Fulcrum Therapeutics

FTX-6058, a novel HbF-inducing agent for the treatment of Sickle Cell Disease and β-Thalassemia

Christopher Moxham PhD
Senior Vice President, Discovery Research
September 25, 2020

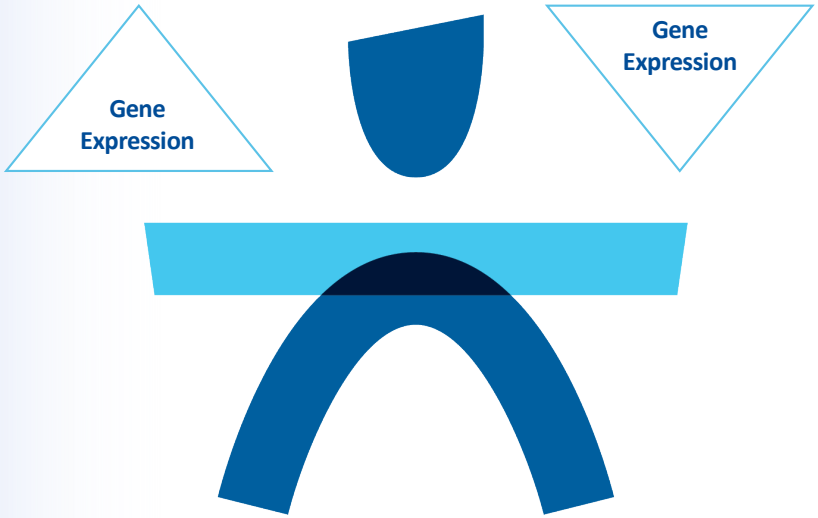
Disclaimer and Notice

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 our product candidates, the timing of regulatory filings, initiation and enrollment of clinical trials and the timing of availability of clinical trial data and the Company’s ability to fund its operations with cash on hand . All statements, other than statements of historical facts, contained in this 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 later clinical trials positive results found in earlier preclinical studies and early-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.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. Neither Fulcrum nor its affiliates, advisors or representatives makes any representation as to the accuracy or completeness of that data or undertakes to update such data after the date of this presentation.

Fulcrum Overview

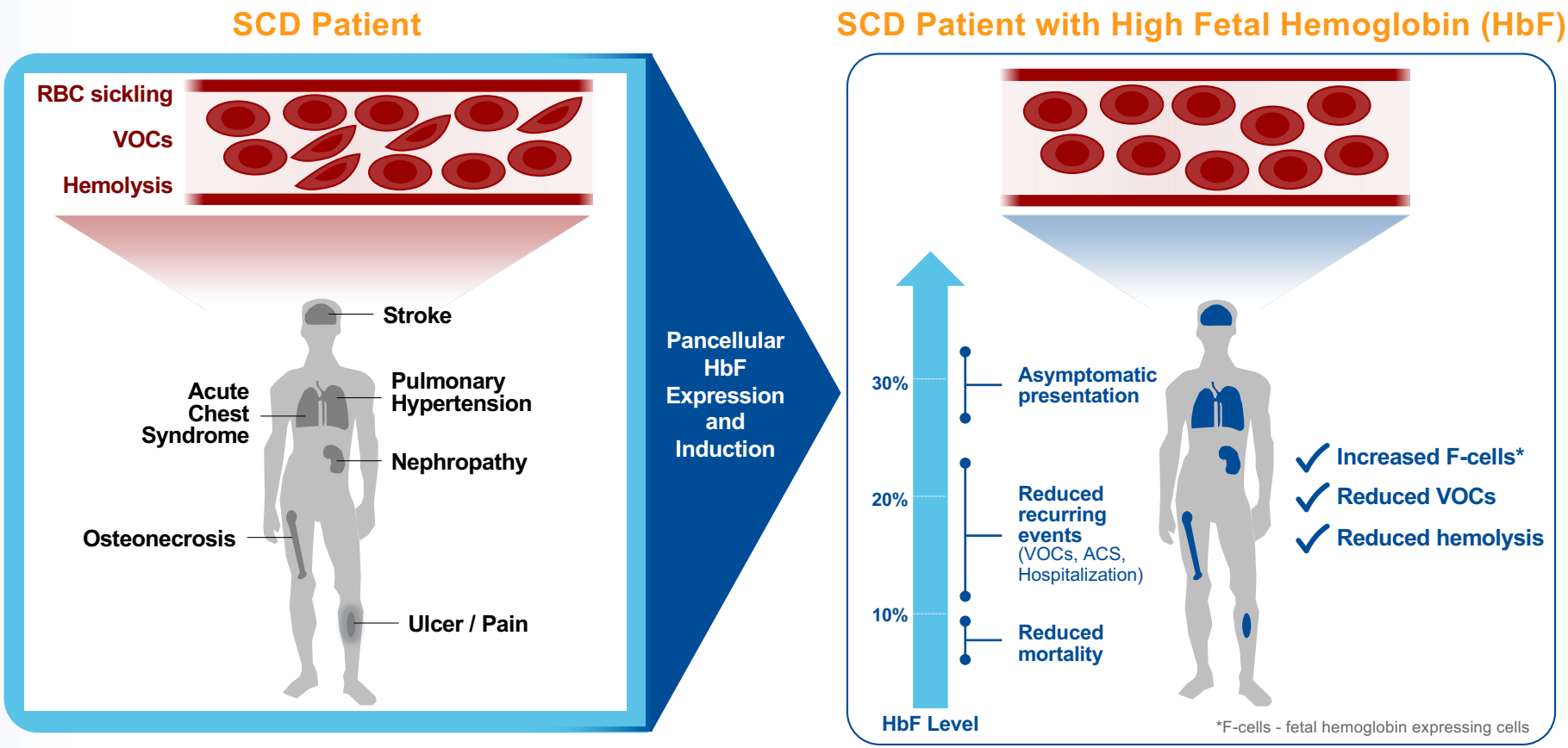
Clinical stage biopharmaceutical company using systematic approach to identify small molecules able to rebalance gene expression



