FTX-6058, A Novel HbF Inducer: Phase 1 Healthy Volunteer Trial Update

August 10, 2021

Fulcrum Therapeutics




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Agenda

- **Corporate Overview and Key Quarterly Updates**
  Bryan Stuart, President and Chief Executive Officer

- **Preclinical Data with FTX-6058**
  Chris Moxham, Ph.D., Chief Scientific Officer

- **Interim Results from FTX-6058 Phase 1 Healthy Adult Volunteer Study**
  Chris Morabito, MD, Chief Medical Officer

- **Q&A Session**

Key Company Highlights

- **Losmapimod demonstrated slowed disease progression and improved function**
  - Plan to meet with the FDA in 2H 2021 to discuss potential next steps
- **Compelling interim results from FTX-6058 healthy adult volunteer trial**
  - Achieved dose-proportional pharmacodynamic changes in HBG mRNA and F-reticulocytes in whole blood in the MAD portion of the trial:
    - Mean 4.5-fold induction in HBG mRNA at 10mg
    - Mean 4.2-fold increase in F-reticulocytes at 10mg, indicating HbF production
  - Generally well-tolerated and predictable pharmacokinetic profiles
  - These pharmacodynamic changes have the potential to translate to meaningful clinical benefits in individuals with sickle cell disease and other hemoglobinopathies
  - Anticipate initiating a SCD clinical trial in Q4 2021 and a non-SCD hemoglobinopathies trial in 2022
- **Expansion of FulcrumSeek screening underway**
- **Cash runway into 1Q 2023**

Mid-year Update from Ongoing Phase 1 Healthy Volunteer Trial

Background on Sickle Cell Disease, Erythropoiesis, and FTX-6058 Preclinical Data

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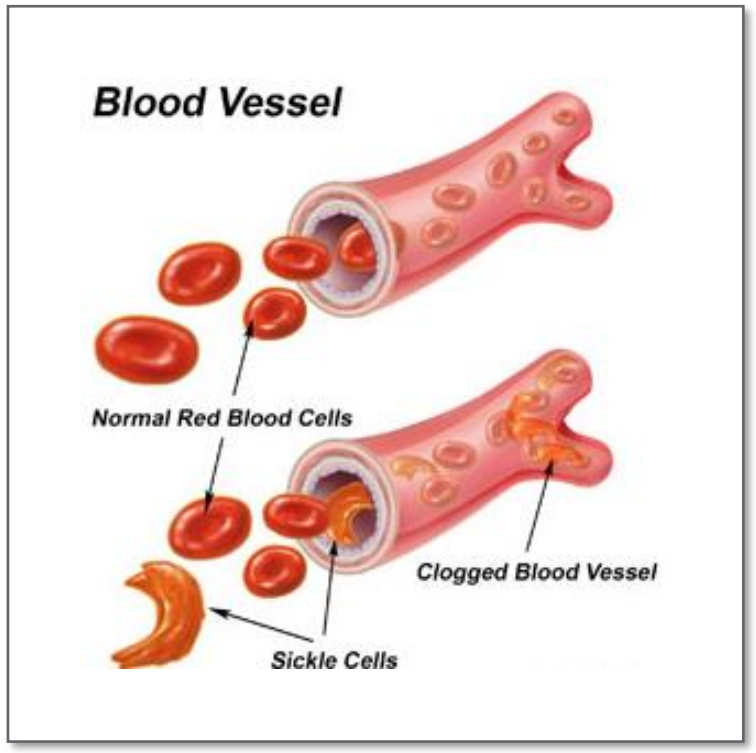
Sickle Cell Disease (SCD) is a Hemoglobinopathy Characterized by Mutated Hb, which Causes RBC Sickling, Hemolytic Anemia, and VOCs

SCD Pathophysiology



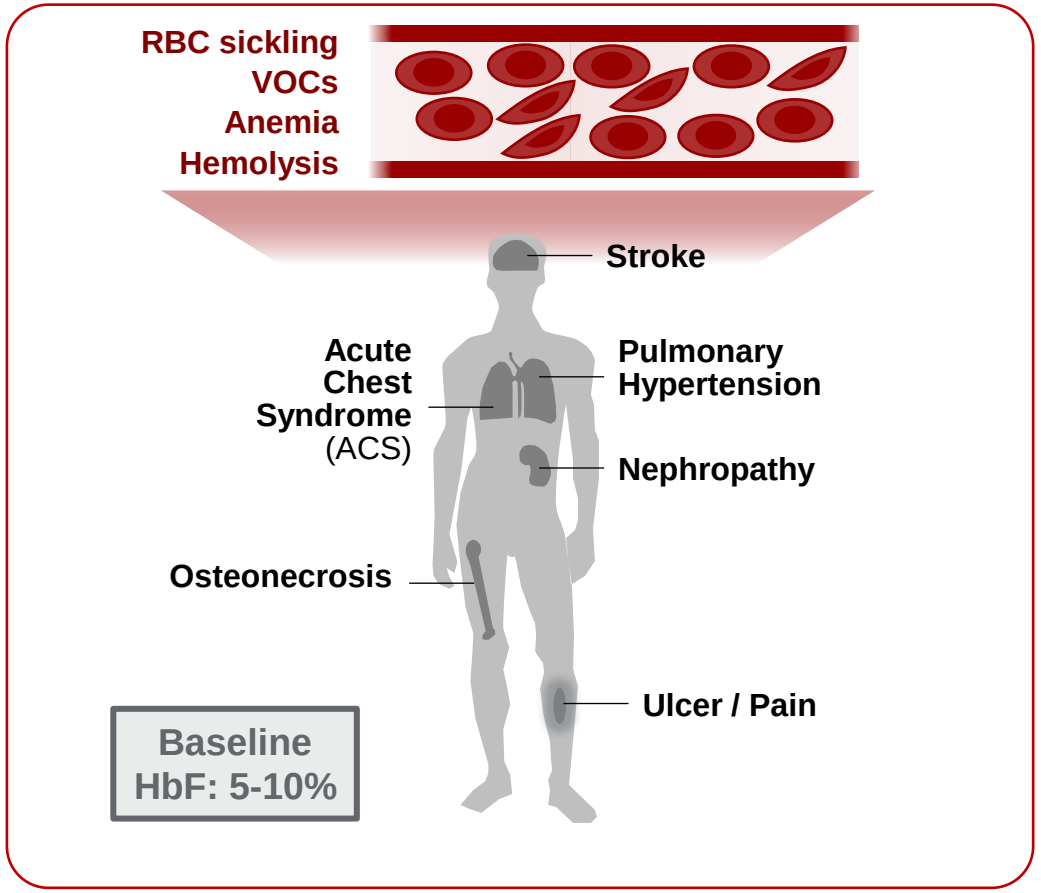
Cleveland Clinic Foundation, 2014.

