Fulcrum Therapeutics

August 2022

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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 planned meetings with regulatory agencies and availability of clinical trial data. All statements, other than statements of historical facts, contained in this press release, 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; 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 press release 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.

Our Mission is to Treat Root Cause of Rare Genetic Diseases

We aim to

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

Two Clinical-Stage Programs

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

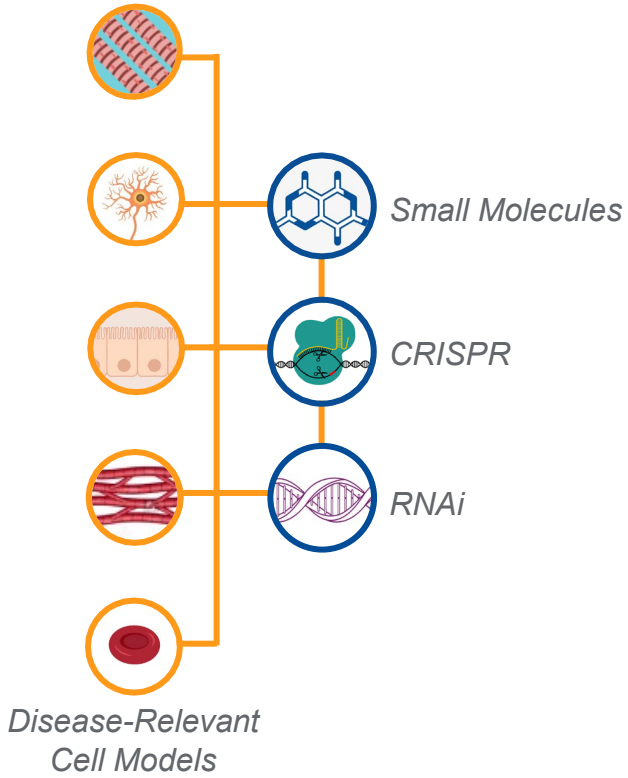
Sickle cell disease: Phase 1b patient study; potential first oral functional cure

FulcrumSeek™

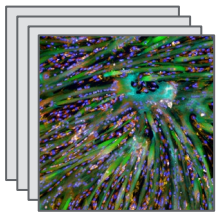
Product engine to systematically identify high-value, de-risked targets at speed and scale for rare genetic diseases

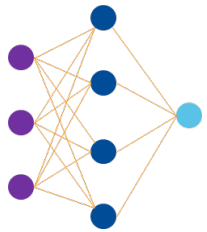
FulcrumSeek™ Systematically Identifies High-value, De-risked Therapeutic Targets for Rare Genetic Diseases

Toolbox of Disease Relevant Cell Models Interrogated with Highly Curated Perturbagens