- ~7,000 genetically defined diseases today
- We are building on decades of research highlighting gene expression role in disease
- High-throughput product engine designed to rapidly identify and validate drug targets that can modulate gene expression and treat disease at its root cause
- Focus on small molecules as therapeutic modality

Our vision is to treat genetically defined diseases by addressing their root cause

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

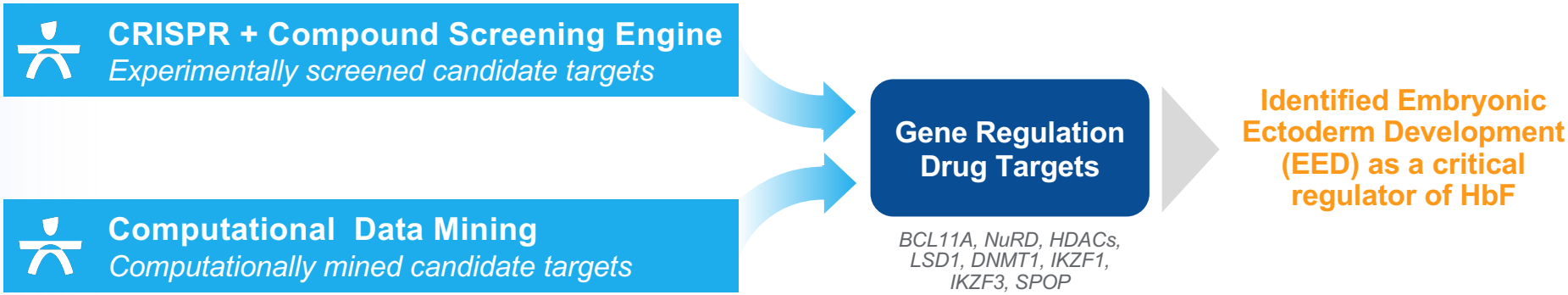


Powars, DR. Blood. 1984; Estepp, JH. Br J Haematol. 2013; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.