- **SCD is a genetic disorder of the red blood cells caused by a mutation in the HBB gene, which results in red blood cell (RBC) sickling**
- **RBC sickling results in hemolysis, vaso-occlusive crises (VOCs), and other complications resulting in increased morbidity and mortality**
- **Current therapies are unable to address broad SCD symptomology:**
  - Hydroxyurea, the current SOC, provides efficacy to a subset of individuals with SCD, and has potential safety (e.g., myelosuppression) and tolerability issues
  - Newly approved therapies address only a subset of SCD symptomology (i.e., anemia or VOCs)
- **Sickle cell disease is a prevalent disease globally, with ~100K U.S. individuals, ~50K EU individuals, and millions more worldwide**

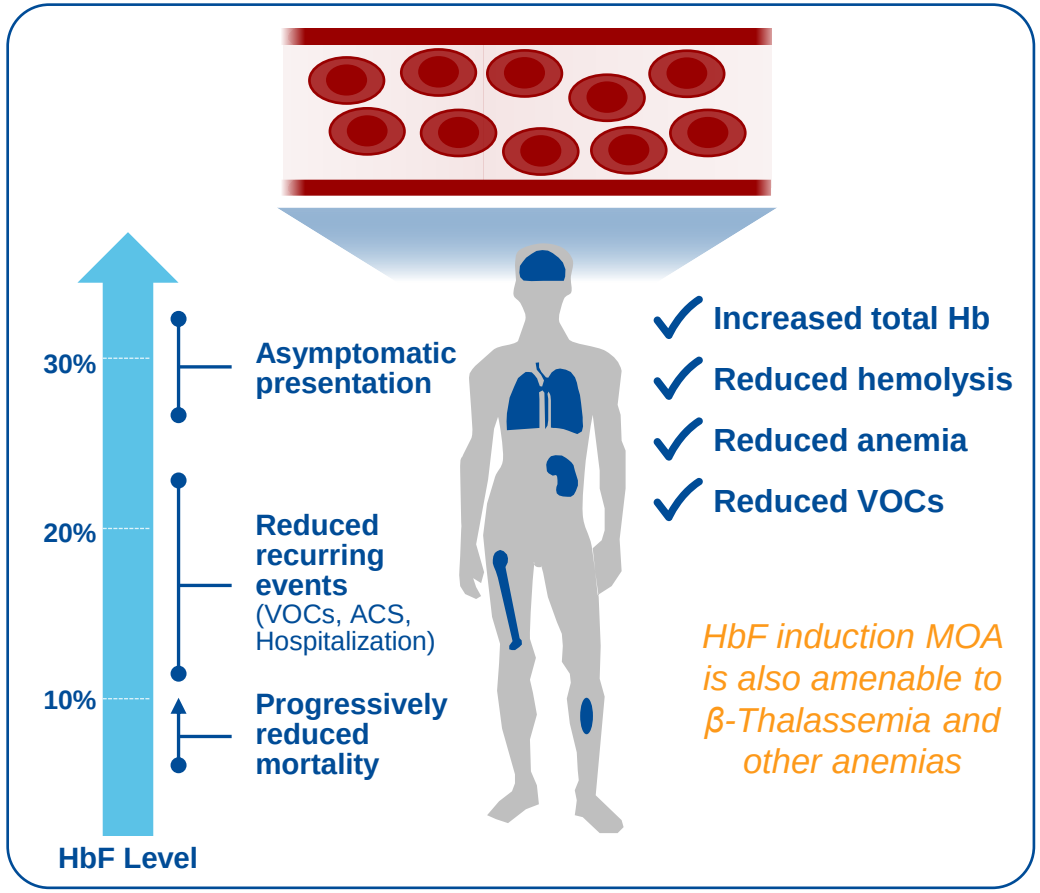
Hb: Hemoglobin; CDC; WHO; UpToDate.

Fetal Hemoglobin (HbF) Mitigates Mortality and Morbidity Risks Associated with Sickle Cell Disease

SCD Patient



SCD Patient with High Fetal Hemoglobin (HbF)



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

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

FulcrumSeek Identified Embryonic Ectoderm Development (EED) as a Target for HbF Induction

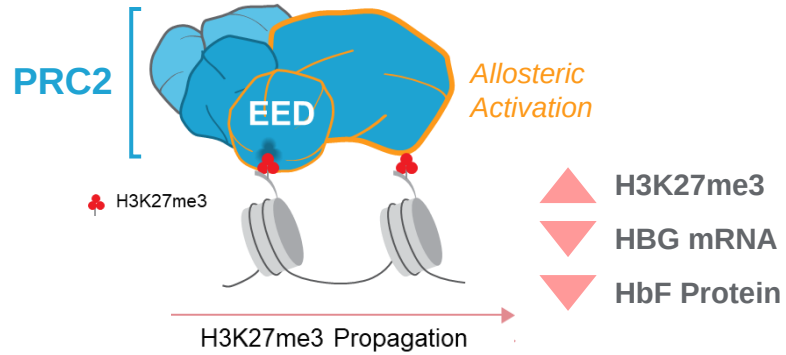
CRISPR + Compound Screening Engine
Experimentally screened candidate targets

Computational Data Mining
Computationally mined candidate targets

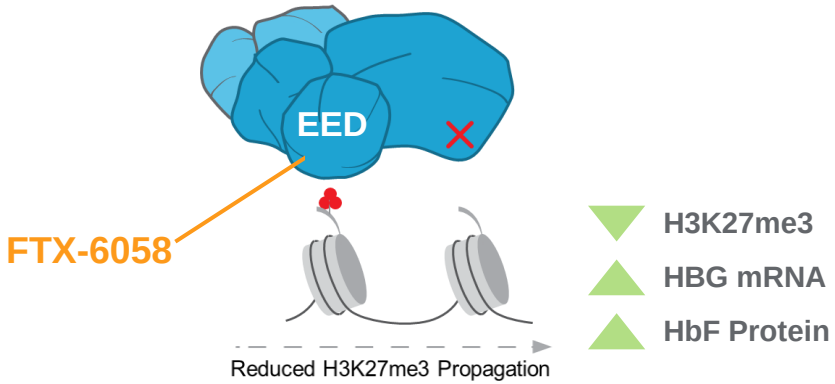
Identified Targets that Regulate HbF

PRC2, BCL11A, NuRD, HDACs, LSD1, DNMT1, IKZF1, IKZF3, SPOP

Identified EED as a Novel Drug Target of Polycomb Repressor Complex 2 (PRC2)



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



FTX-6058

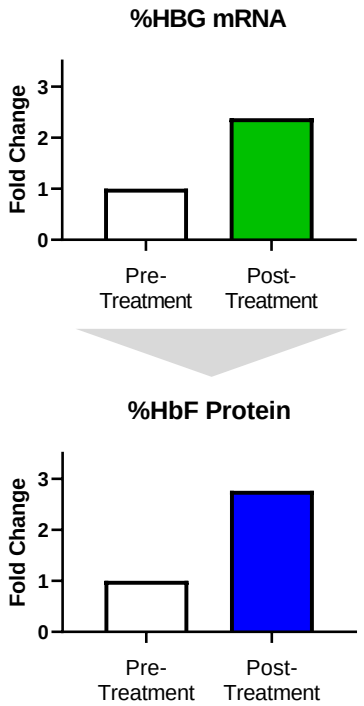
- EED K_D = 0.163 nM
- PRC2 IC_{50} < 5 nM
- Highly Selective
- Clean Off-target Profile
- Composition of Matter Patent Expires 2040