Insights Harvested from Rich Data Readouts



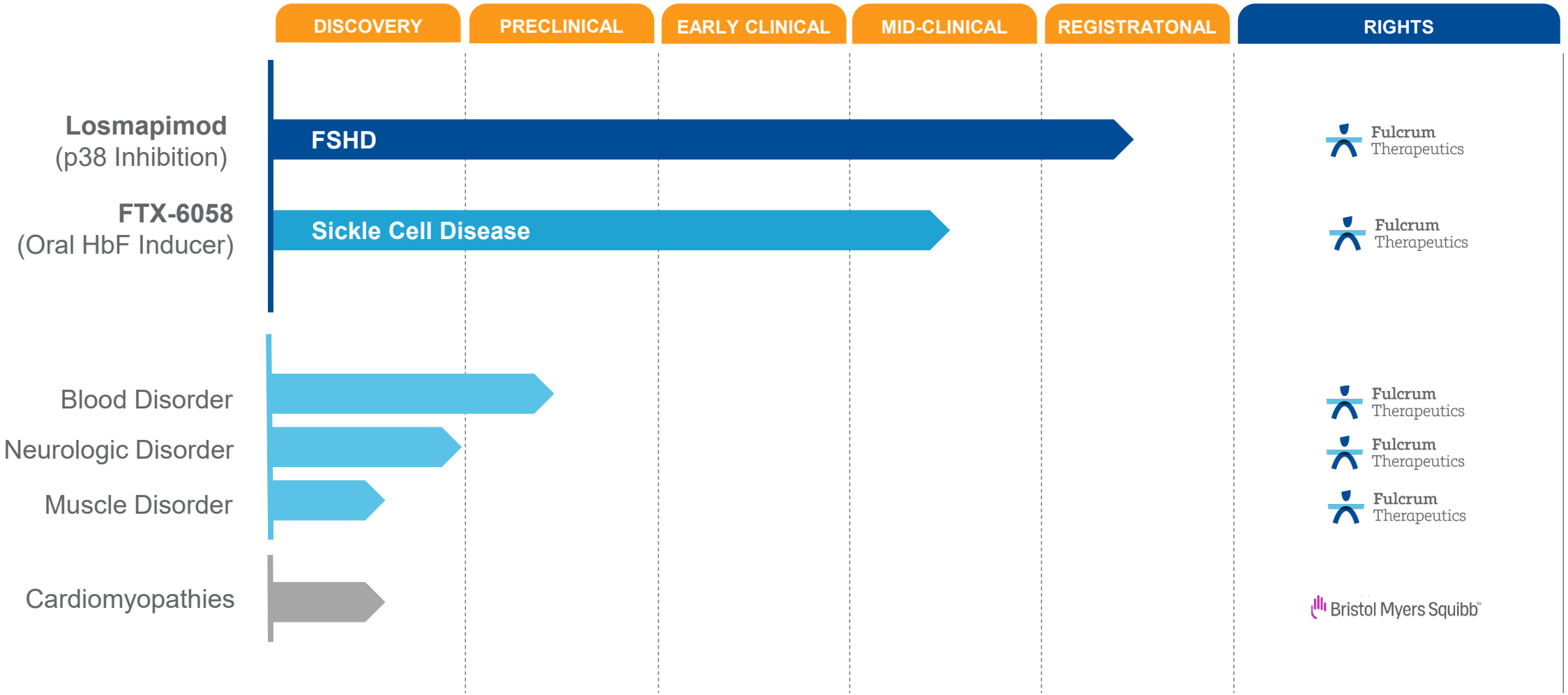


Disease-Modifying Targets and Value-Unlocking Datasets

Targets with **specificity** and **selectivity**

Comprehensive data set that **significantly accelerates development**

Pipeline of Potentially Disease-modifying Therapies



Next IND in 2023

Multiple Value-Driving Milestones

Cash runway into mid-2024; $169M as of 6/30/2022

Poised for Continued Momentum in 2023 and Beyond

Losmapimod for Facioscapulohumeral Muscular Dystrophy (FSHD)

Fulcrum Therapeutics

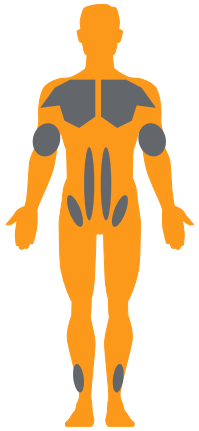
FSHD is Second Most Common Muscular Dystrophy

The Disease

Rare, genetic disorder in which skeletal muscle is replaced by fat

Caused by aberrant expression of DUX4 gene

2/3 of cases are hereditary



Fat infiltrates muscle

Symptoms

- Progressive weakening of muscles
- Significantly impaired upper and lower function
- Increasing difficulties with activities of daily living, leading to loss of independence
- Many become dependent on wheelchairs
- Chronic pain, fatigue, anxiety, and depression

Robust global opportunity for disease modifying therapy

Estimated US FSHD Population*

16,000-38,000

Estimated Global FSHD Population*

300,000-780,000

*Deenen, JCW, et al. Neurology. 2014; Preston, MK et al. GeneReviews – FSHD. 2020

Losmapimod: Potential First-to-Market Therapy for FSHD

FulcrumSeek™ identified losmapimod as optimal drug candidate to treat root cause of FSHD

- Highly selective p38α/β MAPK inhibitor
- Reduced DUX4 expression in preclinical studies
  - Aberrant expression DUX4 gene is known root cause of FSHD
- Generally well-tolerated, with clinical experience in >3,600 people

Urgent Need for Therapy to Slow or Stop Disease Progression

No approved treatments; losmapimod only program in clinical development

Physicians highlight therapy to slow disease progression as most important need in FSHD

Top attributes patients want in a therapy:

- Slow disease progression
- Improve mobility
- Preserve upper extremity function
- Safety and tolerability

"They told me that I was probably going to die from muscular dystrophy at 30 years old—that I would probably roll over and suffocate myself in my sleep."

Trinity Qualitative Research, June-July 2021; N=20 HCPs and N=30 patients

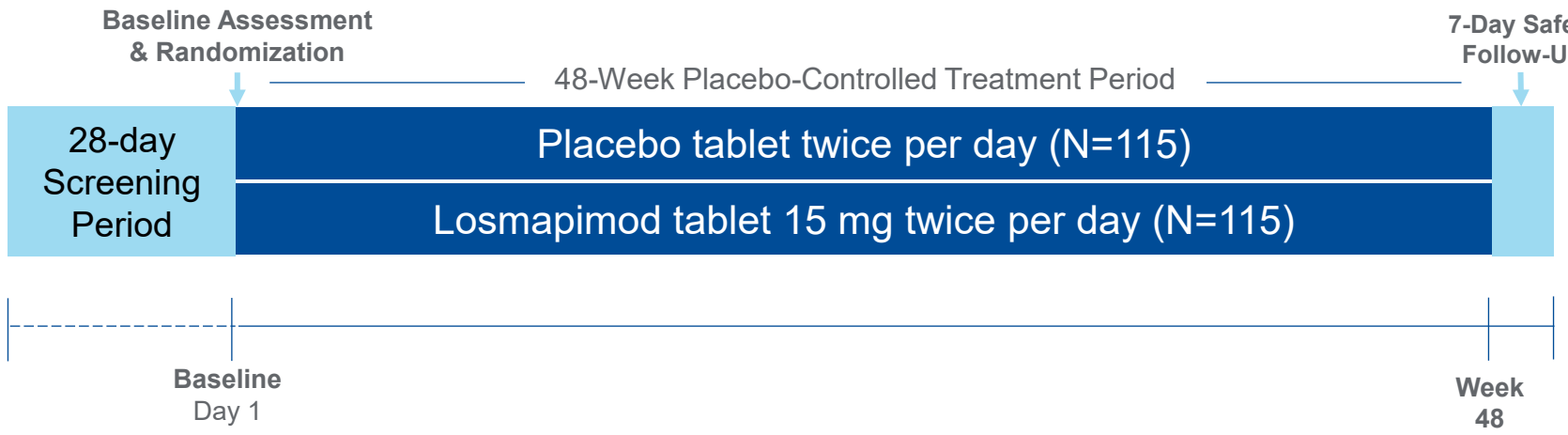
REACH: A Phase 3 Trial of Losmapimod in FSHD

Enrolled 1st patient in REACH; Enrollment completion in 2023

Study Population

~230 subjects with FSHD1 and FSHD2, 18-65 years old, enriched for progression as measured by RWS

