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

December 6th, 2021

Fulcrum Therapeutics




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 statements regarding the development status of the Company's product candidates, the potential advantages and therapeutic potential of the Company's product candidates, initiation and enrollment of clinical trials and availability of clinical trial data, the timing of planned clinical trials and the Company's ability to submit INDs and planned meetings with regulatory agencies. All statements, other than statements of historical facts, contained in presentation, including statements regarding the Company'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 the Company's product candidates; replicate in clinical trials positive results found in preclinical studies and/or earlier-stage clinical trials of losmapimod and its other product candidates; advance the development of its product candidates under the timelines it anticipates in current and future clinical trials; 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 the Company'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 the Company's most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this presentation represent the Company's views as of the date hereof and should not be relied upon as representing the Company's views as of any date subsequent to the date hereof. The Company anticipates that subsequent events and developments will cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so.

Agenda

- **Introduction**
  Bryan Stuart
- **Overview of Fetal Hemoglobin Repression**
  Gerd Blobel, MD, PhD
- **FTX-6058 Preclinical Pharmacology and Mechanistic Insights**
  Judith Dunn, PhD
- **FTX-6058 Phase 1 Healthy Volunteer Update**
  Christopher Morabito, MD
- **Q&A Session**

Introduction

Bryan Stuart

President and Chief Executive Officer

Fulcrum Therapeutics




Overview of Fetal Hemoglobin Repression

Gerd Blobel, MD, PhD

Frank E. Weise III Endowed Chair in Pediatric Hematology at Children's Hospital of Philadelphia

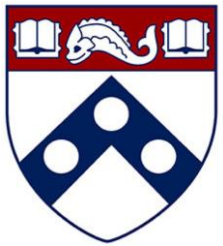
Fulcrum Therapeutics

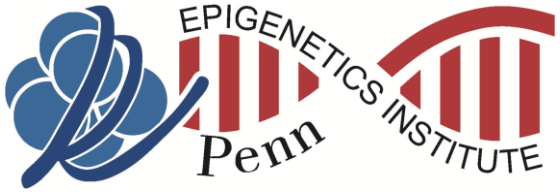



Pursuing HbF Elevation as a Therapeutic Strategy

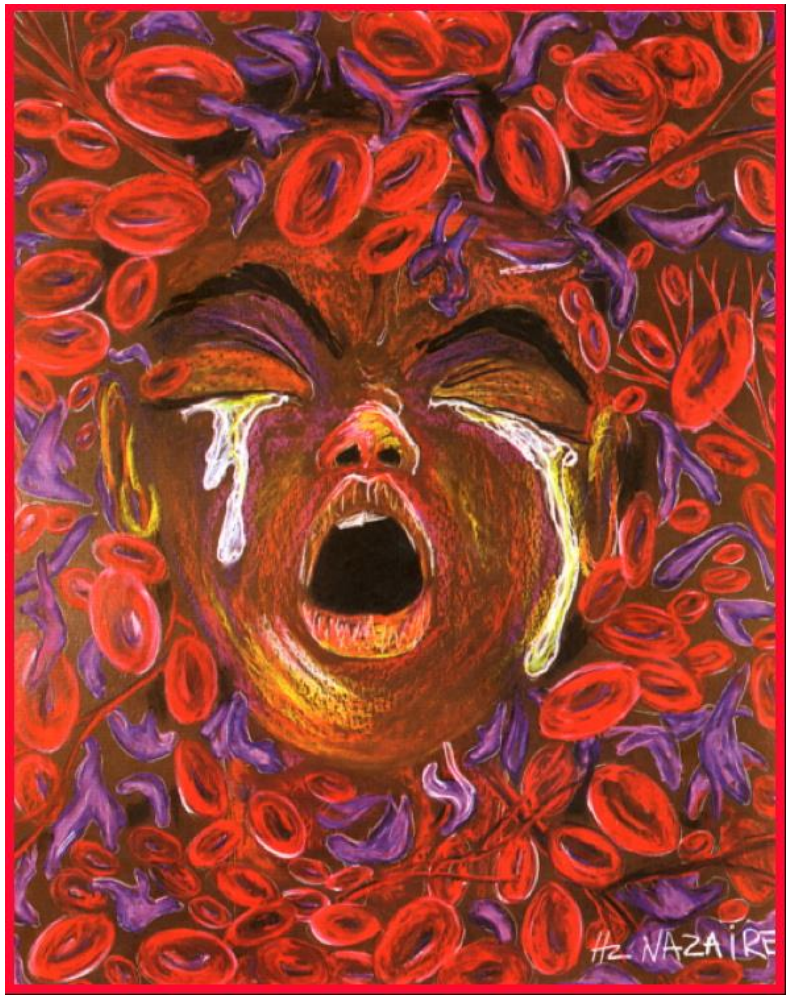
Fulcrum Therapeutics

Gerd Blobel, M.D., Ph.D.
Frank E. Weise III Professor of Pediatrics
The Children's Hospital of Philadelphia
Co-director U-Penn Epigenetics Institute
Perelman School of Medicine
University of Pennsylvania