FTX-6058 Induced HbF 2 – 3-Fold Across Multiple Preclinical Models with Strong Correlation Between mRNA and Protein

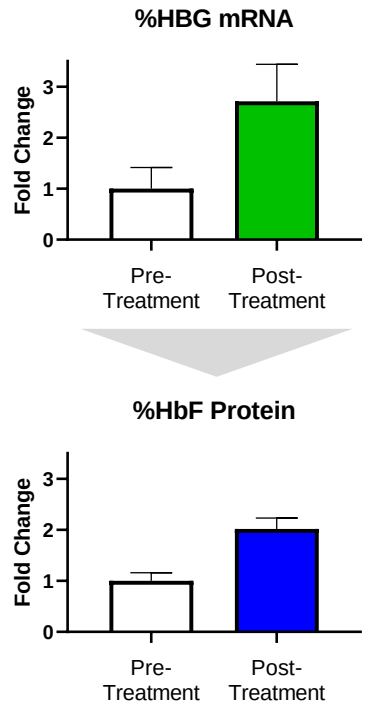
Extensive Preclinical Validation

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

Healthy CD34+ Cells



SCD Townes Mouse

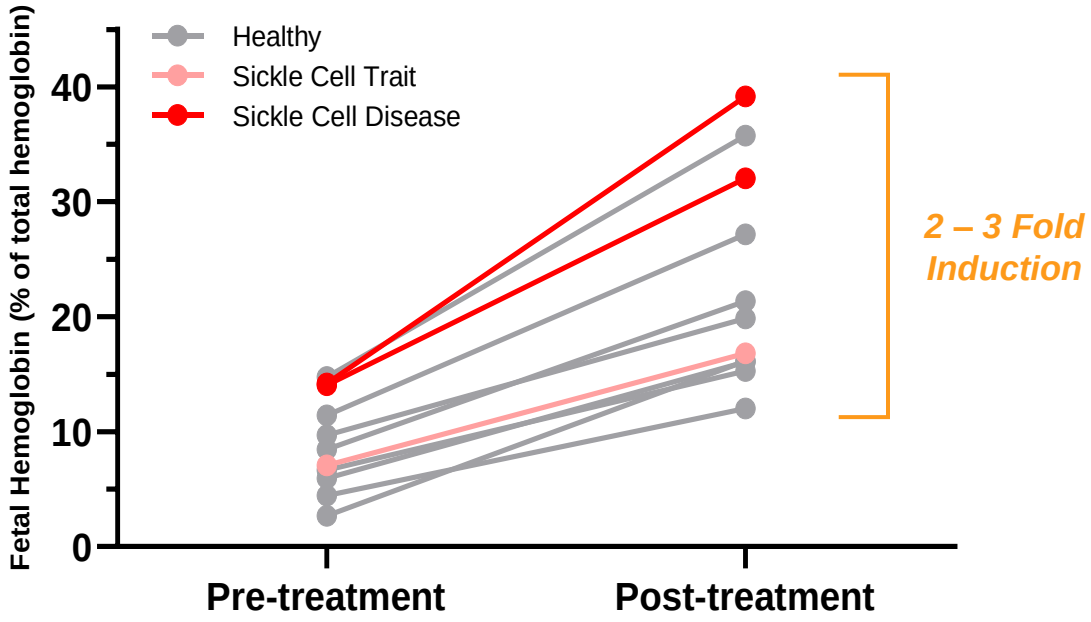


Consistent 2 – 3 fold induction and strong correlation between fetal hemoglobin mRNA and protein observed both *in vitro* and *in vivo*

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

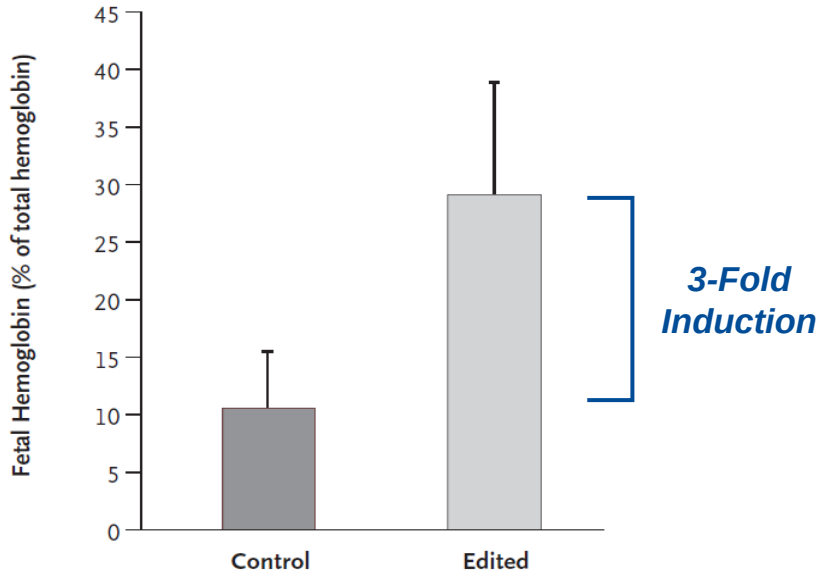
In Preclinical Studies, FTX-6058 Demonstrated HbF Induction Comparable to BCL11A Gene Editing (CTX001)

FTX-6058 HbF Induction in Healthy and SCD CD34+ Donors



- Observed an absolute 8 – 25% increase in HbF upon treatment with FTX-6058, which has the potential to address mortality risk and recurring events in SCD patients
- Demonstrated ability to achieve potentially “curative” HbF levels (e.g., 25 – 35% HbF) associated with asymptomatic disease

HbF Induction with BCL11A Gene Editing in Healthy CD34+ Donors[1]