Preclinical Executive Summary: FTX-6058 for Sickle Cell Disease

- Highly potent (~1 nM) and selective small molecule with clean off-target profile
- Superior pre-clinical activity relative to SOC and competitor compounds
- Potent upregulation of HBG mRNA and pancellular induction of HbF protein in primary human erythroid cells
- Clinically desirable globin profile (e.g., % HbF) in differentiated CD34+ cells from multiple healthy and SCD donors
- PK/Target Engagement relationship established
- Elevation of human fetal hemoglobin mRNA (HBG1), protein (HbF), and F-cells in Townes mouse model of SCD
- 28-day GLP toxicology studies completed, and GMP material scale-up for Phase 1 is complete
- PK and human dose projections support once-daily, oral dosage of FTX-6058

FTX-6058: A Product of Fulcrum Research Laboratories



FTX-6058: A Product of Fulcrum Research Laboratories

CRISPR + Compound Screening Engine
Experimentally screened candidate targets

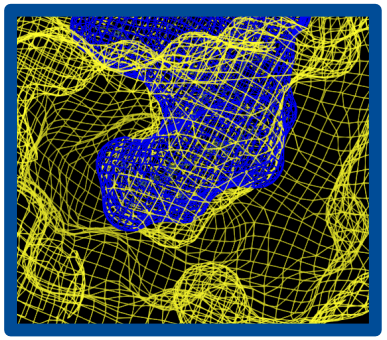
Computational Data Mining
Computationally mined candidate targets

Gene Regulation Drug Targets

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

Identified Embryonic Ectoderm Development (EED) as a critical regulator of HbF

Structure-Based Drug Design

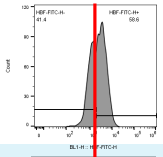
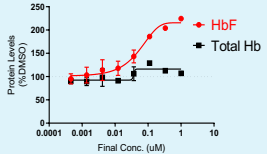
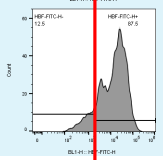
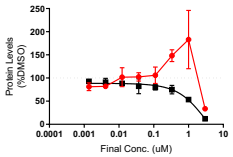
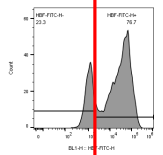
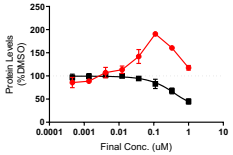
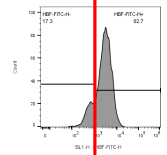
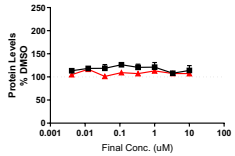
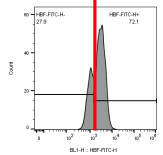


FTX-6058

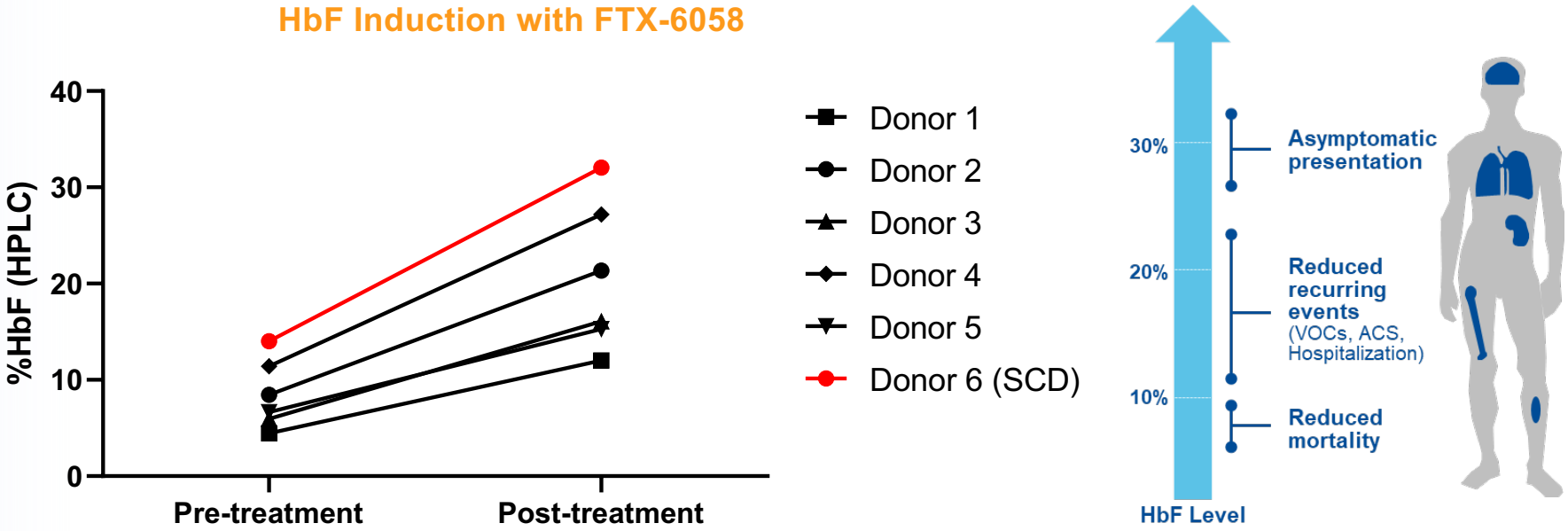
- **EED K_D = 0.163 nM**
- **PRC2 IC_{50} < 5 nM**
- **Highly Selective**
- **Clean Off-target Profile**