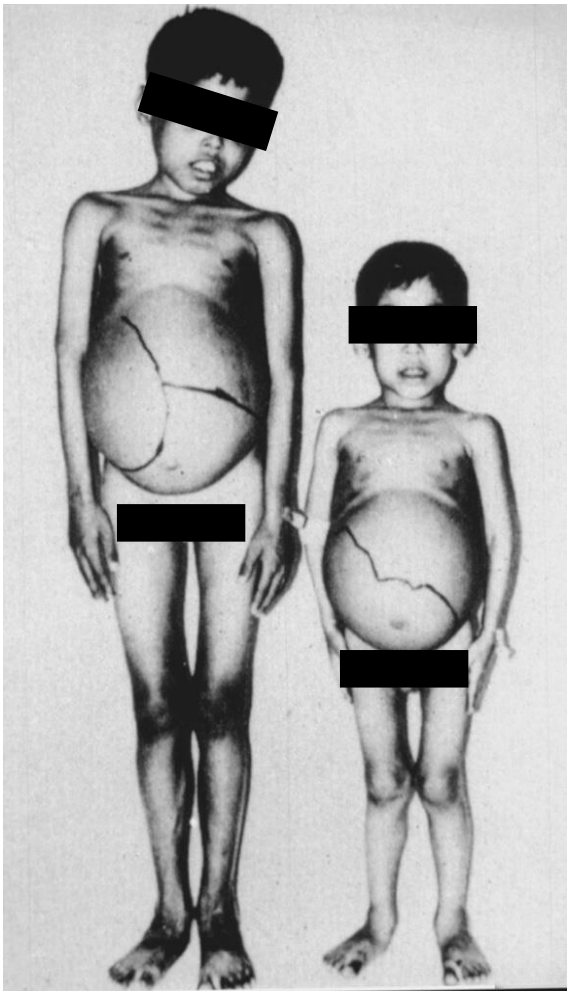




Hemoglobinopathies:
Diseases of multi-system complications



Sickle cell disease



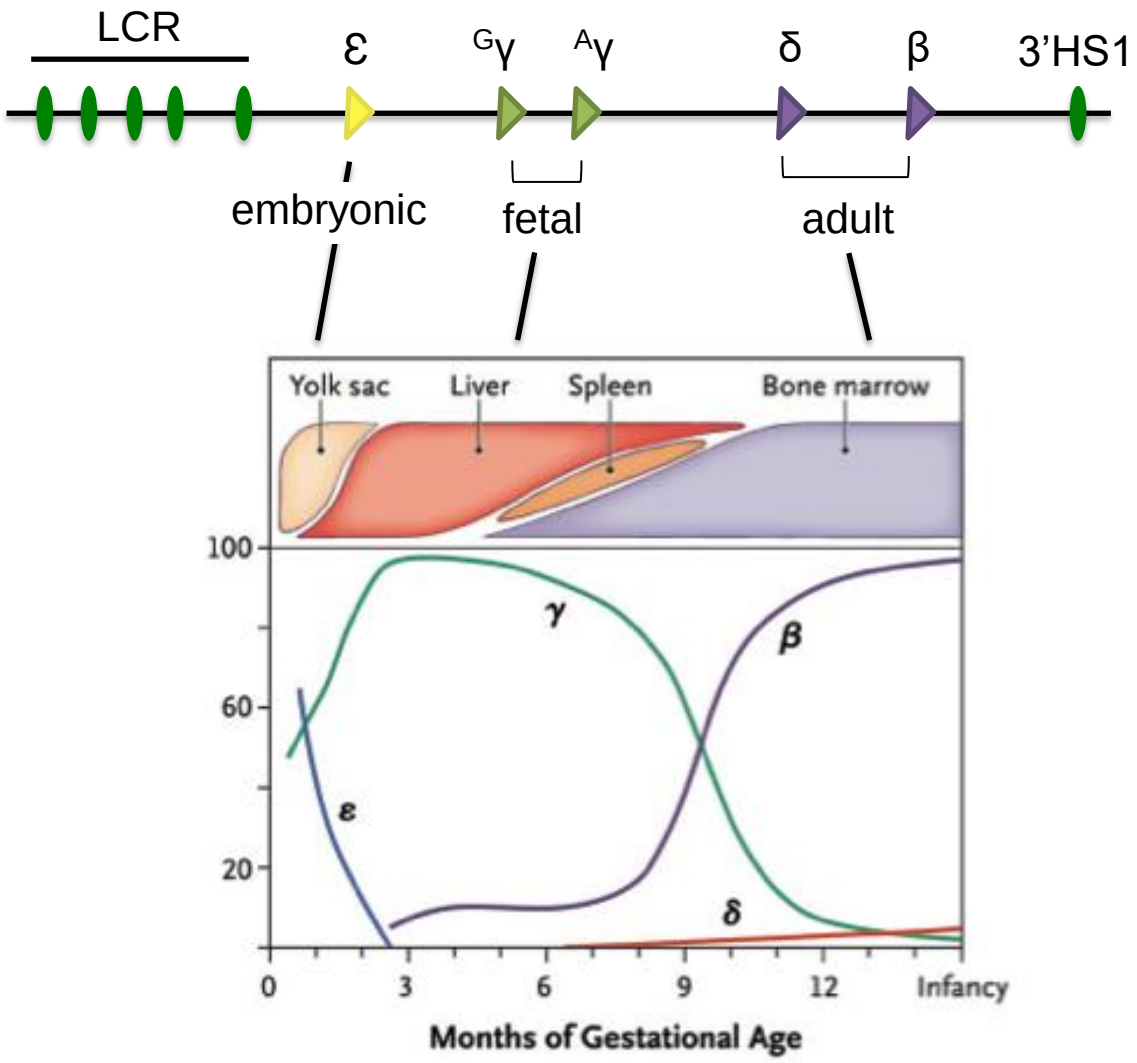
Thalassemia intermedia

Red blood cells contain hemoglobin

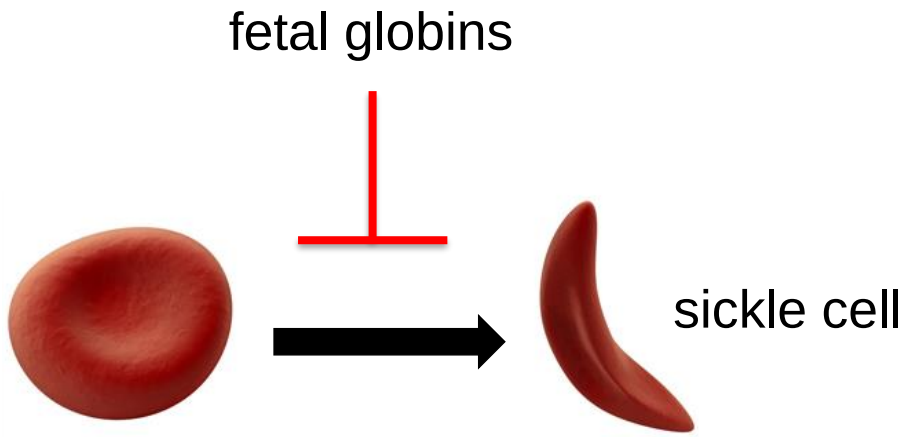
erythrocytes

hemoglobin

Human hemoglobin switching

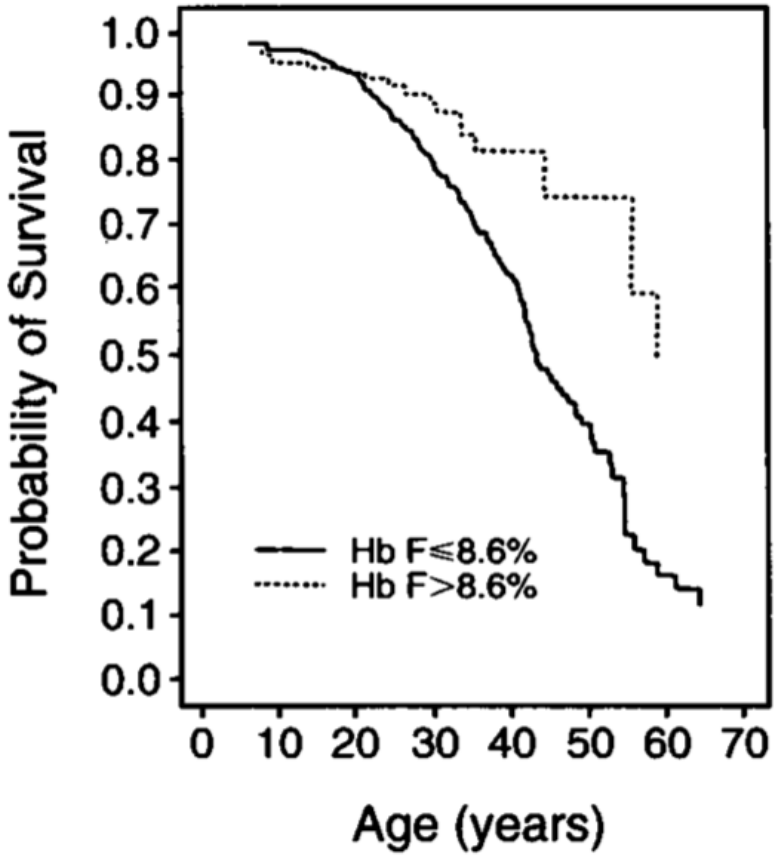


Elevated levels of fetal hemoglobin (HbF) improve the clinical course of patients with sickle cell disease



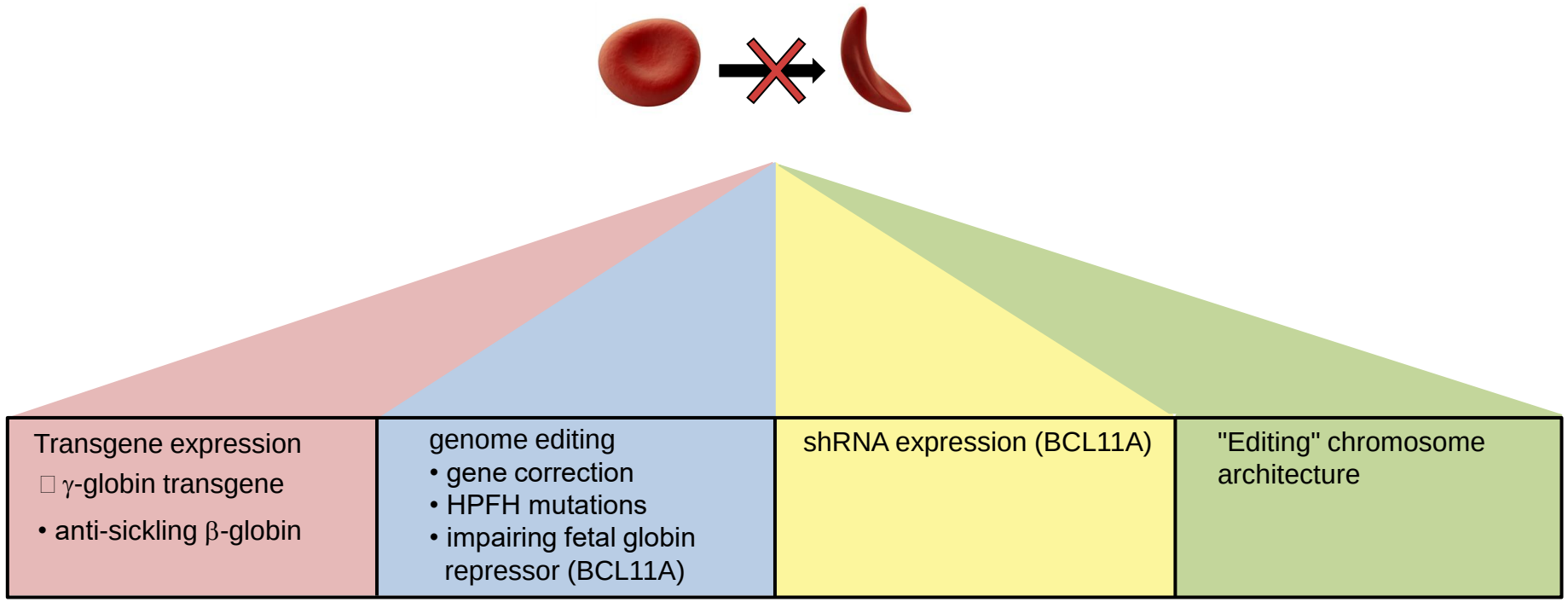
hereditary persistence of fetal hemoglobin (HPFH)

Elevated levels of fetal hemoglobin (HbF) improve the clinical course of patients with sickle cell disease



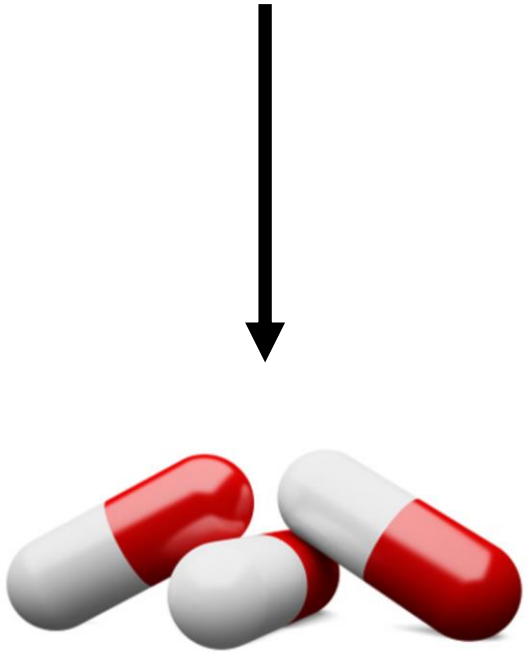
Platt, O. S. et al. N. Engl. J. Med. 1994

Therapeutic approaches for sickle cell disease (a brief scenic tour)



All of these approaches require autologous BM transplants

Goal: Identify HbF regulators that could be targeted with small molecules



What controls the fetal-to-adult switch?

Insights from GWAS

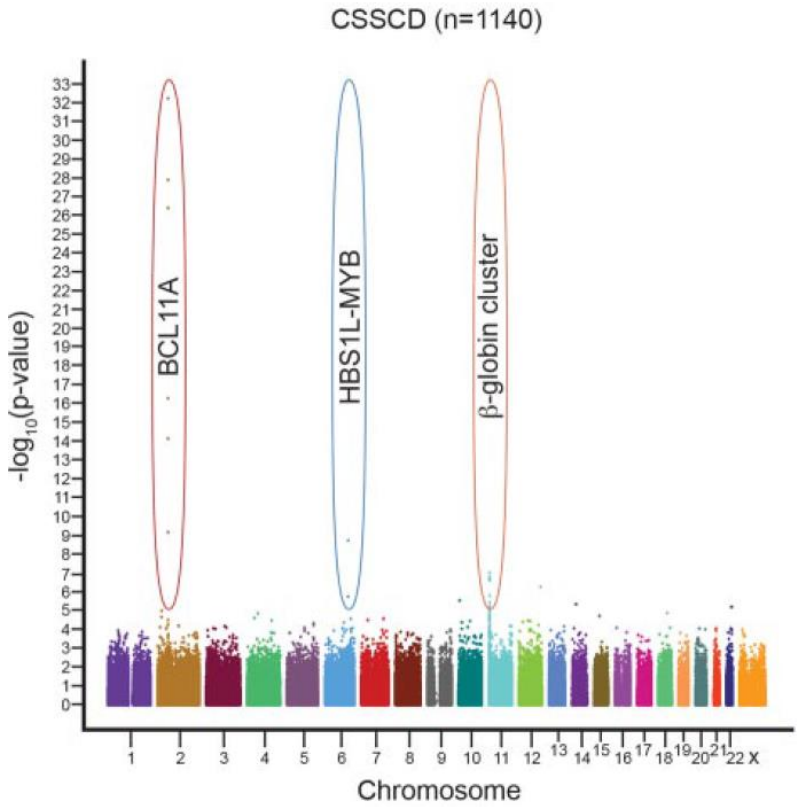
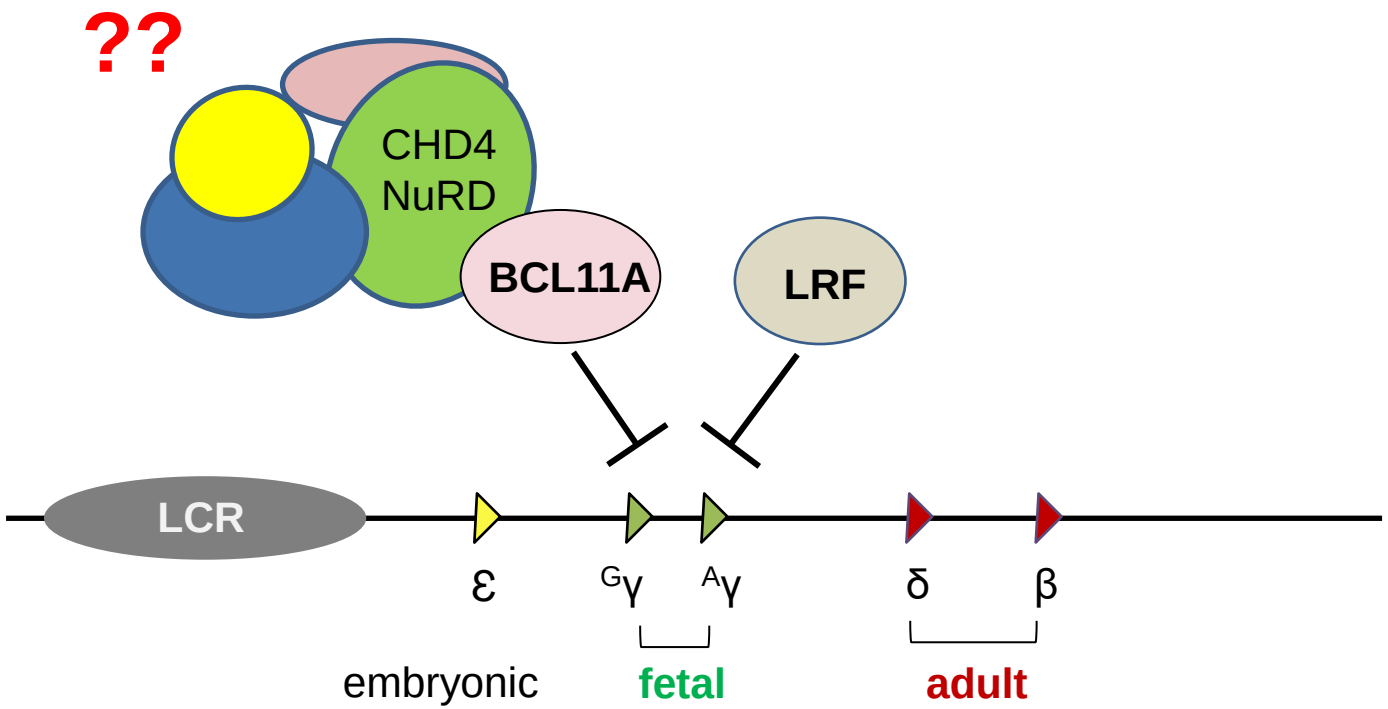


Figure courtesy of Guillaume Lettre

What controls the fetal-to-adult switch?