Study Design



Study Endpoints

Primary	Secondary	Healthcare Utilization
RWS quantification of total relative surface area with 500g wrist weight in dominant arm	▪ MFI ▪ Neuro-QoL Upper Extremity ▪ PGIC ▪ Safety and tolerability	▪ Healthcare utilization questionnaire ▪ EQ-5D questionnaire

REACH Trial Design Leverages Learnings from ReDUX4

What we know from ReDUX4	REACH Phase 3 Trial Design
Losmapimod demonstrated measurable impact on disease progression at 48 weeks of treatment	48-week treatment duration
Reachable Workspace (RWS) is a reliable and quantifiable measure of function and disease progression	RWS is primary endpoint
Muscle Fat Infiltration (MFI) is a sensitive measure of muscle health most susceptible to disease pathology	MFI is secondary endpoint
Patient-reported outcomes are effective measure of disease progression in FSHD	Patient-reported outcomes (PGIC and Neuro-QoL) are secondary endpoints

ReDUX4 Showed Benefits on Endpoints for REACH

Function

Preserved or improved muscle function as measured by **RWS**

Muscle Health

Decreased **MFI** as measured by MRI

Quality of Life

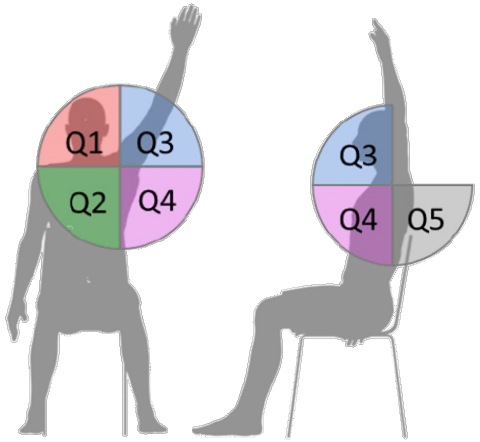
Patients reported feeling better as measured by **PGIC**

Safety and Tolerability

Clinical experience in ~3,600 people

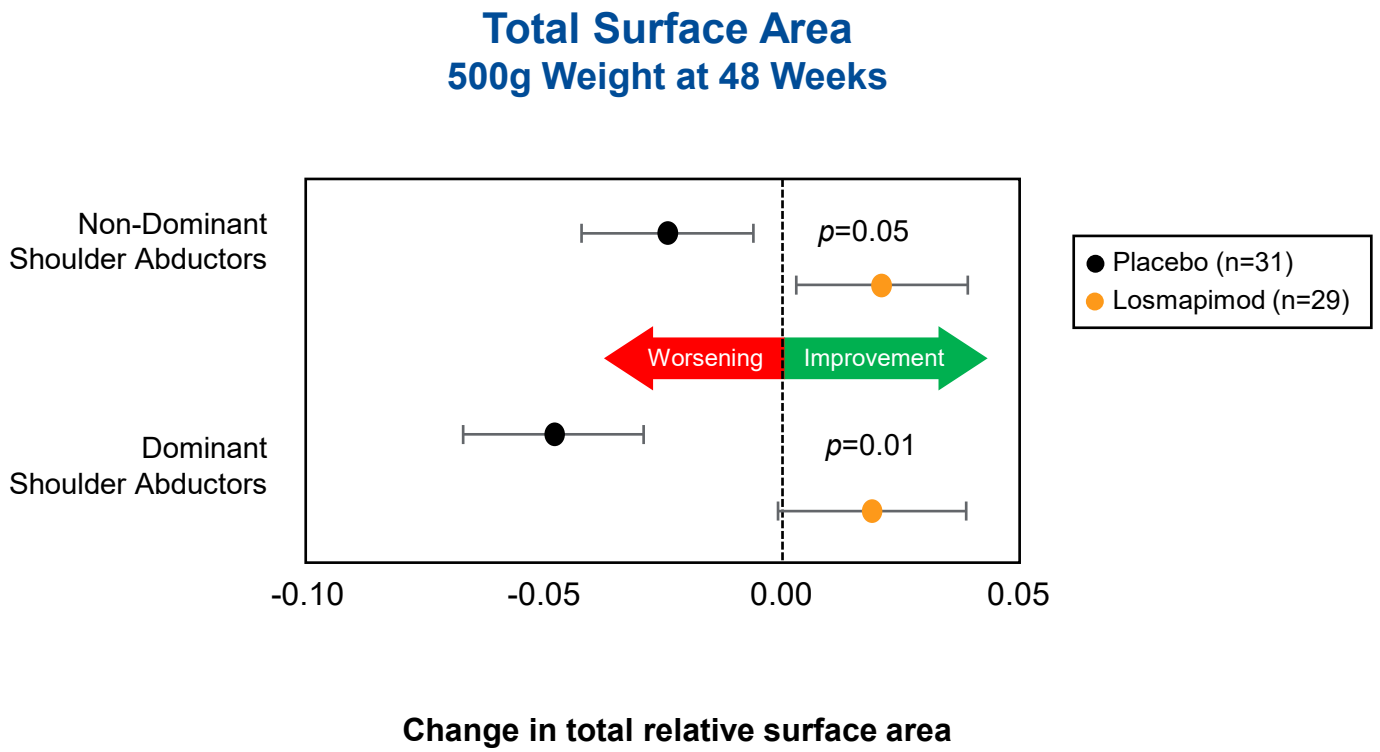
ReDUX4 enrolled 80 people with FSHD in a randomized, double-blind, placebo-controlled Phase 2b trial with a 48-week treatment period