FTX-6058 Displays Robust Increases in HbF *and* F-cells

Superior in vitro Activity Relative to Other Mechanisms

	HUDEP2	CD34⁺ Cells		
Agent	**HbF Elisa**	**HbF HPLC**	**%F-cells**	**HbF/cell**
Vehicle	N/A	N/A	59%	
FTX-6058		**2 – 3 Fold** ⬆	**88%** ⬆	 ⬆
DNMT inhibitor (5-azacytidine)		1.5 – 2 Fold	77%	
G9a inhibitor (EPZ-35544)		1.5 – 2 Fold	83%	
PDE9 inhibitor (PF-04447943 / IMR-687)		None	72%	

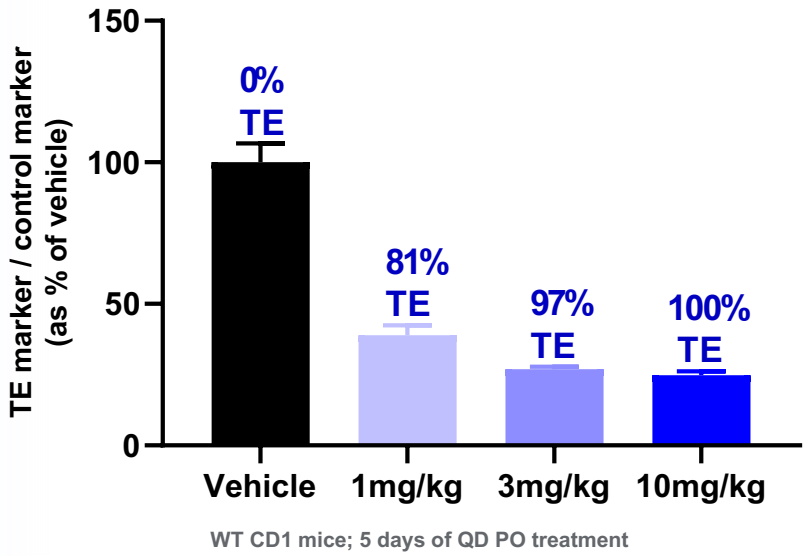
FTX-6058 Robustly Induces Fetal Hemoglobin in CD34+ Cells from Healthy and SCD Donors



- **Observe an absolute 8 – 18% increase in HbF upon treatment with FTX-6058, which has the potential to address mortality risk and recurring events in SCD patients**
- **Small increases in HbF (1 – 5%) have the potential to provide clinical benefits to all SCD patients**

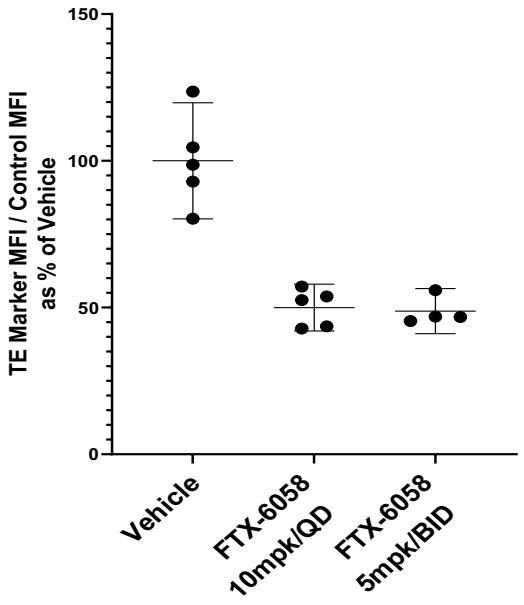
Meaningful Target Engagement is Anticipated in Clinic