(More regulators? Novel therapeutic opportunities?)

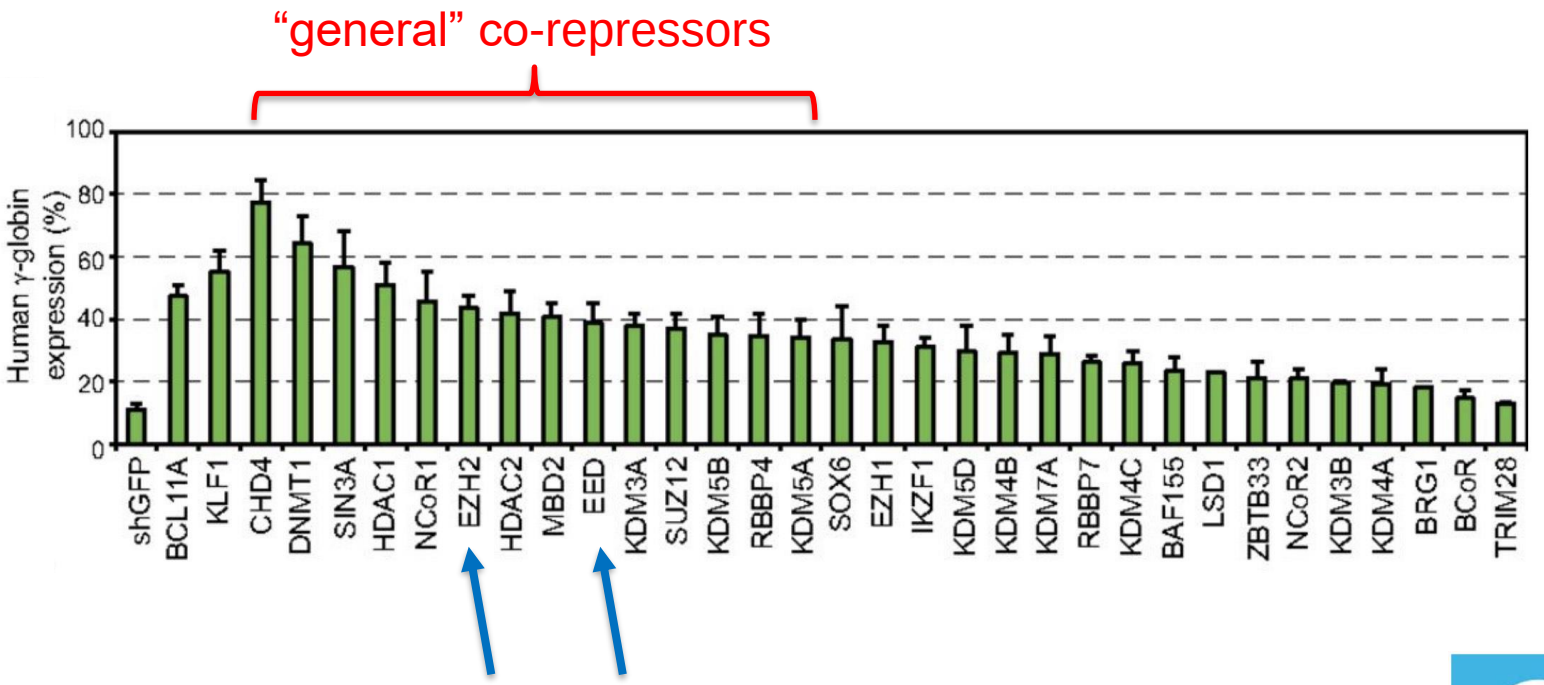


Hemoglobin switching involves widely expressed co-regulators

Corepressor-dependent silencing of fetal hemoglobin expression by BCL11A

Jian Xu[a], Daniel E. Bauer[a], Marc A. Kerenyi[a], Thuy D. Vo[a], Serena Hou[a], Yu-Jung Hsu[a], Huilan Yao[b], Jennifer J. Trowbridge[a], Gail Mandel[b], and Stuart H. Orkin[a,c,1]

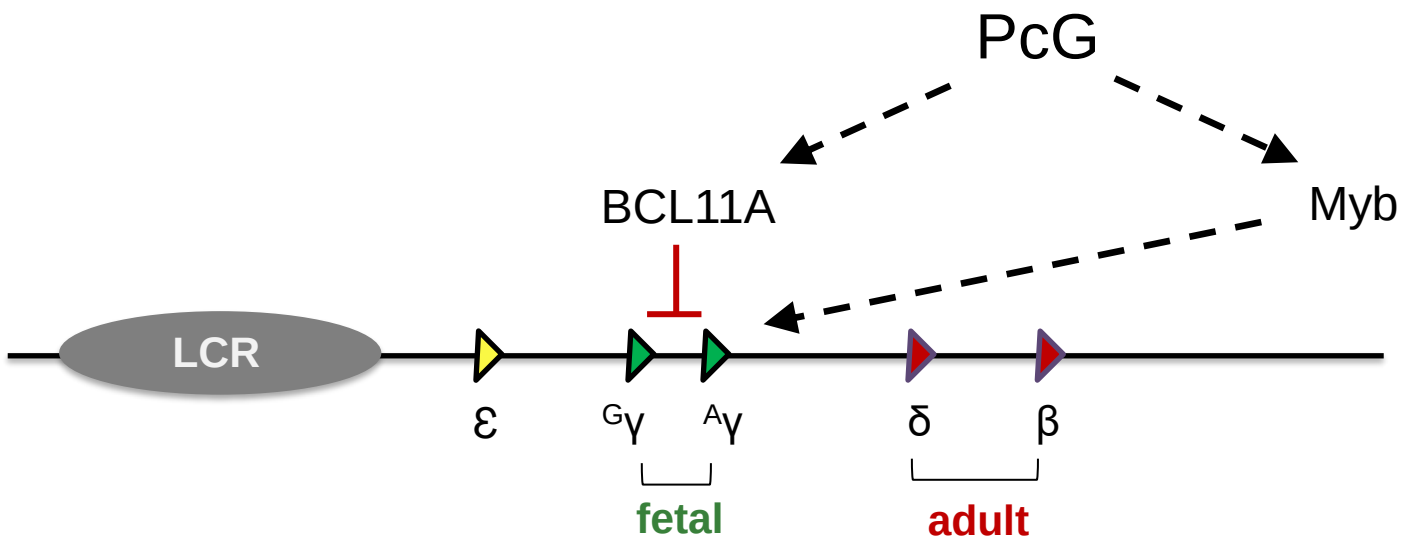
PNAS 2013



Hemoglobin switching involves widely expressed co-regulators

Our screens also identified several PRC2 components as fetal hemoglobin regulators, providing independent validation of PcG as targets.

Polycomb influences BCL11A and Myb levels



FTX-6058 Preclinical Pharmacology and Mechanistic Insights

Judith Dunn, PhD

President, Research & Development

Fulcrum Therapeutics




Sickle Cell Disease (SCD) is Caused by a Mutation in the β-globin Gene Resulting in Sickled Red Blood Cells, VOCs, and Anemia

THE DISEASE

Genetic disorder of red blood cells (RBC) caused by mutation in Hemoglobin-Beta (HBB) gene

RBC sickling

PATIENT EXPERIENCE

- Vaso-occlusive crises (VOCs)
- Anemia
- Other complications, including stroke and organ damage

morbidity and mortality

TREATMENT OPTIONS

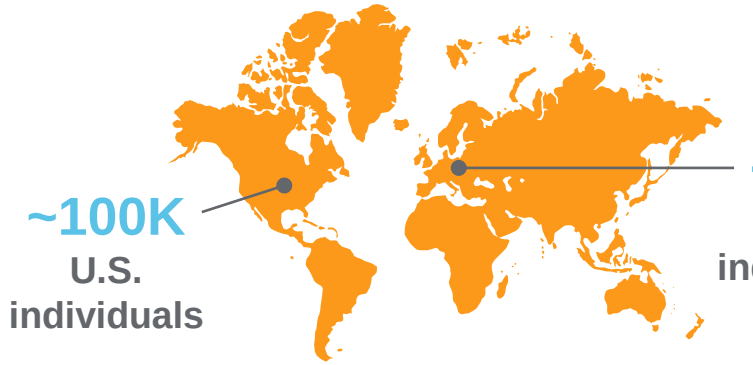
Short of SCT, current therapies are unable to address broad SCD symptomatology

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

only addressing subsets

GLOBAL IMPACT

Sickle cell disease is prevalent globally



Millions more worldwide

SCT: Stem Cell Transplant; CDC; WHO; UpToDate.

Existing Therapeutic Agents Do Not Effectively Address the Unmet Need in SCD, and Underscores the Need for Novel Therapies

Hydroxyurea

Current Standard of Care

- \+ Potential to ameliorate broader SCD disease pathology
- − Significant non-responder population and waning efficacy over time
- − Potential safety risks (i.e., myelosuppression) and tolerability issues