Losmapimod Showed Significant Improvement in RWS



Reachable Workspace (RWS) is:

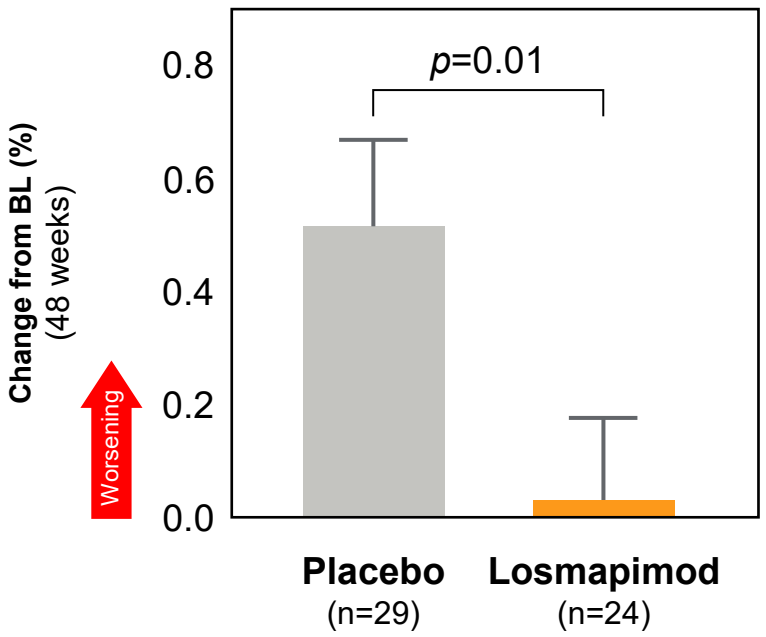
- Quantitative measure of upper extremity range of motion and function
- Objectively measured
- Highly correlated with ability to perform activities of daily living and maintain independence



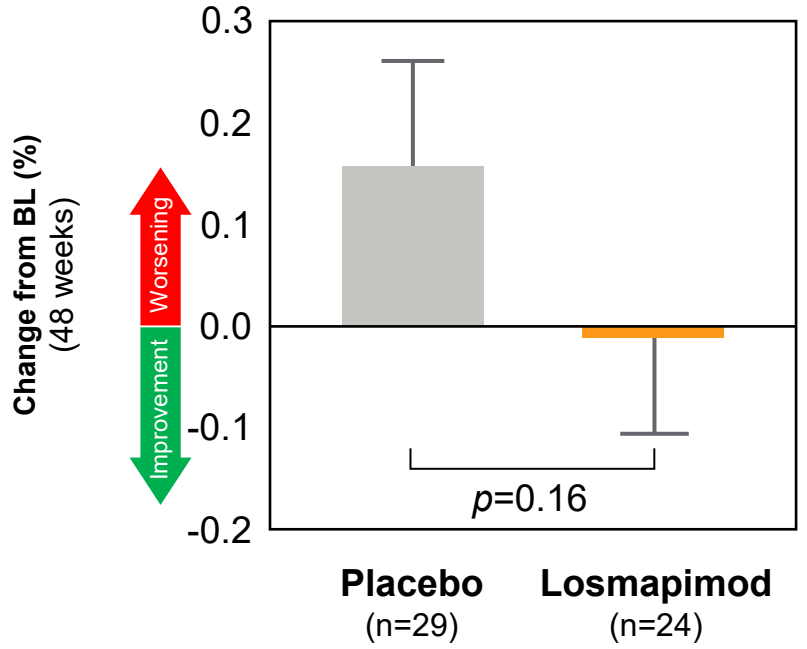
Data from ReDUX4 trial

Losmapimod Decreased Muscle Fat Infiltration

Losmapimod slowed fat infiltration in muscles already affected by disease



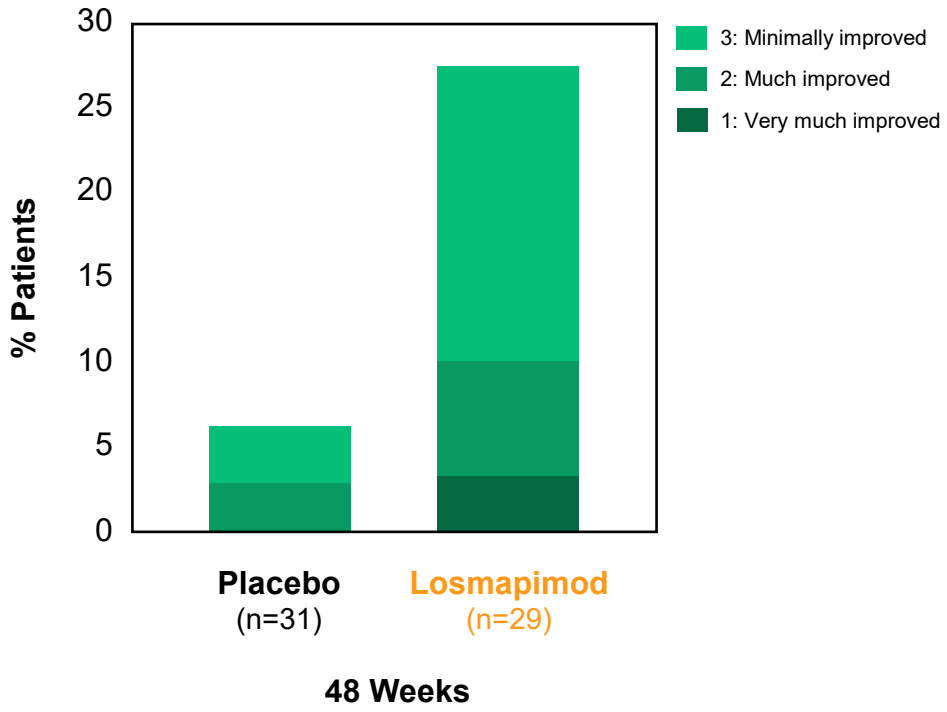
Losmapimod preserved health of normal-appearing muscles