Target Engagement
(Bone Marrow)



WT CD1 mice; 5 days of QD PO treatment

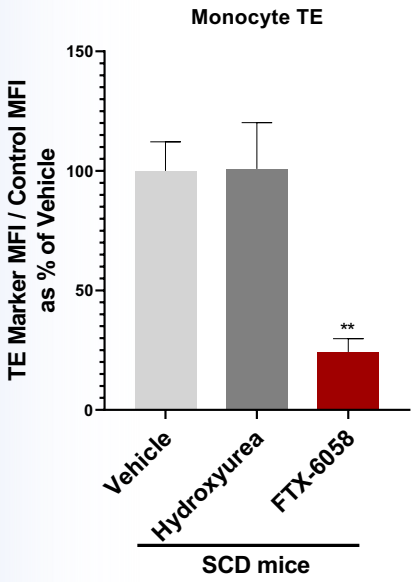
Target Engagement
(Blood Monocytes)



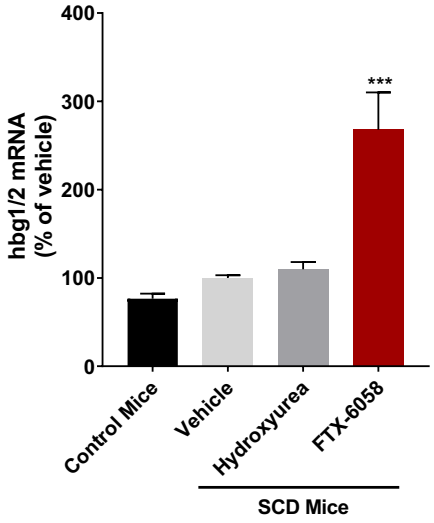
- **Provides Fulcrum a facile way to measure target engagement in peripheral blood**

Superior Induction of Human Fetal Hemoglobin mRNA and Protein Versus HU in Townes SCD Mice