HbS Polymerization Inhibitors

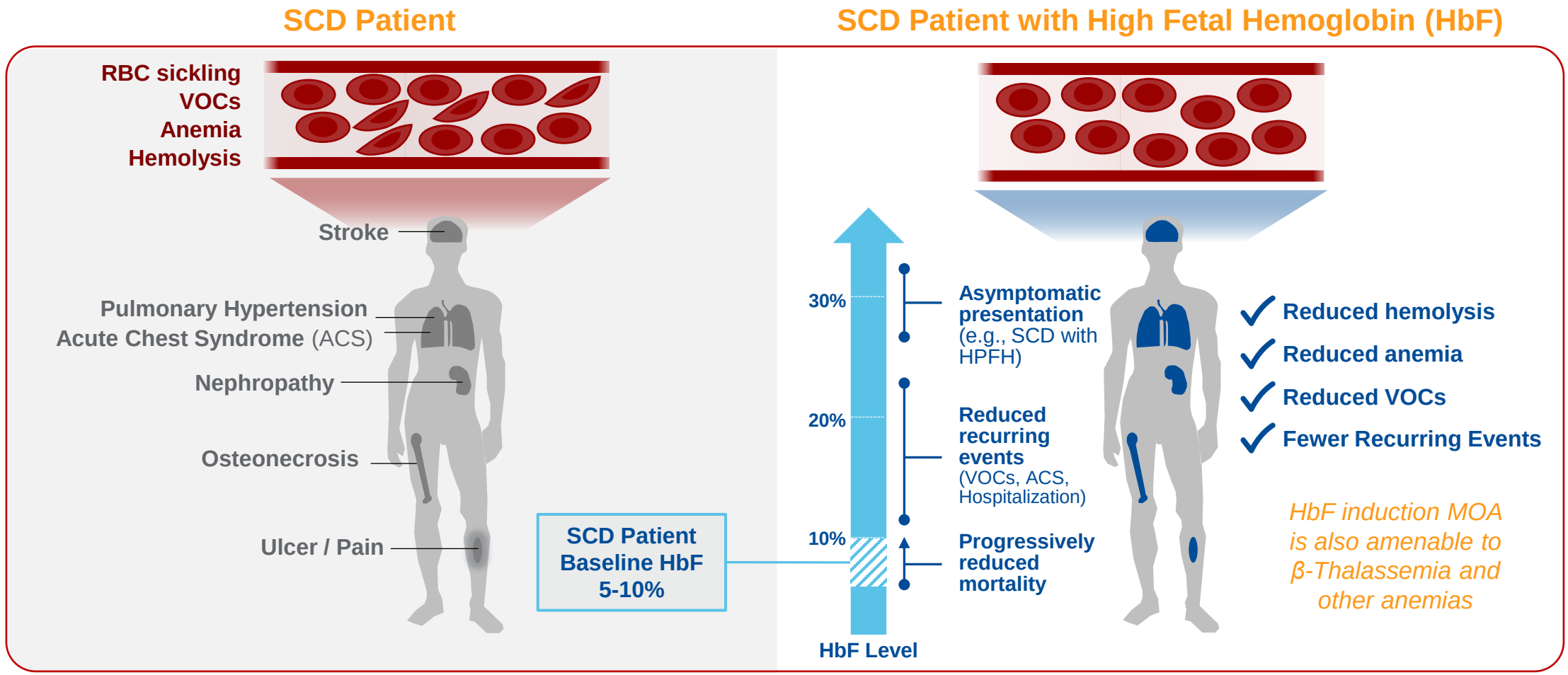
Increasing Total Hemoglobin

- \+ Addresses anemia (i.e., low total hemoglobin) by increasing levels of sickled hemoglobin (HbS)
- − Increasing HbS has not translated to clinical outcomes, such as VOCs
- − Approach does not address broad SCD disease pathology

P-Selectin Inhibitors

- \+ Demonstrated ability to reduce the number of VOCs
- − Approach does not address broad SCD disease pathology
- − IV administration impacts patient convenience

Increasing Fetal Hemoglobin (HbF) is the Only Mechanism Shown to Broadly Improve Outcomes in SCD



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

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

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

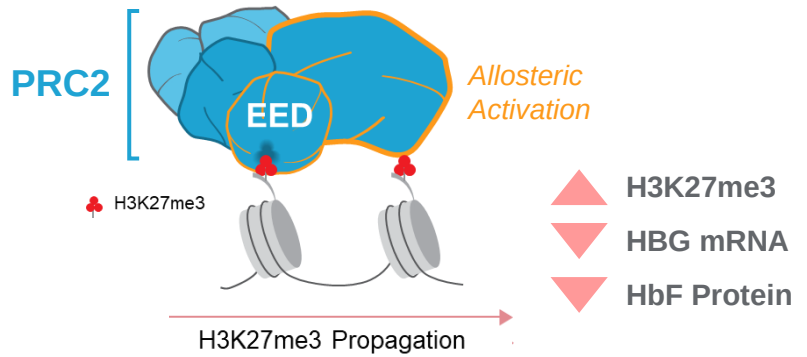
CRISPR + Compound Screening Engine
Experimentally screened candidate targets

Computational Data Mining
Computationally mined candidate targets

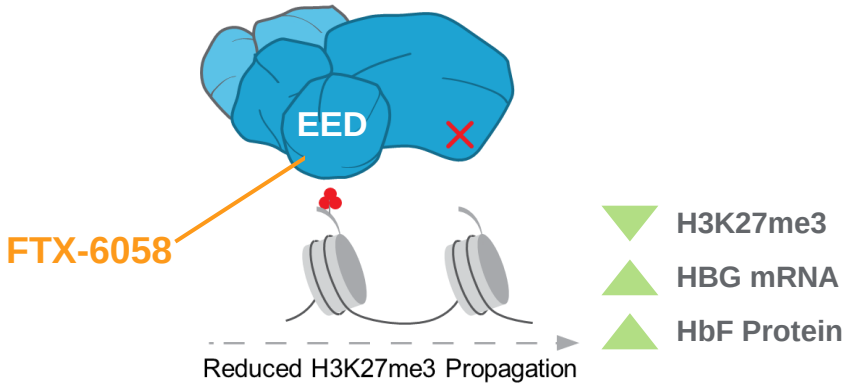
Identified Targets that Regulate HbF

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

EED is a Component of Polycomb Repressor Complex 2 (PRC2)



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



FTX-6058

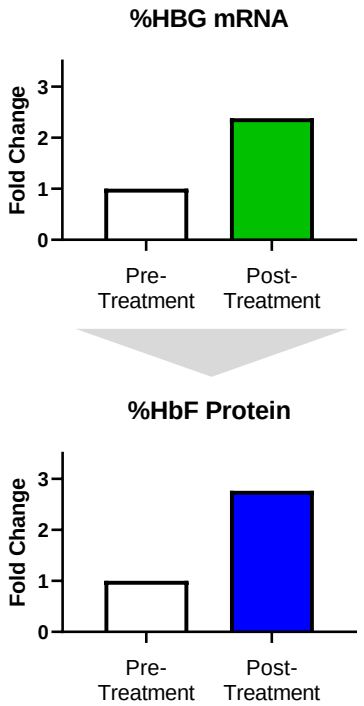
- **Highly Selective**
- **Clean Off-target Profile**
- **Composition of Matter Patent Expires 2040**

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

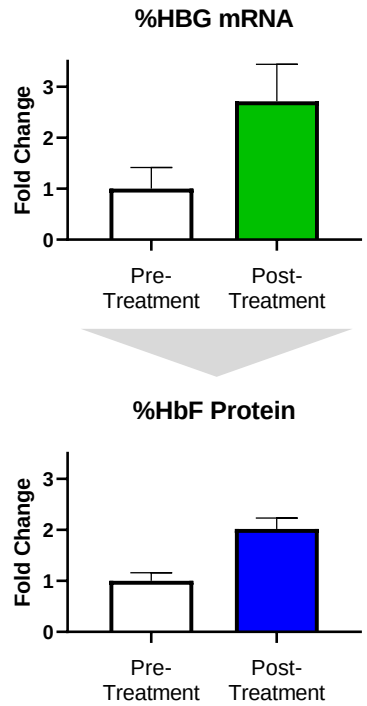
Extensive Preclinical Validation

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

Healthy CD34+ Cells



SCD Townes Mouse

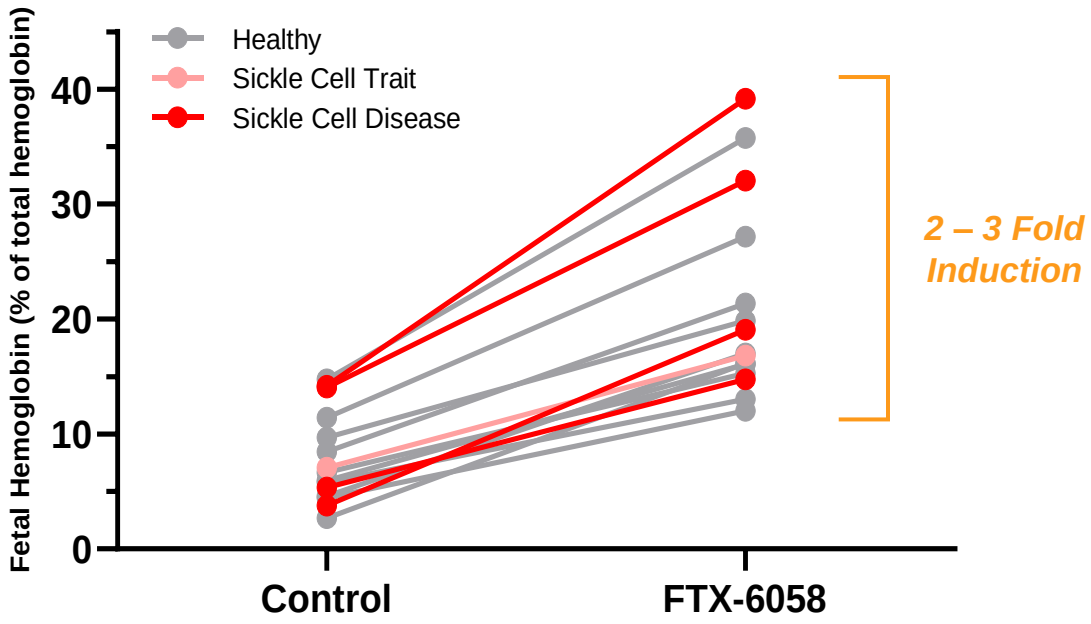


Consistent 2 – 3 fold induction and strong correlation between fetal hemoglobin mRNA and protein observed both *in vitro* and *in vivo*

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

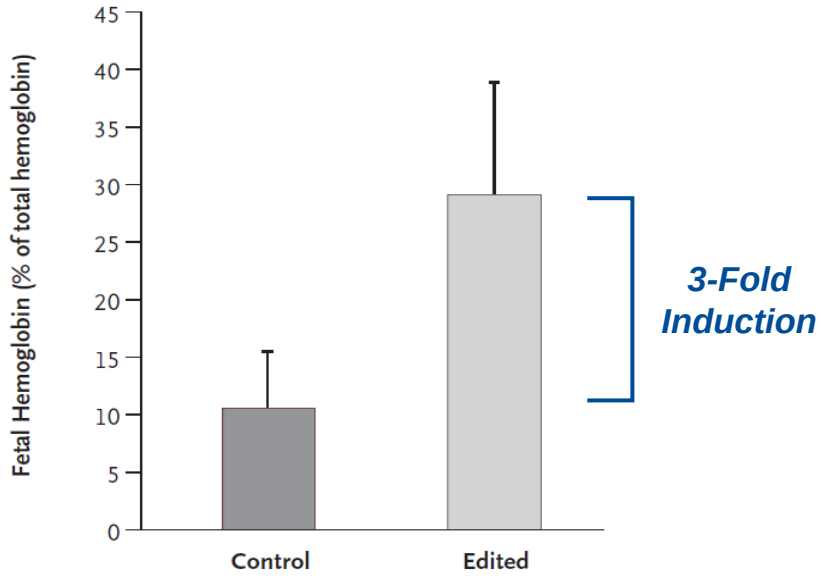
In Preclinical Studies, FTX-6058 Demonstrated HbF Induction Comparable to BCL11A Gene Editing

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



- FTX-6058 achieved an absolute 8 – 25% increase in HbF, which has the potential to broadly address SCD symptomatology
- Demonstrated ability to achieve potentially "curative" HbF levels (e.g., 25 – 35% HbF) associated with asymptomatic disease

HbF Induction with BCL11A Gene Editing (CTX001) 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.*

HbF Fold Induction from CD34+ Cell Assay is Highly Translatable to the Clinic, with Initial HbF Induction Observed After ~1 Month of Treatment