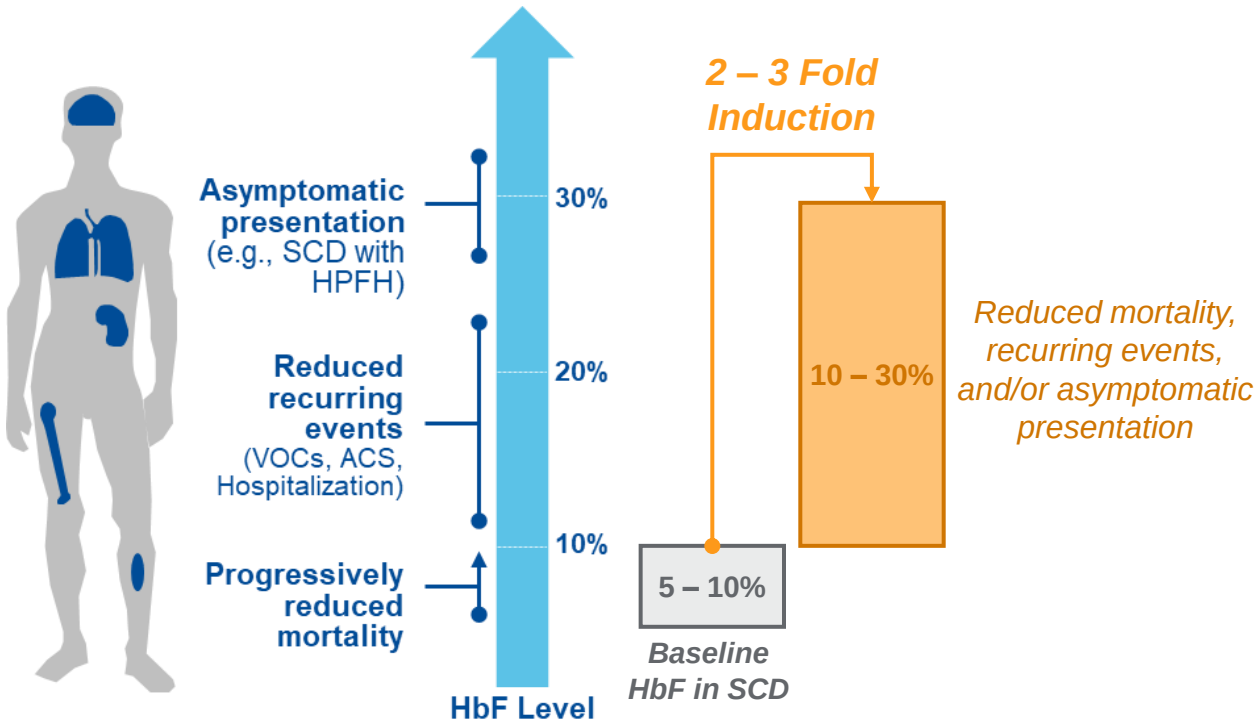


- CTX001, a gene editing therapy targeting BCL11A, achieved ~3-fold HbF induction in healthy donor CD34+ cells
- Robust preclinical HbF induction has translated to the clinic, achieving “curative” HbF levels and asymptomatic disease

[1]*Vertex / CRISPR Therapeutics Company Data and Frangoul, H. NEJM. 2020; Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.*

Small Molecule HbF Inducer has the Potential to be the Preferred SCD Treatment Option for Patients, Providers, and Payors

Small Molecule HbF Inducer has Potential to Provide Broad Clinical Benefits in SCD



Potential Future Therapy Preferences of Patients, Providers, and Payors

1 Potent, Oral HbF Inducer

- Addresses root cause of disease using proven mechanism to ameliorate anemia, VOCs, and other SCD symptoms
- HbF levels of 25 – 35% may provide a functional cure
- Potential for improved safety and tolerability over HU
- Convenient oral therapy and ability to distribute globally

2 Symptomatic Therapies

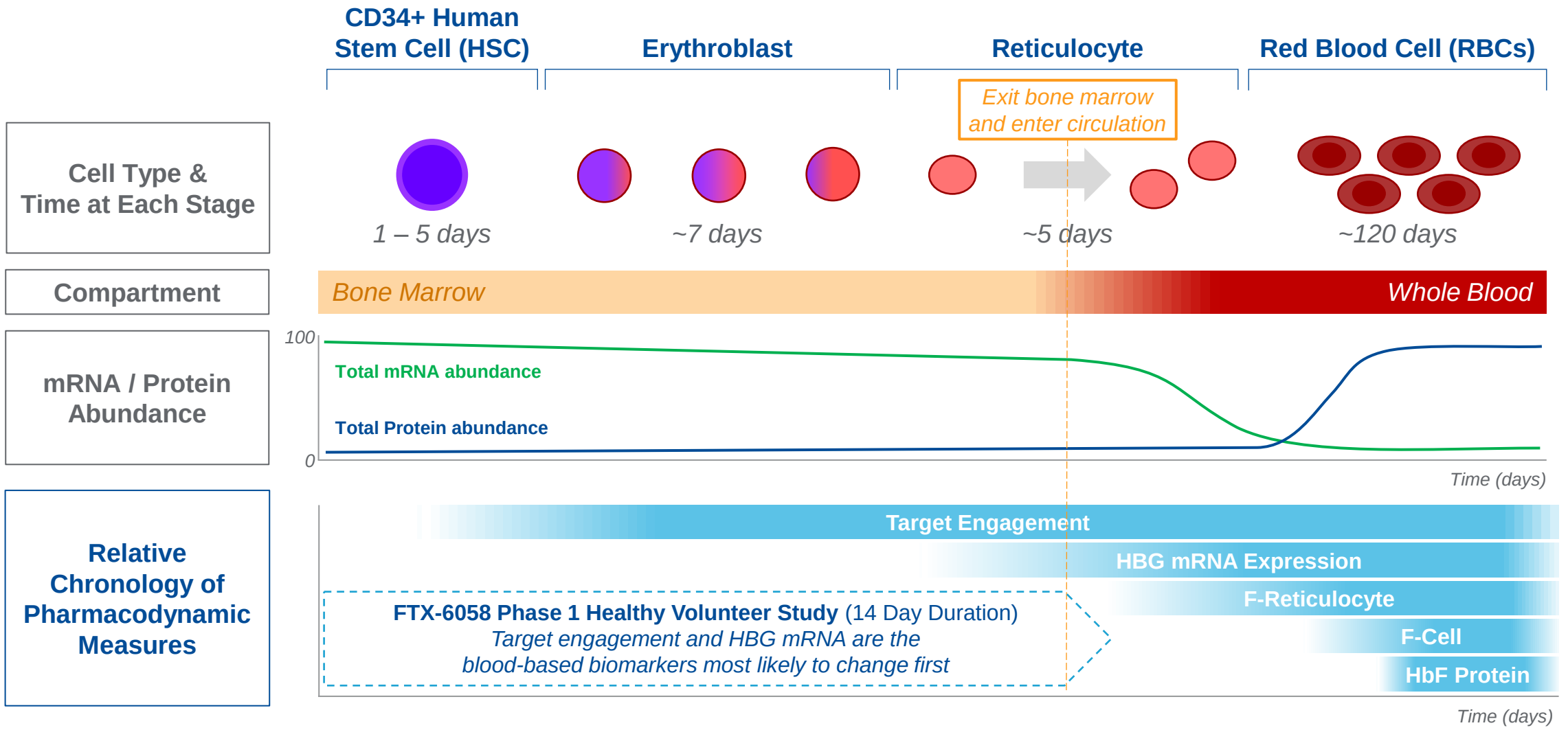
- Treat individual aspects of SCD (e.g. ↑ total Hb or ↓VOC)
- Potential for improved convenience (e.g., oral pill)
- Inability to readily access intravenous therapies

3 Gene Editing / Human Stem Cell Transplant

- Potential for functional cure by addressing root cause of disease, though highly invasive
- Myeloablation safety risks and unknown efficacy durability
- Likely significant barriers to access

HU: Hydroxyurea.