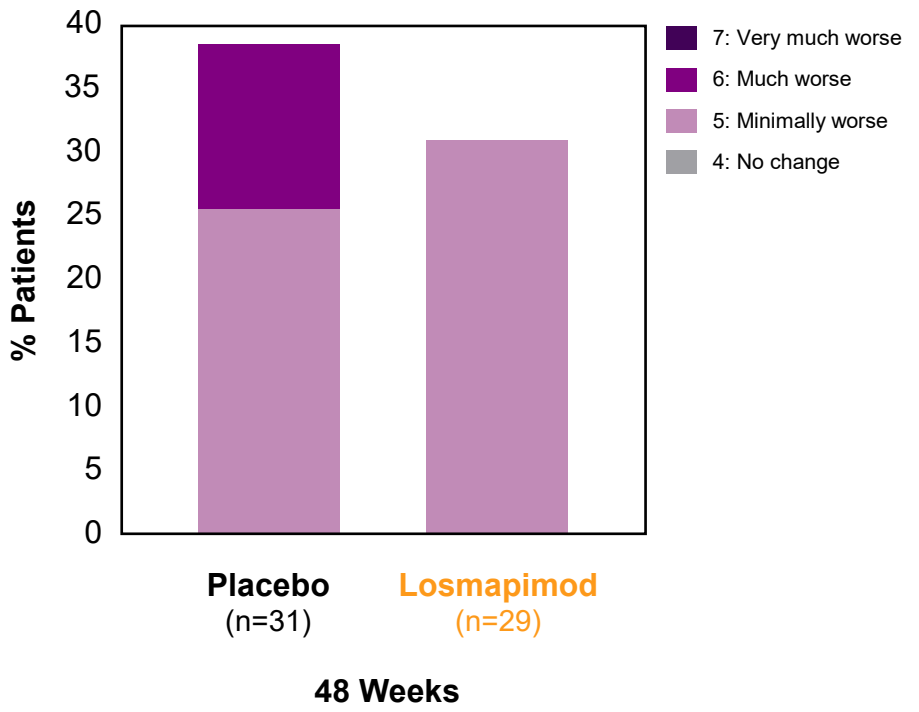
Data from ReDUX4 trial

Losmapimod-treated Patients Reported Feeling Better

Four times as many losmapimod-treated patients felt better vs placebo



20% fewer losmapimod-treated patients felt worse vs placebo



Patients' Global Impression of Change (PGIC)

Data from ReDUX4 trial

Extensive Safety and Tolerability Data

- Majority of treatment-emergent adverse events (TEAEs) were mild or moderate
- No TEAE led to treatment discontinuation or study withdrawal
- No significant changes in vital signs, laboratory studies, or electrocardiogram were observed
- Majority of TEAEs assessed as unlikely related or not related to study drug
- Most common AEs: fall, procedural pain, back pain, and headache
- Majority of AEs resolved with continued dosing
- Observed safety and tolerability data are consistent with prior losmapimod experience in **>3,600** clinical study participants

Losmapimod has been generally well-tolerated with no serious treatment-related adverse events

Data from ReDUX4 trial.

FTX-6058 for Sickle Cell Disease & Other Hemoglobinopathies

Fulcrum Therapeutics

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 block blood vessels or rupture cells

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)

SCT: Stem Cell Transplant; 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 outcomes

P-Selectin Inhibitors

Leukocyte Binding to P-selectin

- \+ Reduces VOCs
- − Does not address broad disease pathology
- − IV administration

BCL11A gene editing

Increasing Fetal Hemoglobin

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

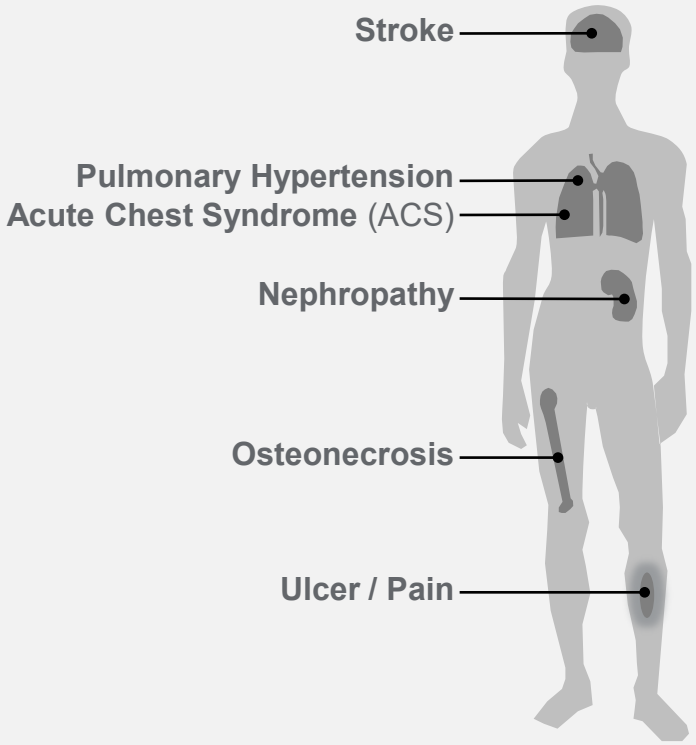
Human Genetics Demonstrate that Only Elevated Fetal Hemoglobin (HbF) Addresses All SCD Symptoms