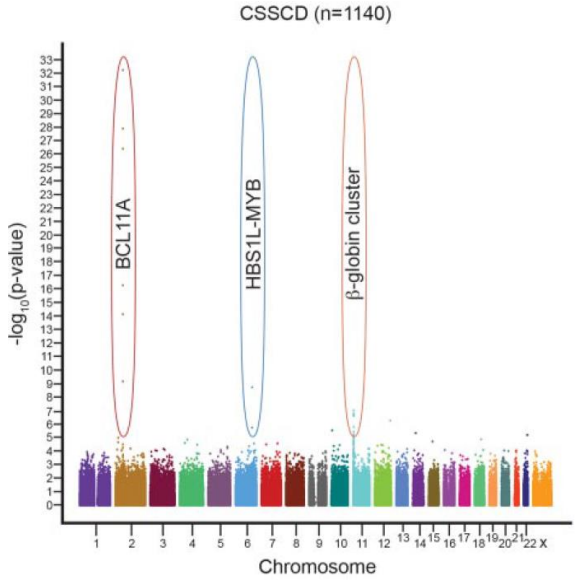
Mechanism / Asset	BCL11A KO	DNMT1i	HU	PDE9i	FTX-6058
Preclinical HbF Fold Induction[1]	3-fold	1.5 – 2 fold	1.1 – 1.2 fold	No Change	**2 – 3 fold**
SCD Clinical HbF Fold Induction[2]	~10-fold[3]	2 – 2.5 fold[4]	~1.7-fold[5]	<1.1 fold[6]	**TBD** *(Phase 1b)*
Time to Maximal HbF Induction	~5 months	>2 months[7]	Up to 6 months	4 – 6 months	**~3 months** *(projection)*

Therapeutic goal is to induce HbF 2 – 3 fold over baseline levels

[1] Fulcrum generated data in erythroid cells derived from healthy CD34+ cells; [2] Calculated as fold change over baseline %HbF (as a % of total hemoglobin) [3] CRISPR Therapeutics EHA 2021 virtual congress (SCD); [4] Molokie, R. PLoS Med. 2017; utilizing cohort 5 data (0.16 mg/kg data); [5] Data from the Multicenter Study of Hydroxyurea (MSH); Steinberg, MH. Blood.1997; [6] Data from IMR-687 monotherapy in parent study provided in Imara 2021 EHA investor event; [7] based on 8-week treatment period

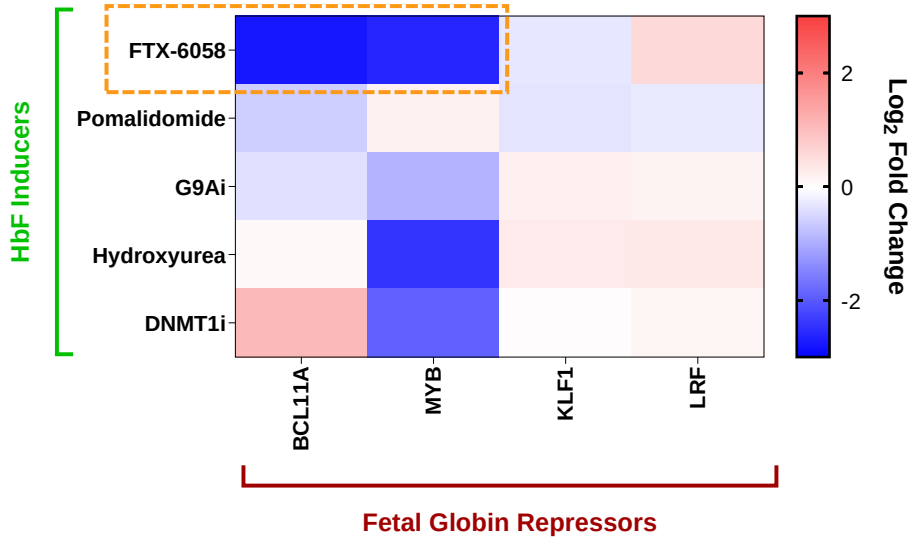
FTX-6058 Demonstrates Potent Downregulation of Key Fetal Globin Repressors, including BCL11A and MYB

Genome-wide Association Studies in SCD Have Identified Key Fetal Hemoglobin Repressors



- HPFH results from polymorphisms in BCL11A, the intergenic region of HSB1L-MYB, and the β-globin cluster
  - Downregulation of BCL11A and MYB have been demonstrated to induce fetal hemoglobin
  - Increased HbF levels also result from mutations in the β-globin gene

FTX-6058 Potently Downregulates BCL11A and MYB in Erythroid Cultures Derived from CD34+ Cells

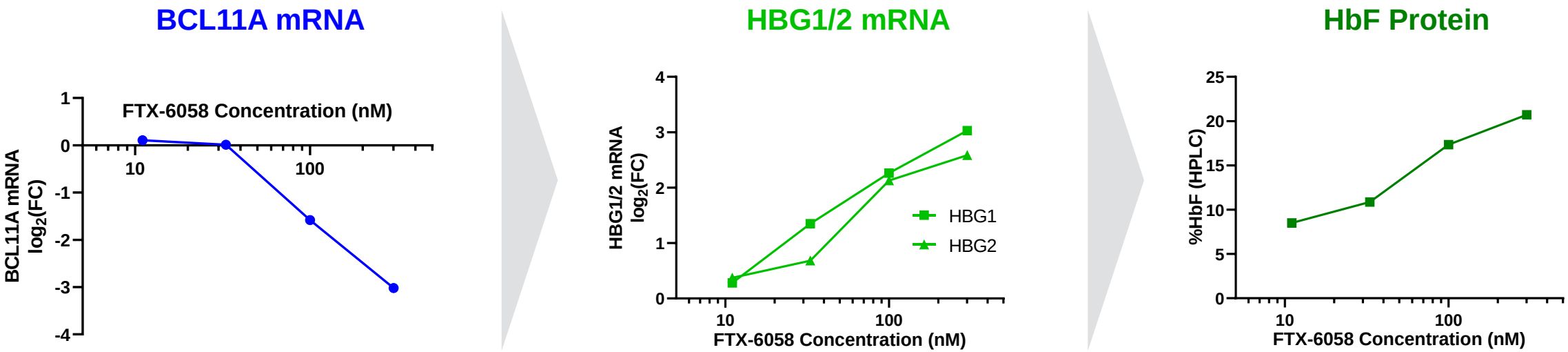


- FTX-6058 potently downregulates master fetal globin repressors BCL11A and MYB
- Robust reduction of BCL11A mRNA only observed with FTX-6058
- No effect on other validated HbF repressors, such as KLF1 or LRF

Bauer, DE. Blood. 2012; HPFH: Hereditary Persistence of Fetal Hemoglobin; CSSCD: Cooperative Study of Sickle Cell Disease; Representative RNASeq mRNA expression from one healthy CD34+ donor.

FTX-6058 Demonstrates Robust Relationship Between BCL11A Downregulation and Fetal Hemoglobin Induction in Erythroid Cells

EEDi Modulation of BCL11A and HBG1/2 mRNA Translates to Robust HbF Protein Induction

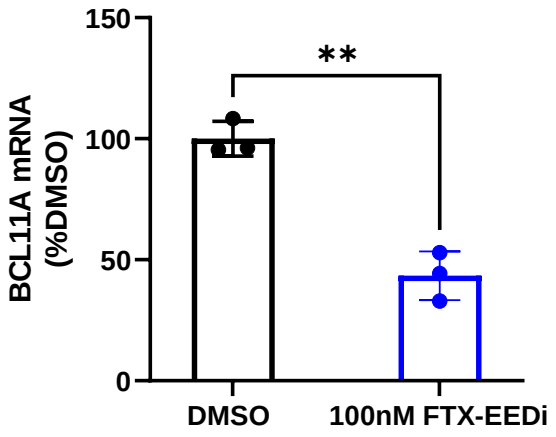


- FTX-6058 treatment results in dose-dependent BCL11A downregulation, and subsequent HBG1/2 upregulation and HbF induction
- Observe 2 – 3 fold HbF protein induction when BCL11A expression is reduced >50%
- Continue to establish relationship between MYB downregulation and HBG mRNA / HbF protein induction

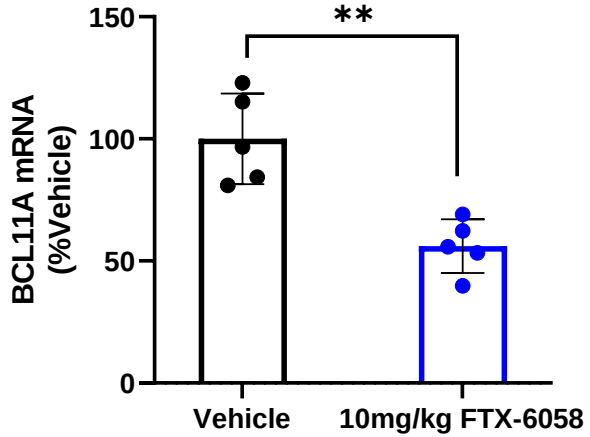
Representative RNASeq mRNA expression from one healthy CD34+ donor

In Vitro BCL11A Downregulation Observed with EED Inhibition Translates In Vivo

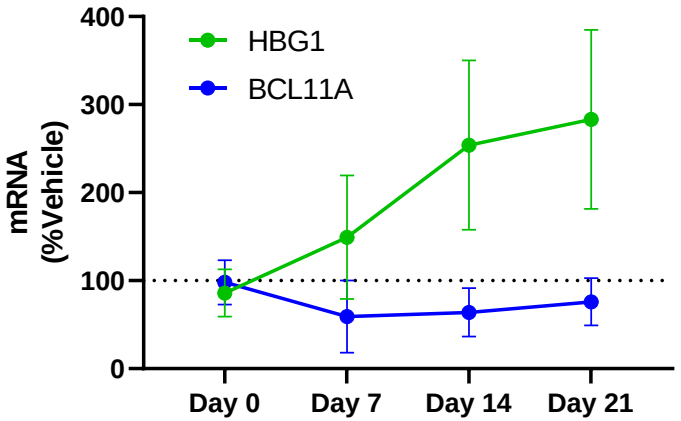
CD34+ Cell Derived Erythroid Culture



Wild-Type Mouse



Townes SCD Mouse

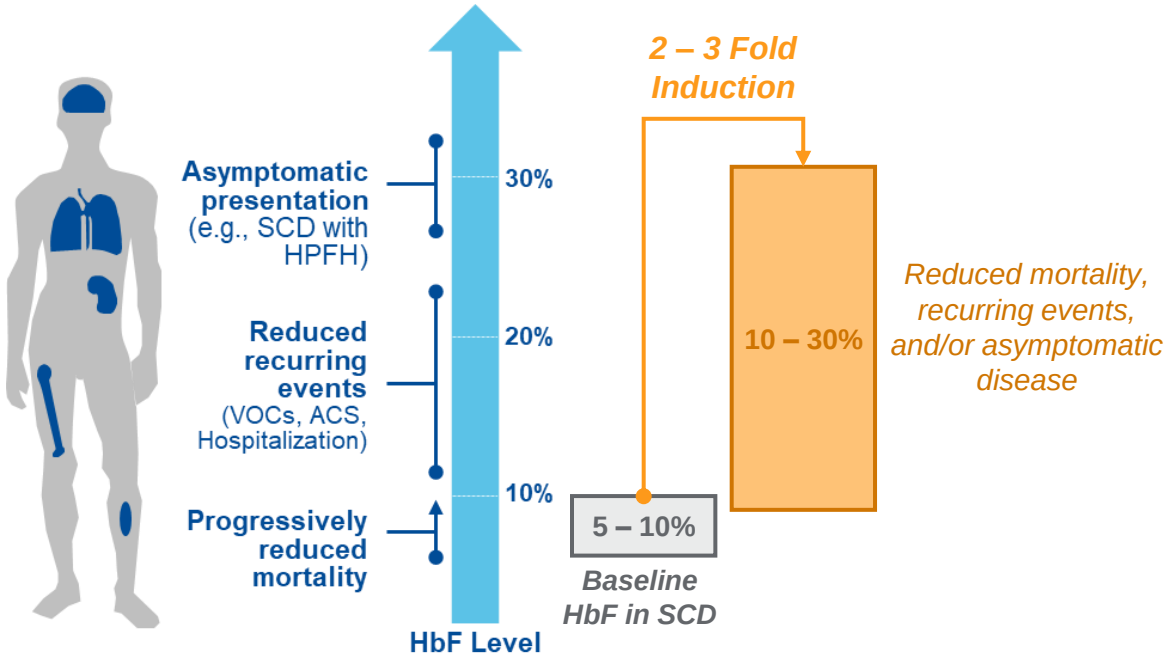


- Observe consistent ~50% reduction in BCL11A across *in vitro* and *in vivo* studies
- In WT and Townes mouse, achieve ~50% reduction in BCL11A by day 5 – 7 of FTX-6058 treatment
- Durable BCL11A reduction achieved in Townes mouse model translates to robust 2 – 3 fold HBG1 induction