Erythropoiesis Time-course Influences mRNA and Protein Detection in Healthy Adults and Informed Biomarker Selection of 14-day Ph 1 Study



F-reticulocyte: HbF-containing reticulocyte; F-cell: HbF-containing RBC; Palis, J. Front Physiol. 2014; Mescher, AL. Junqueira's Basic Histology: Text and Atlas, 12th Edition, http://www.accessmedicine.com

Mid-year Update from Ongoing Phase 1 Healthy Volunteer Trial

Clinical Results

Results are from ongoing, blinded Phase 1 clinical trial

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FTX-6058 Phase 1 Healthy Volunteer Trial

Phase 1 Design and Endpoints

Primary
- Safety and tolerability

Secondary
- Pharmacokinetic measurements (bioavailability and half-life measurements)

Exploratory
- Target engagement
- HBG (fetal hemoglobin) mRNA
- F-reticulocytes (i.e., reticulocytes containing HbF protein)

Opportunistically assessing HBG mRNA and F-reticulocytes in whole blood after FTX-6058 treatment

PK/PD Modeling Predictions

SAD Cohorts	Dose (mg)	MAD Cohorts (QD, 14d)	Expected Target Engagement level	Expected PD effect
Cohort 1 ✓	2	Cohort 1 ✓		
Cohort 2 ✓	4			
	6	Cohort 2 ✓	TE80	
Cohort 3 ✓	10	Cohort 3 ✓	TE100	HbF EC50-EC80
Cohort 4 ✓	20	Cohort 4	TE100	HbF EC80-EC100
Cohort 5 ✓	30			
Cohort 6 ✓	40	*Additional SAD / MAD cohorts may be added*		
	60			
	90			

✓ *Completed cohorts*

- **Predicted human dose from PK/PD modeling is 4mg, and supports QD dosing**
- **The 6, 10, and 20mg doses are projected to achieve maximal target engagement and HbF induction**
- **Maximal target engagement maintains ~30% of H3K27me3 mark preclinically**

TE: Target Engagement; PD: Pharmacodynamic.

FTX-6058 was Generally Well-Tolerated in All SAD and MAD Cohorts Completed to Date

Summary of Adverse Events

SAD

	Placebo	FTX-6058					
Adverse Event	N = 12	**2mg** N = 3	**4mg** N = 3	**10mg** N = 5	**20mg** N = 5	**30mg** N = 5	**40mg** N = 5
Eosinophilia	1 (8%)	0	0	0	0	0	0
Leukopenia	0	0	0	0	1 (20%)	0	0

- **No SAEs reported to date and no discontinuation due to TEAE**
- **All treatment-emergent adverse events possibly related to FTX-6058 were Grade 1 or 2**
- **One Grade 4 TEAE: unrelated to FTX-6058**
  - Asymptomatic, incidental creatine phosphokinase (CPK) increase detected at safety follow-up visit (i.e., 7 – 10 days post-treatment) in the 10mg MAD cohort

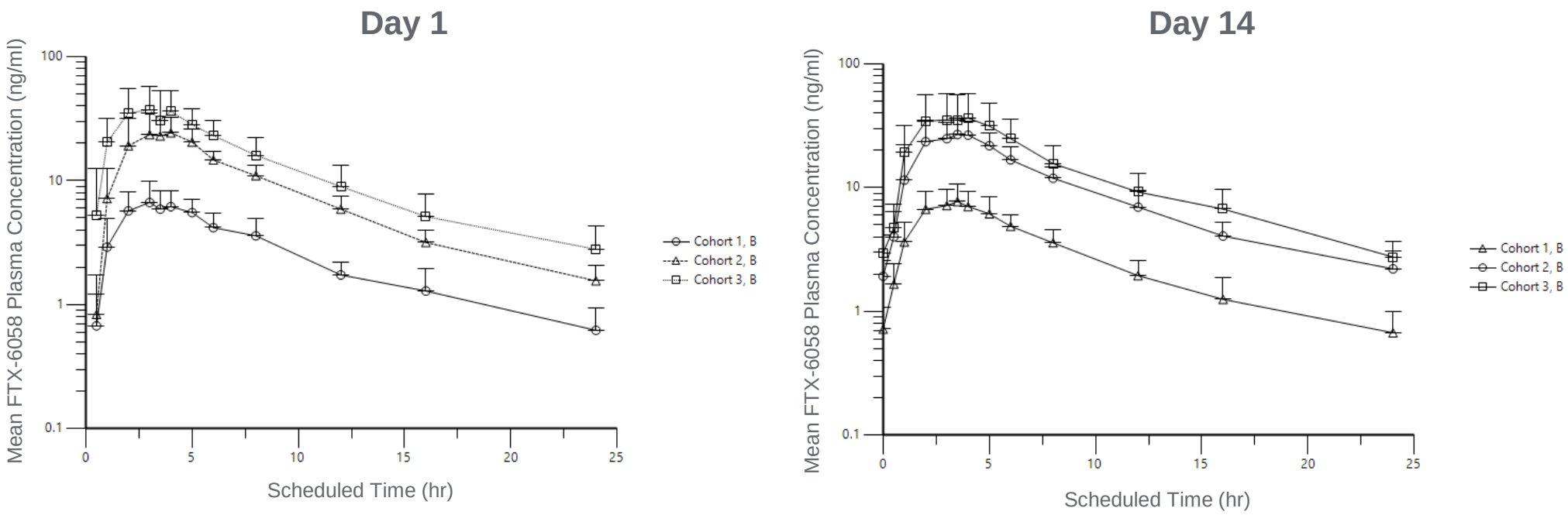
MAD

	Placebo	FTX-6058		
Adverse Event	N = 6	**2mg** N = 6	**6mg** N = 6	**10mg** N = 6
[a]Loose Stool	1 (17%)	0	0	0
Dry Mouth	0	1 (17%)	0	0
Abnormal Stool	0	0	0	1 (17%)
Neutrophil Count Decrease	0	0	0	1 (17%)
Headache	0	0	0	1 (17%)

[a] *Did not meet the WHO definition of diarrhea per protocol*

FTX-6058 PK Profiles have Demonstrated Dose Proportionality in both SAD and MAD Cohorts