- HbF is typically silenced at birth and Hemoglobin-Beta gene turns on to produce red blood cells
- Subset of people with SCD have additional mutations that cause a condition known as hereditary persistence of fetal hemoglobin (HPFH)
- In these people, the fetal globin gene stays on and produces elevated levels of HbF, leading to reduced or no symptoms

HbF induction provides a direct path to addressing all aspects of disease symptomatology

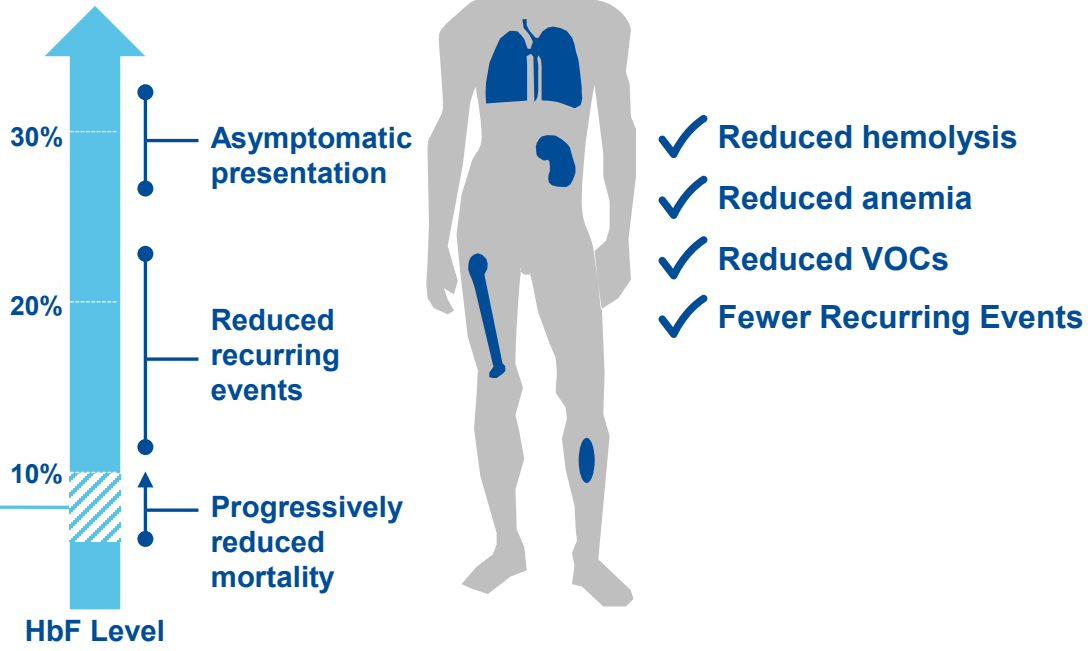
Increasing HbF is Only Mechanism Shown to Broadly Improve Outcomes in SCD