FTX-EEDi is structurally and pharmacologically similar EED inhibitor to FTX-6058. Representative mRNA expression from one healthy CD34+ donor. WT mouse whole blood mRNA, 5-days of 10mg/kg. Townes whole blood mRNA at 5mg/kg FTX-EEDi

Oral HbF Inducer has the Potential to be the Preferred SCD Treatment Option for Patients and Providers

HbF Induction has the Potential to Provide Broad Clinical Benefits in SCD



FTX-6058 has Significant Advantages Over Gene Editing / Therapy Approaches

Oral HbF Inducer (FTX-6058)	• Convenient once daily oral pill with the potential to address broad SCD symptomology • Achieving 25 – 35% HbF levels has the potential to provide a functional cure • Potential for improved safety and tolerability compared to myeloablative conditioning and stem cell transplant • Oral pill is favorable for global distribution
Gene Editing / Therapy	• Potential for a functional cure, though requires a highly invasive procedure • Myeloablation safety risks and unknown efficacy durability • Likely significant barriers to access

FTX-6058 Phase 1 Healthy Volunteer Update

Christopher Morabito, MD

Chief Medical Officer

*****Results are from ongoing, blinded Phase 1 clinical trial*****

Fulcrum Therapeutics




FTX-6058 Phase 1 Healthy Volunteer Trial Design

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

Overview of Phase 1 SAD / MAD Cohorts

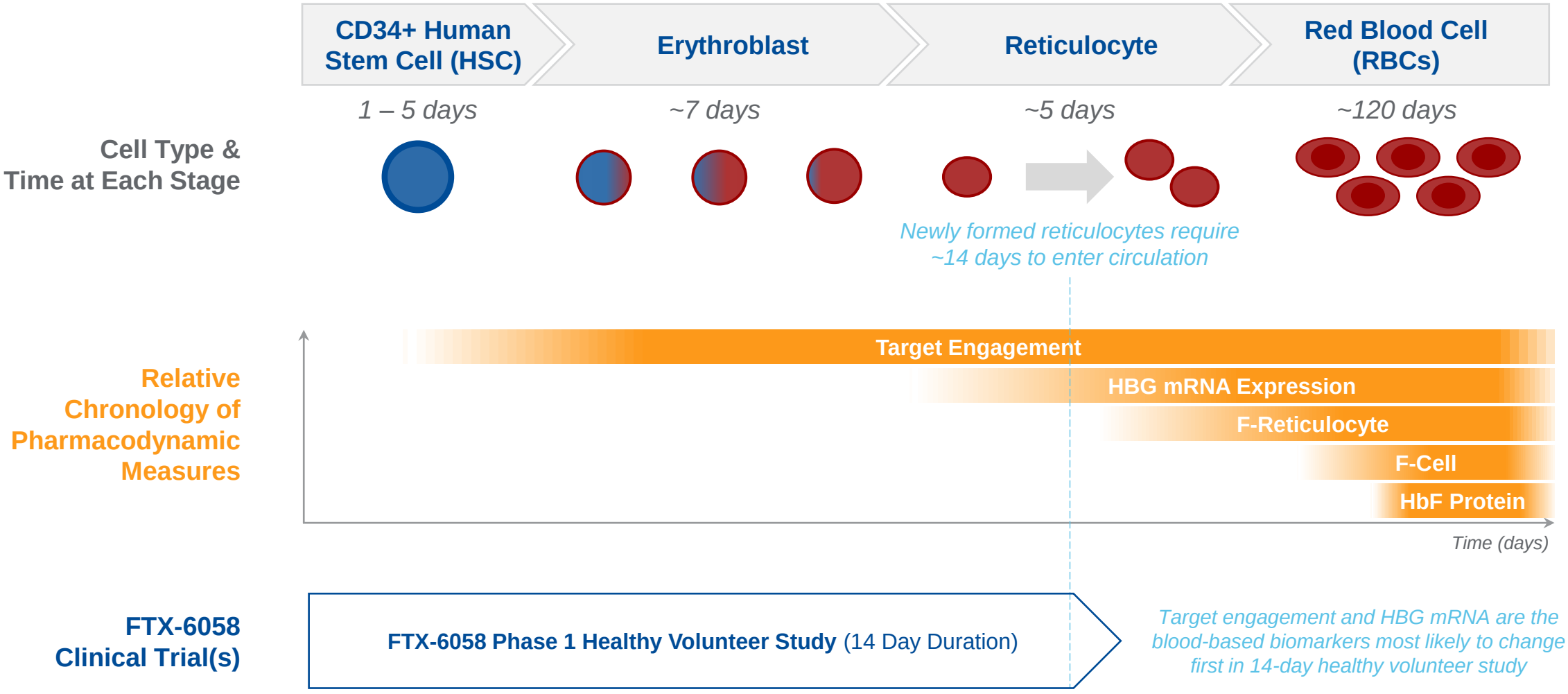
SAD Cohorts	Dose (mg)	MAD Cohorts (QD, 14d)
Cohort 1 ✓	2	Cohort 1 ✓
Cohort 2 ✓	4	
	6	Cohort 2 ✓
Cohort 3 ✓	10	Cohort 3 ✓
Cohort 4 ✓	20	Cohort 4 ✓
Cohort 5 ✓	30	Cohort 5 ✓
Cohort 6 ✓	40	
Cohort 7 ✓	60	
	90	

✓ *Completed cohorts*

SCD Cohort (6 mg) Ongoing

- **Each MAD cohort has 8 subjects (6 on study drug and 2 on placebo)**
- **Predicted human dose from PK/PD modeling is 4mg, and supports QD dosing**
- **The 6, 10, and 20mg doses were projected to achieve maximal target engagement and HbF induction**

Erythropoiesis in Healthy Volunteers Influenced 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

FTX-6058 has been Generally Well-Tolerated

Summary of Related TEAEs

SAD

	Placebo	FTX-6058						Blinded
Adverse Event	N = 14	**2mg** N = 3	**4mg** N = 3	**10mg** N = 5	**20mg** N = 5	**30mg** N = 5	**40mg** N = 5	**60mg** N=5
Eosinophilia Count Increased	1 (7%)	0	0	0	0	0	0	0
Leukopenia	0	0	0	0	1 (20%)	0	0	0
Headache	0	0	0	0	0	0	0	1 (20%)[a]

[a] *Blinded data from SAD 60mg cohort*

Food Effect

	FTX-6058
Adverse Event	**20mg**[c] N = 10
Nausea	1

[c] *Cross-over study design*

MAD

	Placebo	FTX-6058				
Adverse Event	N =10	**2mg** N = 6	**6mg** N = 6	**10mg** N = 6	**20 mg** N=6	**30 mg** N=6
Diarrhoea (Loose Stool)[b]	1 (10%)	0	0	0	0	0
Dry Mouth	0	1 (17%)	0	0	0	0
Abnormal Stool	0	0	0	1 (17%)	0	0
Diarrhoea	1 (10%)	0	0	0	0	0
Neutrophil Count Decrease	0	0	0	1 (17%)	0	0
Headache	0	0	0	1 (17%)	0	0

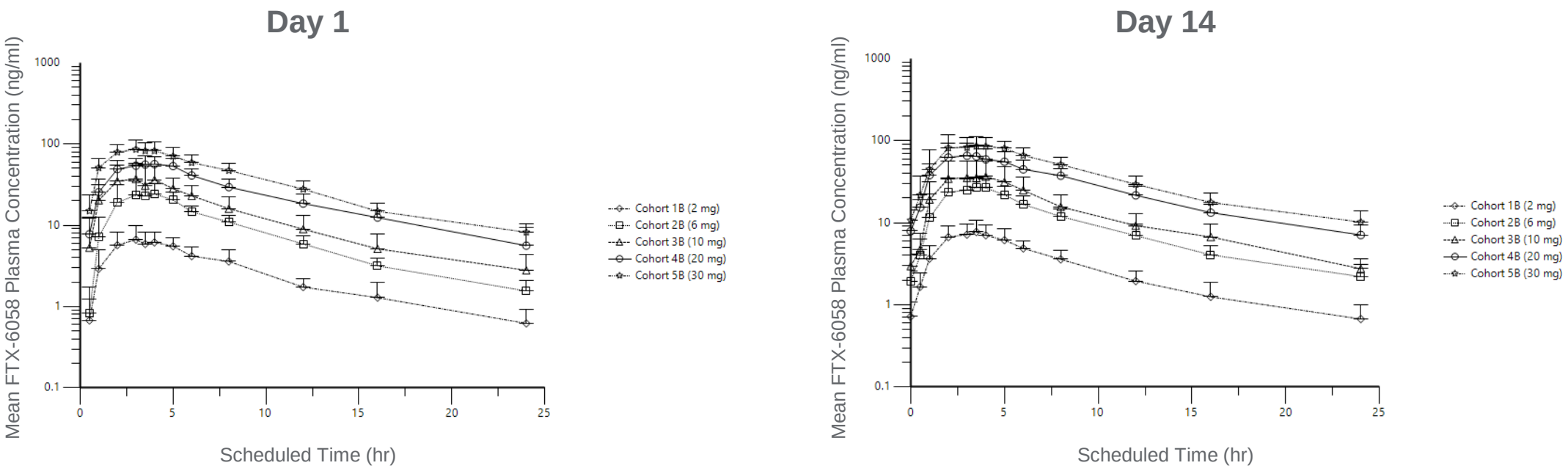
[b] *Did not meet the WHO definition of diarrhea per protocol*

- **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 severity per CTCAE criteria and resolved**
- **One Grade 3 and one Grade 4 TEAE: both unrelated to FTX-6058**
  - Both TEAEs were asymptomatic, incidental creatine phosphokinase (CPK) increases detected at safety follow-up visit (i.e., 7 – 10 days post-treatment) in the 20mg food effect cohort and 10mg MAD cohort, respectively