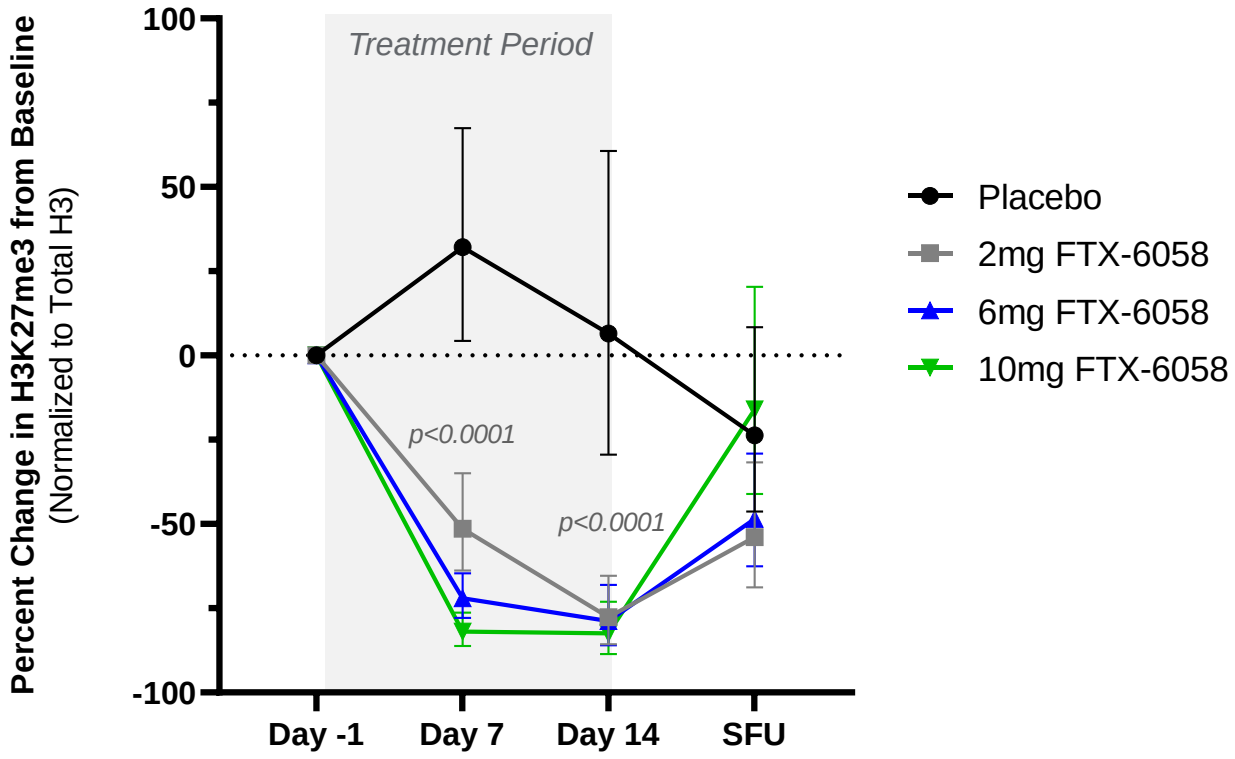
Plasma FTX-6058 Pharmacokinetics from MAD Cohorts



- **Dose-proportional pharmacokinetics demonstrated across both SAD and MAD cohorts**
- **Mean half-life was approximately 6-7 hours in the MAD cohorts, and supports QD dosing**

Maximal Target Engagement Achieved by Day 7 in 6mg and 10mg MAD Cohorts

Mean Reduction (%) of H3K27me3 Levels



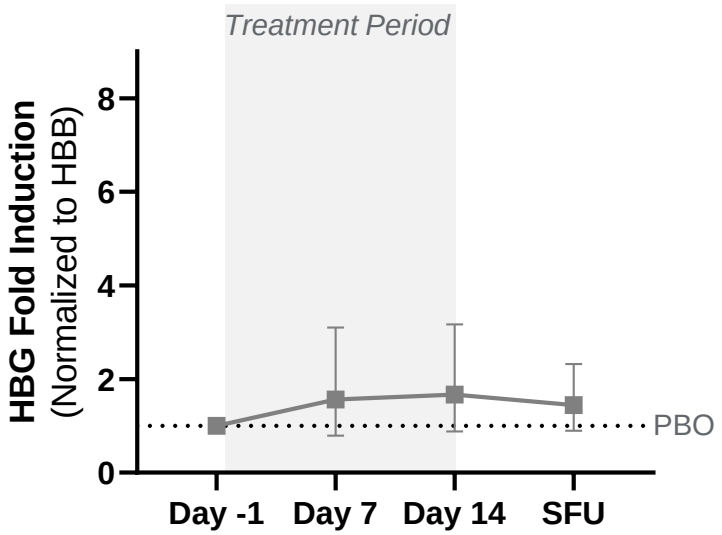
- Demonstrated proof-of-mechanism as evidenced by inhibition of H3K27me3 levels
- Maximal target engagement observed in doses as low as 2mg
- Retain 20 – 30% of H3K27me3 levels at maximal target engagement, consistent with preclinical data
- Safety follow-up (SFU) samples were collected 7 – 10 days post 14-day treatment period

Data presented as estimate of mean % change based on geometric LS mean with 95% confidence interval; mixed-effects model for repeated measures (MMRM) analysis performed for Day 7 and Day 14 data; analysis of covariance (ANCOVA) utilized for SFU data.

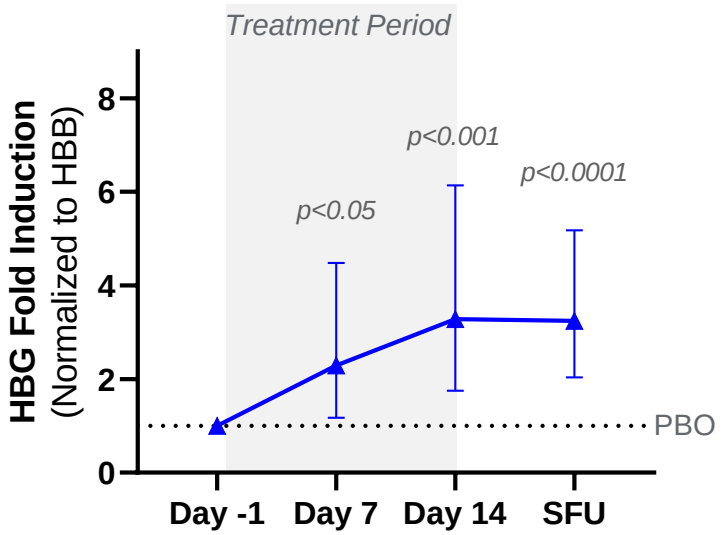
FTX-6058 Achieved Dose-Proportional HBG mRNA Induction, Up to Mean 4.5-fold in the 10mg Cohort

HBG mRNA Induction is both Time- and Dose-dependent in MAD Cohorts

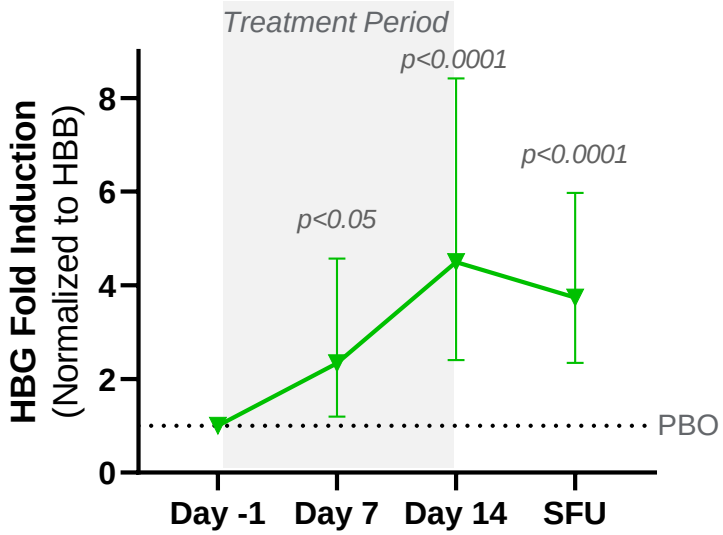
2mg (versus placebo)