Typical SCD Patient



SCD Patient Baseline HbF 5-10%

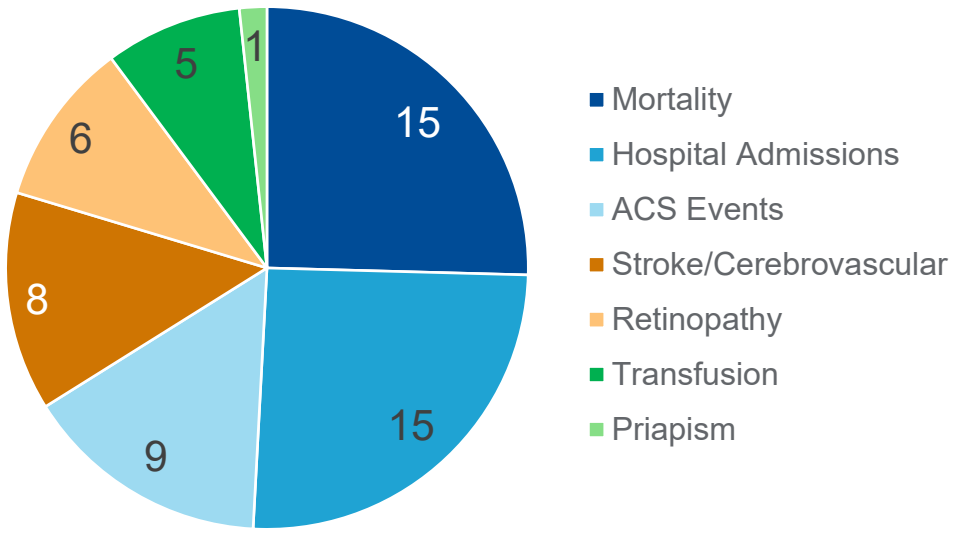
SCD Patient with HPFH



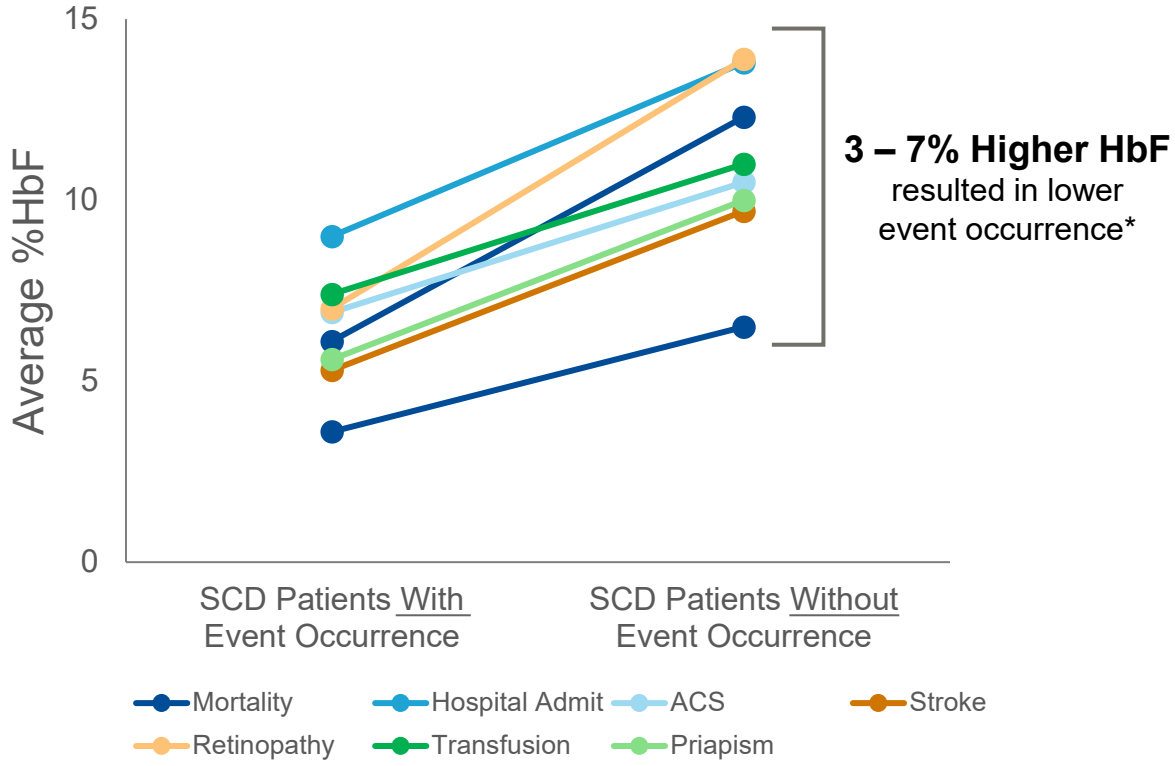
VOCs: Vaso-occlusive crisis; HPFH: Hereditary Persistence of Fetal Hemoglobin; *Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.*

Higher Levels of HbF Protein Provide Broad Clinical Benefit

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



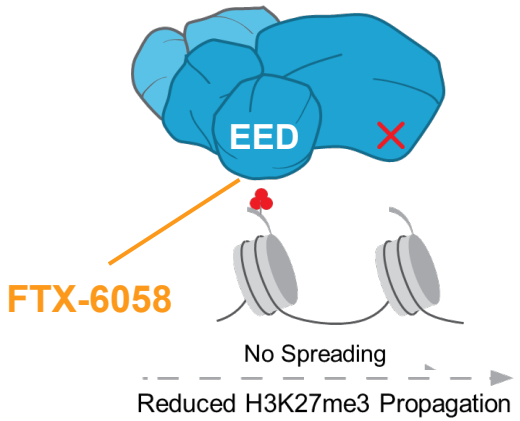
Higher HbF Levels are Associated with Improved Clinical Outcomes



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

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

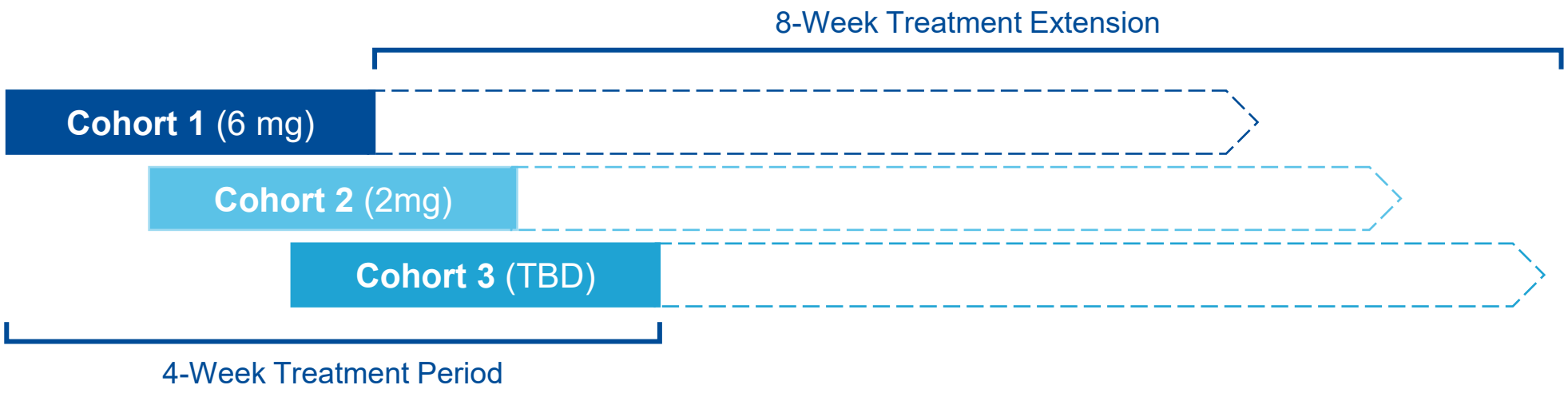
SAE: Serious adverse event; TEAE: Treatment-emergent adverse event; CTCAE: Common criteria for adverse events