Additional cohorts completed since August disclosure

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

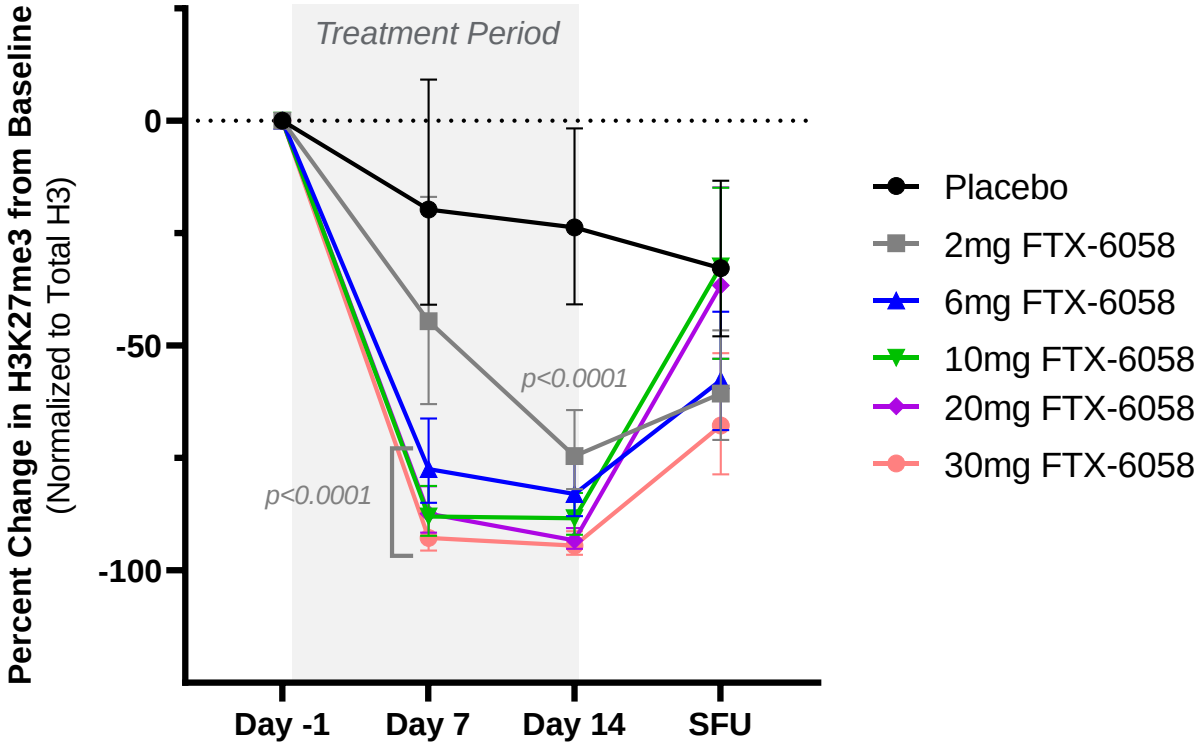
Plasma FTX-6058 Pharmacokinetics from MAD Cohorts



- 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
- No food effect observed with FTX-6058

All MAD Cohorts Demonstrate Approximately 75 – 95% Reduction in H3K27me3 Levels After 14 Days of FTX-6058 Treatment

Mean Reduction (%) of H3K27me3 Levels

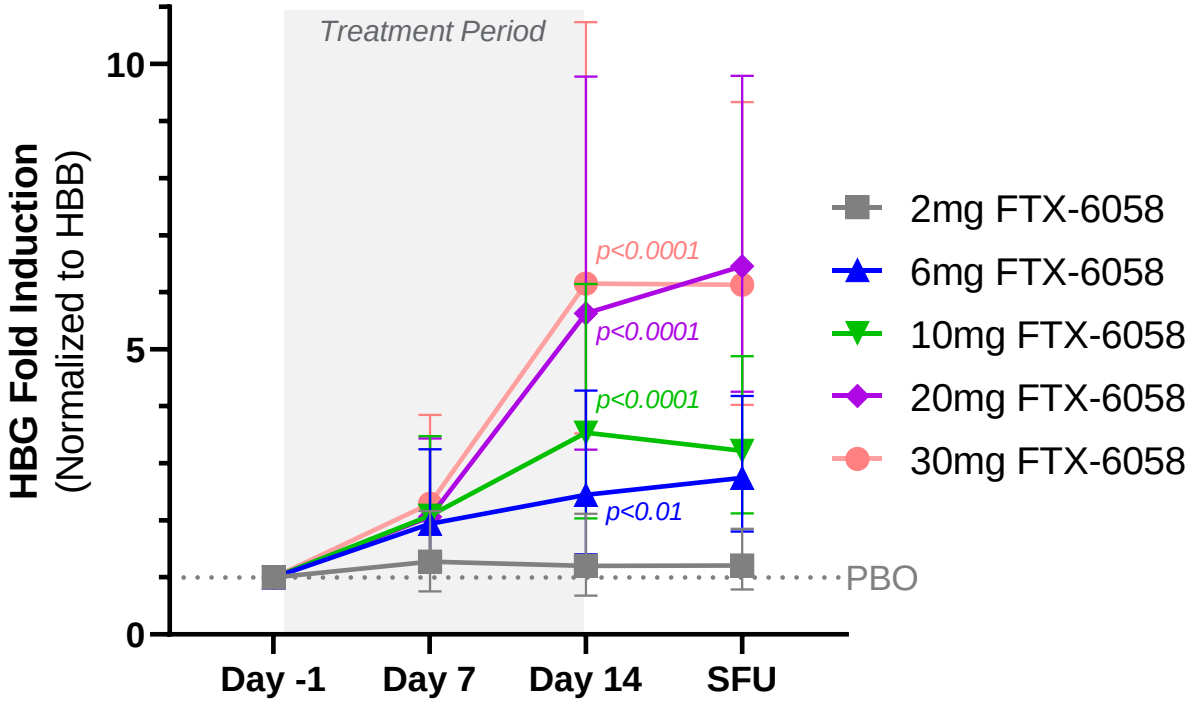


- Demonstrated proof-of-mechanism as evidenced by inhibition of H3K27me3 levels
- Robust target engagement observed in doses as low as 2mg
- Safety follow-up (SFU) samples were collected 7 – 10 days post 14-day treatment period

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; Placebo pooled from MAD cohorts 1 – 5; Percent reduction in H3K27me3 levels for 2, 6, 10mg cohorts was updated using pooled placebo from MAD 1 – 5 cohorts (versus MAD 1 – 3 cohorts in August disclosure).

FTX-6058 Achieved Further HBG mRNA Induction in 20mg and 30mg Cohorts, With Up to a Mean 6.2-fold Induction

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

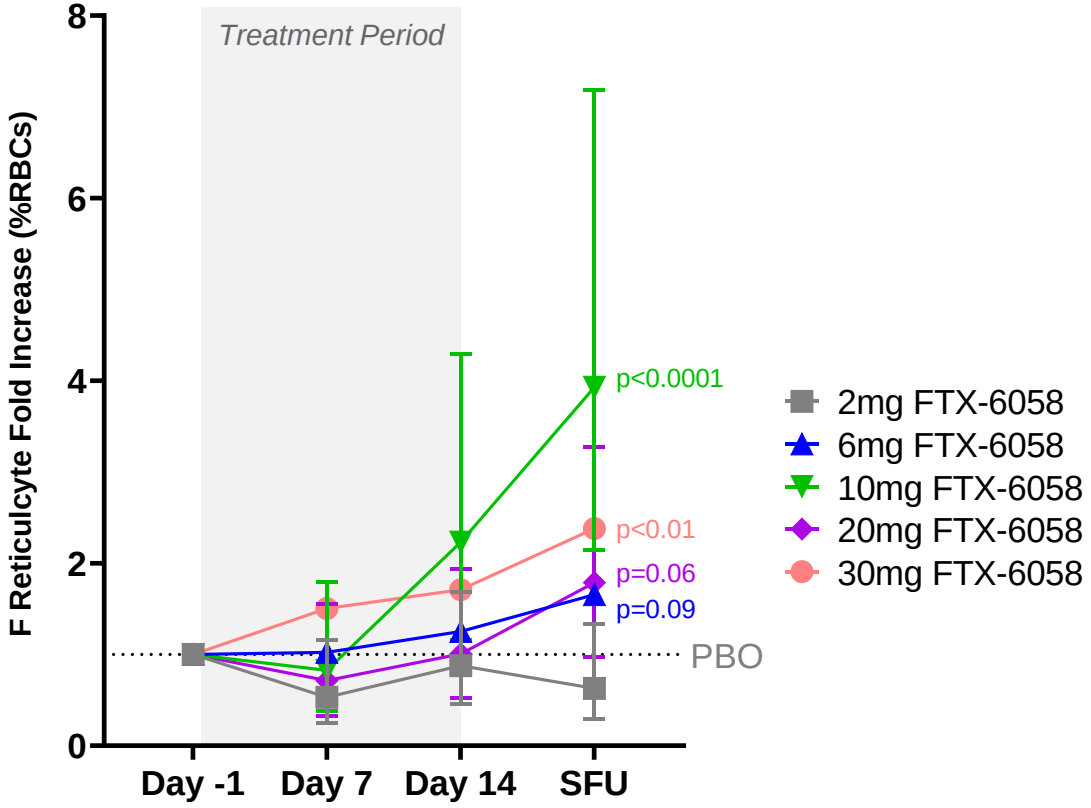


- Demonstrated proof-of-biology as evidenced by HBG mRNA induction
- At Day 14, the 6 – 30mg FTX-6058 cohorts achieved a mean 2.4 – 6.2 fold HBG mRNA induction
- The maximal rate of HBG induction was observed in the 20mg and 30mg cohorts
- Maximal HBG induction has not yet been achieved
- Persistent and durable HBG induction observed 7 – 10 days after treatment (i.e., SFU)

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 fold induction for 2, 6, 10mg cohorts was updated using pooled placebo from MAD 1 – 5 cohorts (versus MAD 1 – 3 cohorts in August disclosure).

Increases in F-Reticulocytes Provide Earliest Indication that HbF Protein Production is Beginning

F-reticulocytes do not Predict HbF Fold Induction, but Demonstrate Translation of HBG to HbF

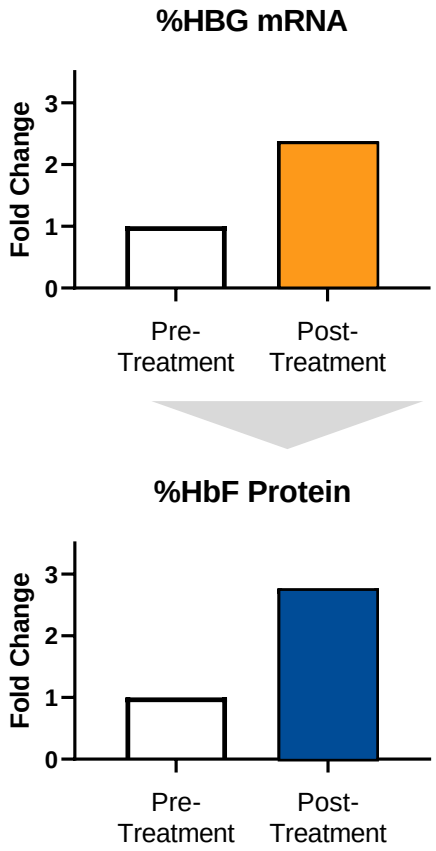


- Observed a mean **1.7 – 3.9 fold increase in F-reticulocytes** at the safety follow-up (SFU) visit with FTX-6058 doses ≥6mg
- Increases in F-reticulocytes indicates that persistent HBG mRNA induction is beginning to translate to HbF production in newly formed reticulocytes
- Further increases in F-reticulocytes, F-cells, and HbF protein are projected with longer FTX-6058 treatment duration