6mg (versus placebo)



10mg (versus placebo)



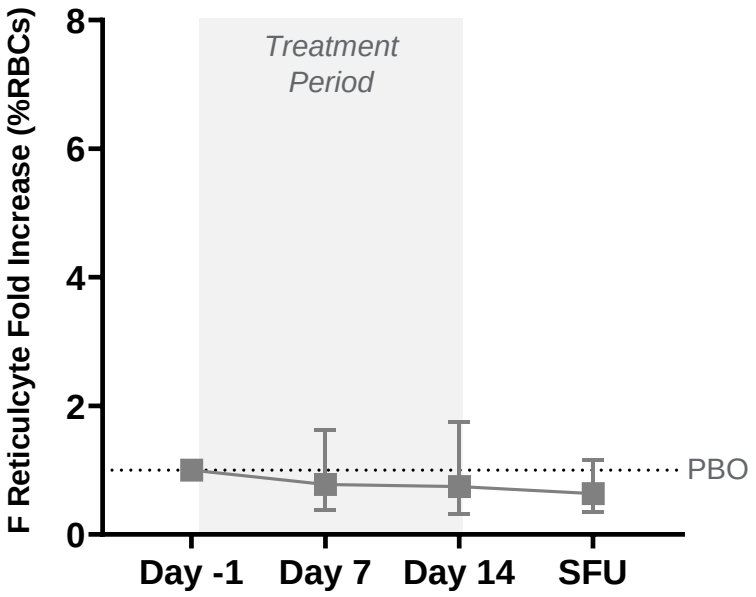
- **Observed trends indicating HBG induction in doses as low as 2mg, though not statistically significant**
- **At Day 14, 6mg and 10mg cohorts demonstrated 2 – 8 fold HBG mRNA induction**
- **Persistent and durable HBG induction observed 7 – 10 days after 6mg and 10mg treatment (i.e., SFU), which is consistent with preclinical Townes mouse data**

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.

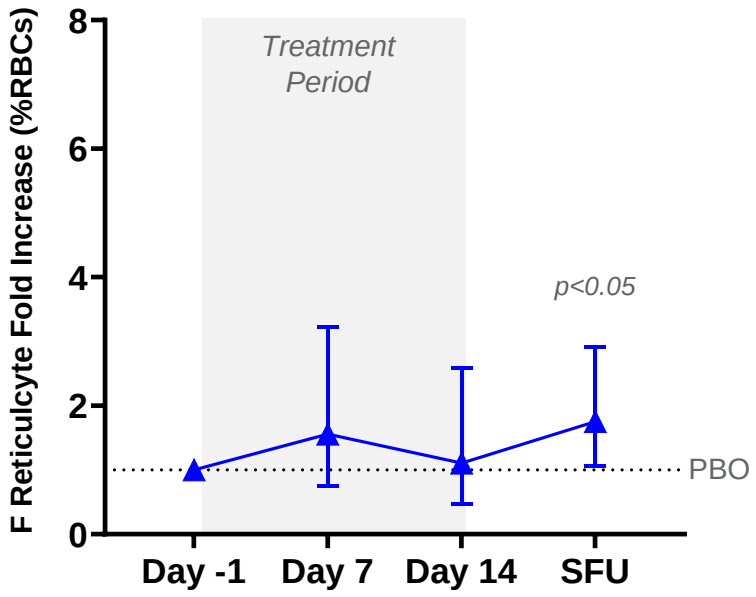
Mean 4.2-Fold Increase in HbF-containing Reticulocytes (F-Reticulocytes) Indicates HBG mRNA is Translating to HbF Protein in 10mg MAD Cohort

HBG mRNA Induction with FTX-6058 Translates to F-Reticulocyte Increases

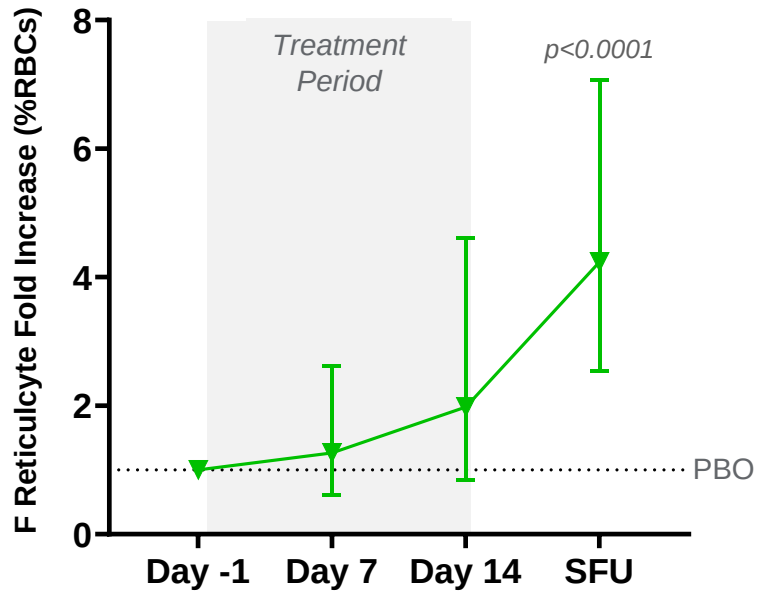
2mg (versus placebo)



6mg (versus placebo)



10mg (versus placebo)

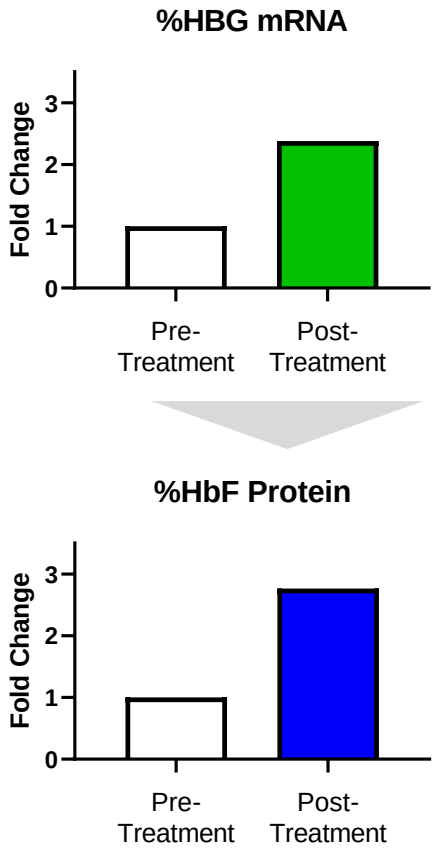


- Observed a **2.5 – 7 fold increase in F-reticulocytes** at the safety follow-up (SFU) visit in the 10mg dose cohort, indicating that persistent HBG mRNA induction is translating to HbF production in newly formed reticulocytes
- Further increases in F-reticulocytes, F-cells, and HbF protein are projected with longer FTX-6058 treatment duration

