/or pill count; Subject 6 was discontinued due to protocol deviation*

### FTX-6058 Decreases Hemolysis

**Absolute Reticulocyte Count**

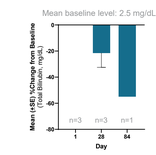



**Total Hemoglobin**




*Reductions in reticulocytes and increases in total hemoglobin indicate less anemia and hemolysis*

**Total Bilirubin**




*Bilirubin decreases indicate less hemolysis*

*Data analysis cutoff as of May 25th, 2022; Data presented are from Subjects 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)

## Conclusions

- **Initial FTX-6058 data in SCD subjects demonstrates compelling proof-of-concept**
- **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**
- **Data supports the potential for FTX-6058 to provide broad benefit to SCD patients**

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