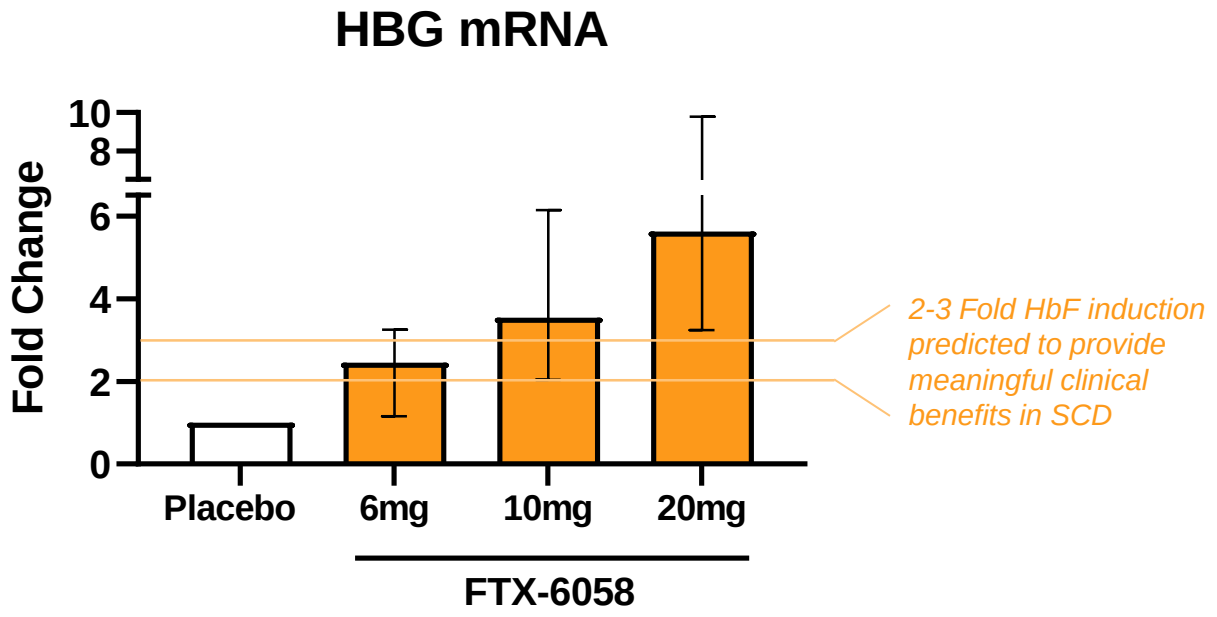
Safety follow-up (SFU) samples were collected 7 – 10 days post 14-day treatment period; PBO: placebo; Data presented as geometric LS mean ratio (to placebo) with 95% confidence interval; mixed-effects model for repeated measures (MMRM) analysis performed for Day 7 and Day 14; analysis of covariance (ANCOVA) utilized for SFU data; F-reticulocyte fold increases for 2, 6, 10mg cohorts was updated using pooled placebo from MAD 1 – 5 cohorts (versus MAD 1 – 3 cohorts in August disclosure).

FTX-6058 Clinical Results Achieve Induction Thresholds Predicted to Provide Meaningful Therapeutic Benefits and Potential Functional Cure to SCD Patients

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 individuals with SCD

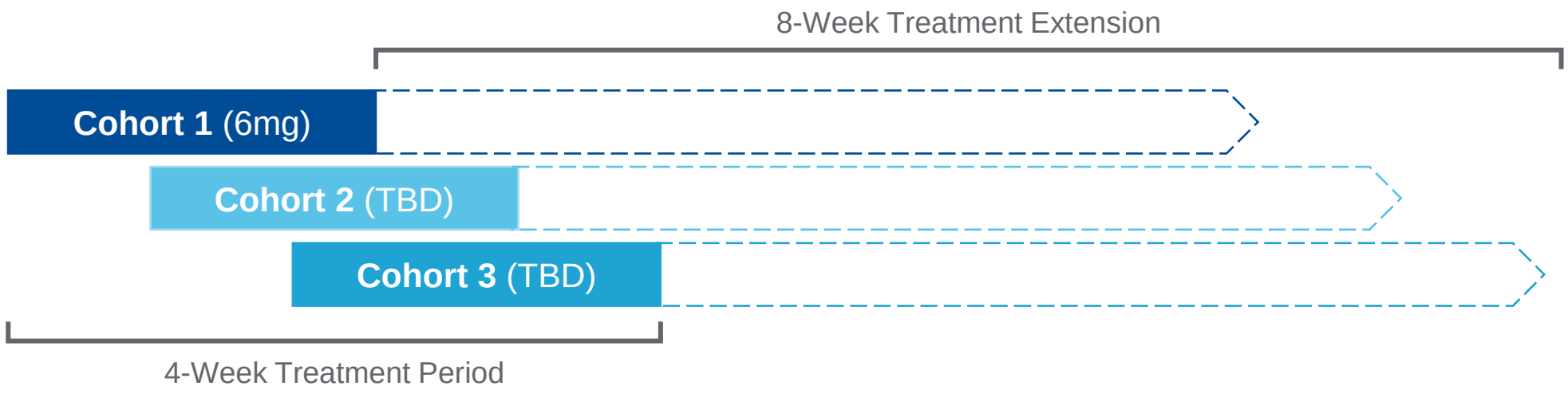
Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.

Phase 1b Clinical Trial Design

Study Population

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

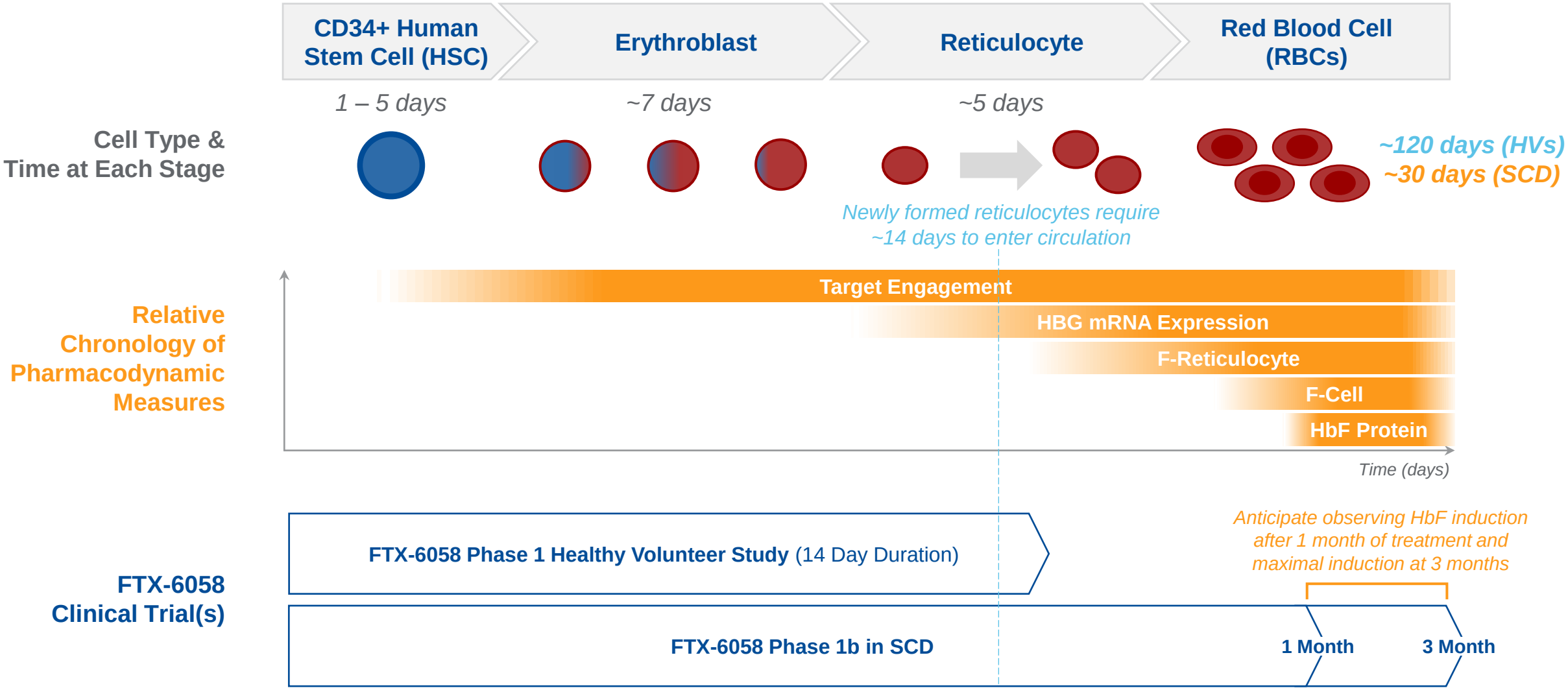
Study Design



Study Endpoints

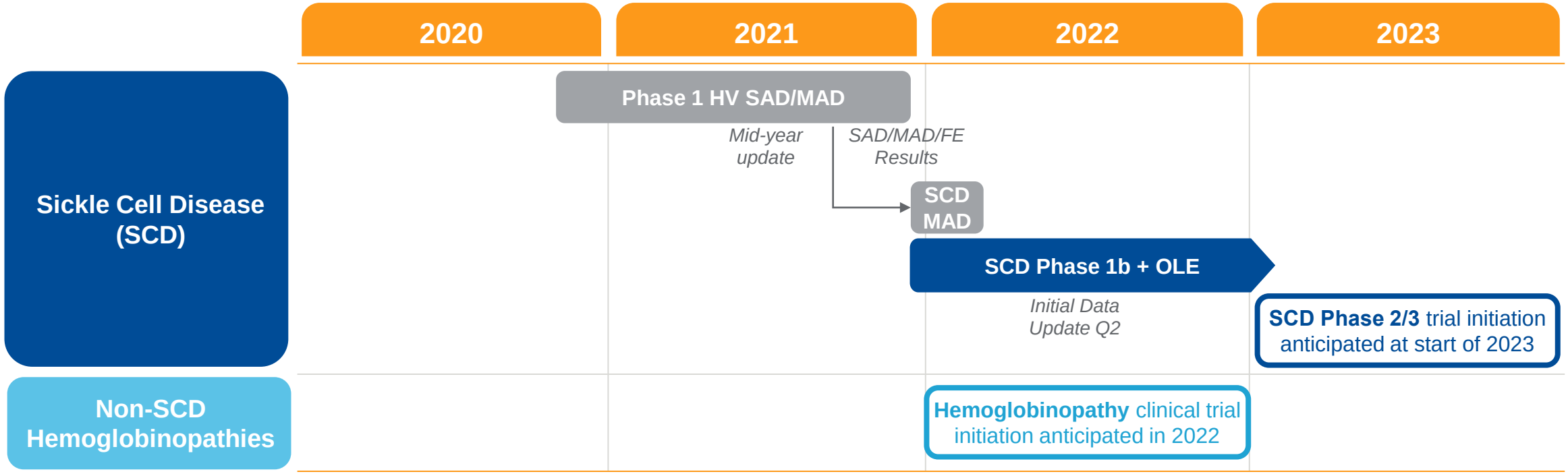
Primary	Secondary	Exploratory
▪ Safety and tolerability ▪ Pharmacokinetic measurements	▪ %HbF protein by HPLC ▪ %F-cells by flow cytometry	▪ Target engagement ▪ Incidence of VOCs ▪ Biomarkers of hemolysis ▪ QOL measures

Increased Hemolysis and Short SCD RBC Lifespan Enables Quantitative Protein Measurements After 1 – 3 Months of Treatment in Phase 1b



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

FTX-6058 Anticipated Program Milestones



- Initiate Phase 1b SCD clinical trial by year-end
- Submit IND in additional hemoglobinopathies (e.g., β-Thalassemia) by year-end
- Report initial data from Phase 1b SCD clinical trial in Q2 2022
- Initiate Phase 2/3 SCD clinical trial in 2023

Fulcrum Therapeutics

Q&A