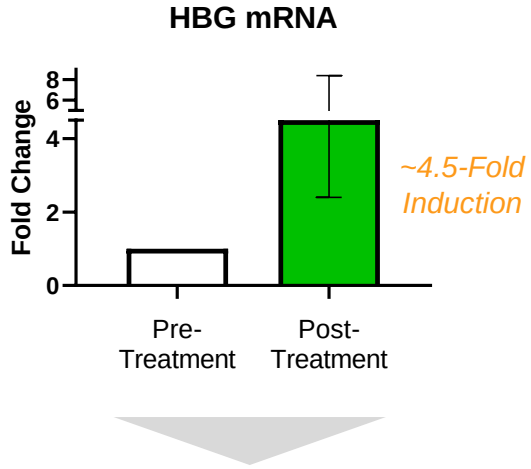
Safety follow-up (SFU) samples were collected 7 – 10 days post 14-day treatment period; PBO: placebo; Data presented as geometric LS mean ratio (to placebo) with 95% confidence interval; mixed-effects model for repeated measures (MMRM) analysis performed for Day 7 and Day 14; analysis of covariance (ANCOVA)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

FTX-6058 Interim Clinical Results Meet the Induction Thresholds Predicted to Provide Meaningful Therapeutic Benefits to Individuals with SCD

Strong Correlation Between mRNA and Protein in Healthy CD34+ Cells

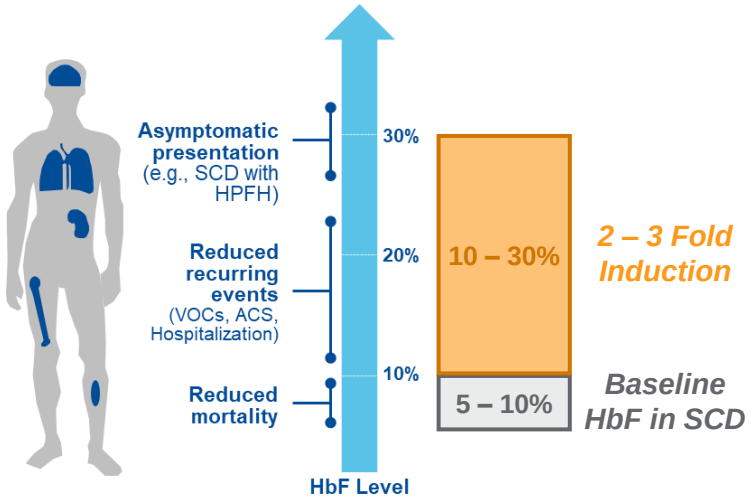


Clinical Data is Predictive of Meaningful HbF Induction



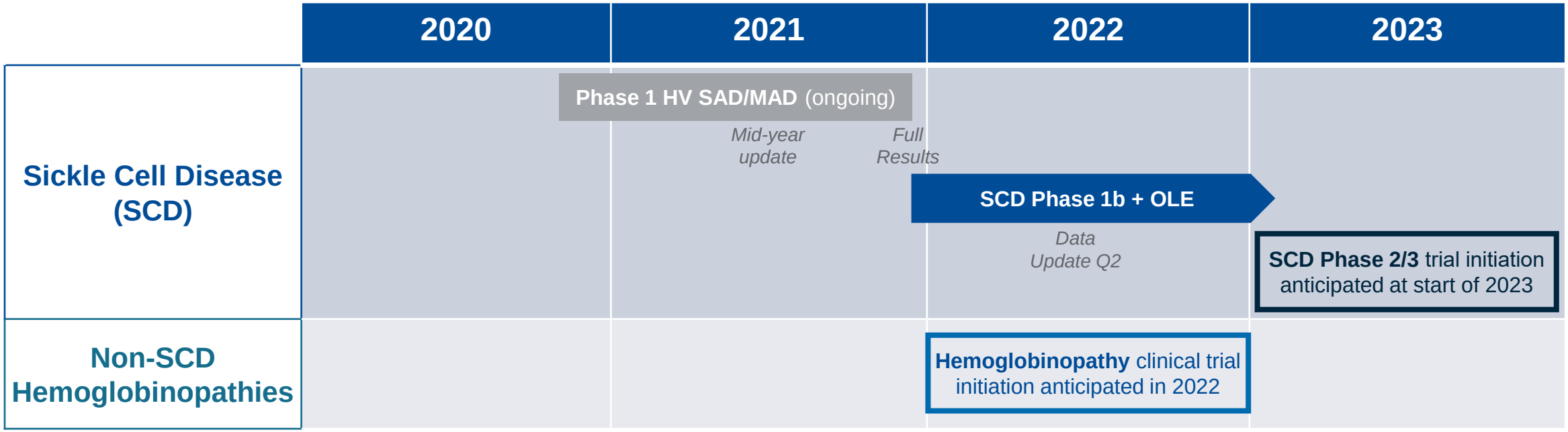
Anticipate similar HbF protein induction to translate in the clinic

2 – 3 Fold HbF Induction Results in Meaningful Clinical Benefits in SCD



Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.

FTX-6058 Clinical Development Plan



- **Expected to report full results of ongoing Phase 1 HV study in Q4 2021**
- **Anticipate initiating a Phase 1b SCD clinical trial in Q4 2021**
  - An open-label, multiple dose trial starting at 6mg QD; treatment period up to 3 months
  - Phase 1b trial will aim to demonstrate, safety, tolerability, PK, and PD effects (HbF protein induction) in SCD and will inform the Phase 2/3 SCD trial
- **Clinical results support initiation of a clinical trial in non-SCD hemoglobinopathies (e.g., β-Thalassemia)**
  - Anticipate submitting IND by year-end

FTX-6058 Phase 1 Healthy Volunteer Interim Results Demonstrated Proof of Mechanism and Biology as well as Predictable Pharmacokinetics

- **FTX-6058 treatment in MAD cohorts resulted in dose-proportional increases:**
  - Mean 4.5-fold induction of HBG mRNA in 10mg cohort
  - Mean 4.2-fold increase in F-reticulocytes, indicating HbF production in 10mg cohort
- **Maximal target engagement achieved by Day 7 in 6mg and 10mg MAD cohorts**
- **Predictable and dose-proportional pharmacokinetic profiles demonstrated across SAD and MAD doses supportive of oral, QD dosing**
- **FTX-6058 generally well-tolerated in all SAD and MAD cohorts completed to date**

Phase 1b SCD clinical trial to be initiated Q4 2021

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Q&A