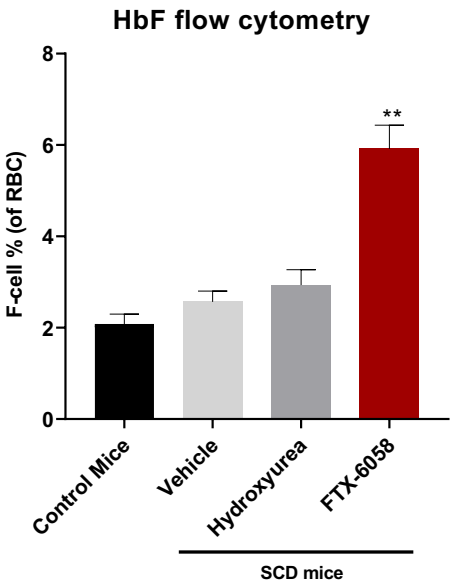
Target Engagement

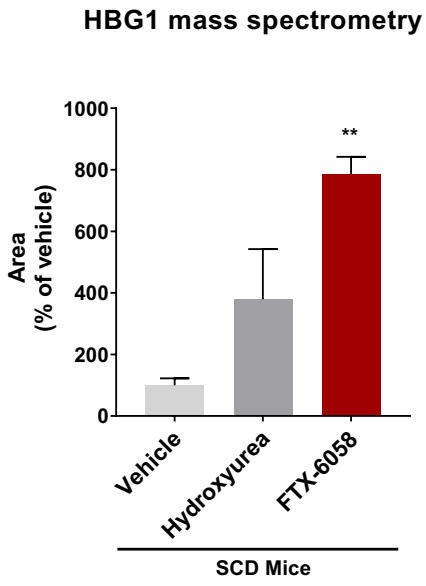


HBG1 mRNA levels



Fetal hemoglobin protein levels



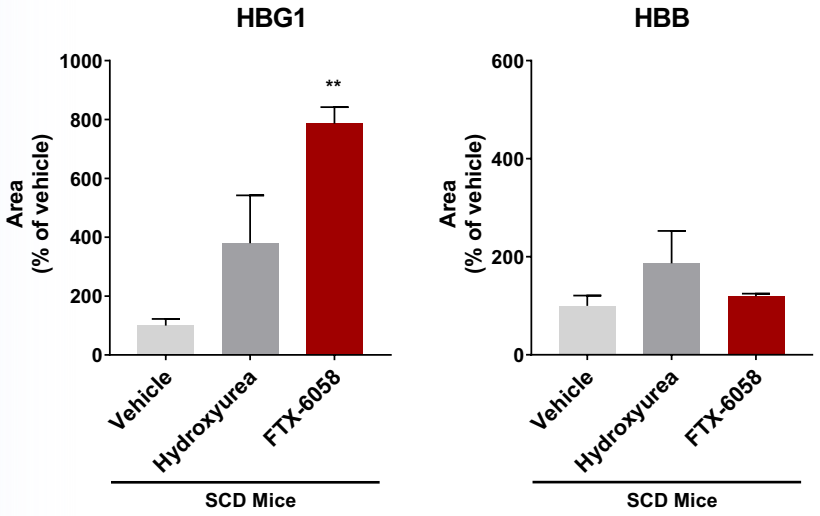


Hydroxyurea was administered once daily at 100 mg/kg for 28 days;
FTX-6058 was administered twice per day at 5 mg/kg for 28 days

**p<0.01; ***p<0.001

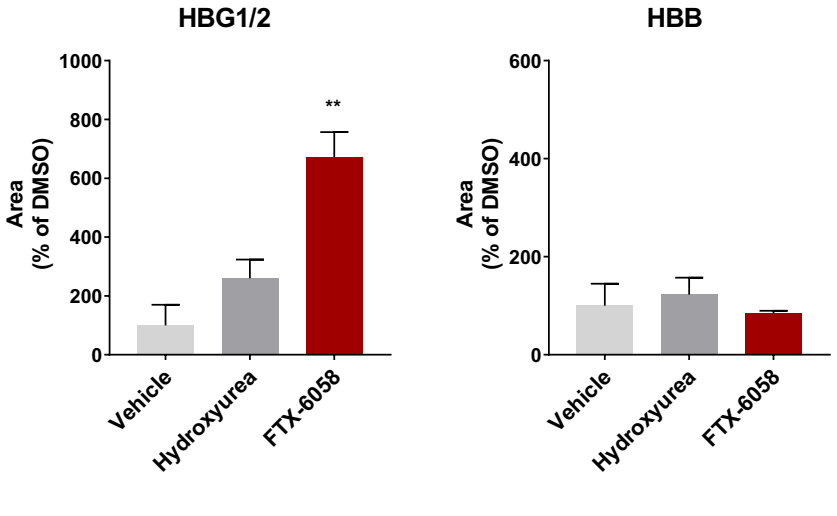
FTX-6058 Selectively Upregulates Fetal Globin, with No Observed Effect on Beta Globin Expression

In vivo pharmacology
(Townes SCD mouse model)



Townes mouse model (28 days treatment):
Hydroxyurea was administered once daily at 100 mg/kg;
FTX-6058 was administered twice per day at 5 mg/kg

In vitro pharmacology
(Human CD34+ cells)



Human primary CD34+ cells (Donor 224):
CD34+ cells expanded and differentiated for 14 days
in a two-phase culture system; treated for final 7 days

FTX-6058 Has Potential to be Transformative Therapy for SCD

- Target identified from Fulcrum Product Engine
- Delivered a potent and selective EED Inhibitor
- Oral, once-daily dosing supported by PK and human dose projections
- Anticipated plasma exposures required to elevate HbF in clinic are predicted to be achievable
- Demonstrates impressive preclinical pharmacological profile to act as disease-modifying therapeutic

Acknowledgements

Fulcrum Team
Billy Stuart
Michael Cameron
Mark Roth
Steven Kazmirski
Kinglsey Appiah
Richard Barnes
Qingyi Li
Madison Stulir
Alia Zeid
Lucienne Ronco
Angela Cacace
Lorin Thompson
David Peters
Keqiang Xie
Ivan Efremov
Peter Rahl
Paul Bruno
Bryan Stuart
Robert Gould
Diego Cadavid
Owen Wallace

UPenn / CHOP
Gerd Blobel
Osheiza Abdulmalik

Boston University
Martin Steinberg

Dana Farber
Maureen Achebe

Thank you!

Fulcrum Therapeutics

Additional questions:

Please contact us at **info@fulcrumtx.com**

fulcrumtx.com