Ongoing Phase 1b Clinical Trial in SCD Subjects

Study Population

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

Study Design



Study Endpoints

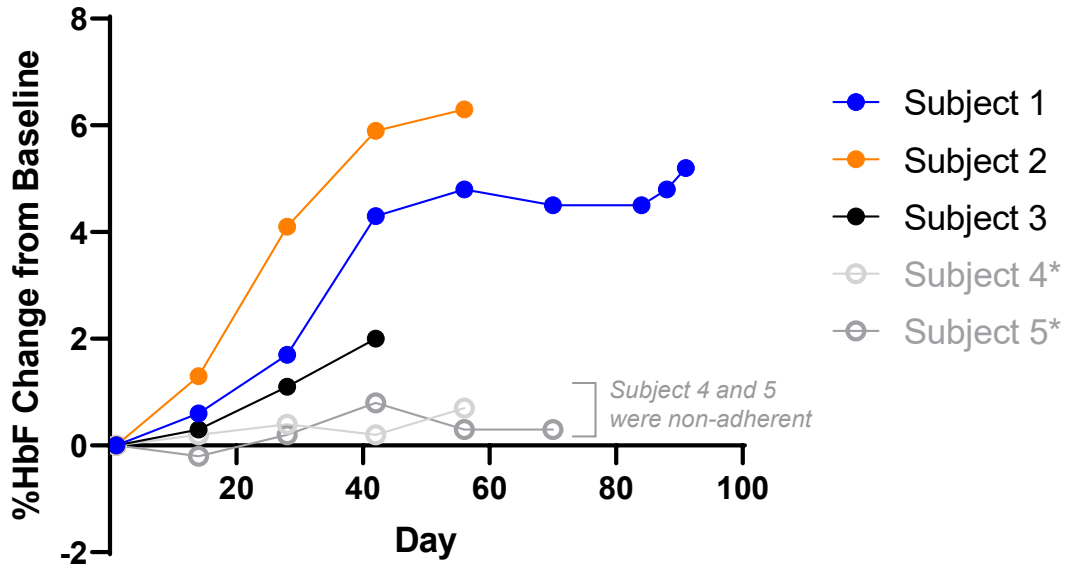
Primary	Secondary	Exploratory
▪ Safety and tolerability ▪ Pharmacokinetic measurements	▪ %HbF protein by HPLC ▪ %F-cells by flow cytometry	▪ Target engagement ▪ Incidence of VOCs ▪ Biomarkers of hemolysis ▪ QOL measures

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

Initial FTX-6058 Data in Subjects with SCD Validates 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**

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



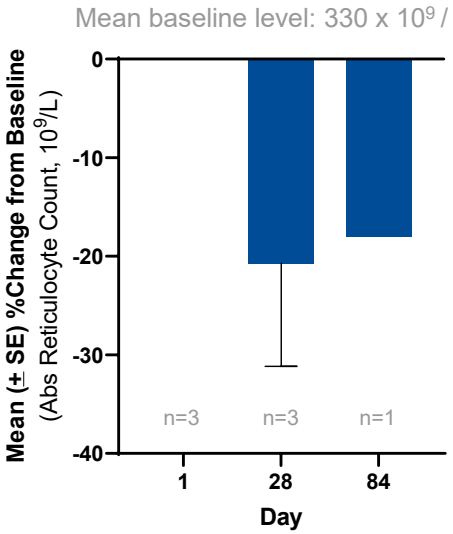
Subject	Baseline %HbF	%HbF at Data Cutoff	Δ%HbF
Subject 1	9.2	14.4	5.2
Subject 2	3.7	10	6.3
Subject 3	6.2	8.3	2.1
Subject 4*	4.8	5.3	0.7
Subject 5*	7.0	7.3	0.3

- 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

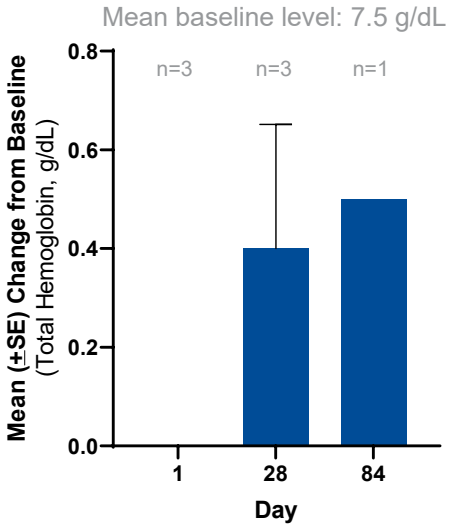
*Data analysis cutoff as of May 25th, 2022; Subject 1 was not dispensed drug after Day 56; Subject 3 withdrew from the study; *Per SAP, Subjects 4 and 5 were determined to be non-adherent based on investigator and patient reporting, and/or pill count; Subject 6 was discontinued due to protocol deviation*

FTX-6058 Decreased Hemolysis

Absolute Reticulocyte Count

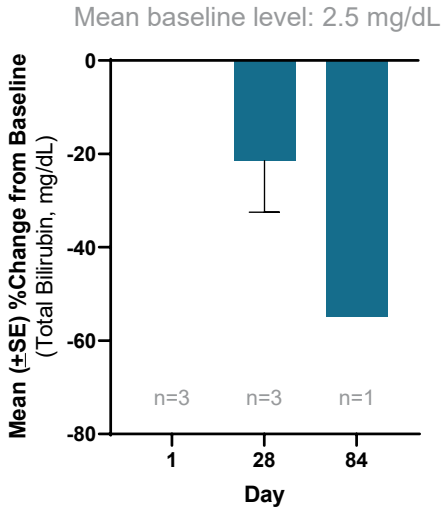


Total Hemoglobin



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

Total Bilirubin



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

Our Mission and Our Purpose

Fulcrum Therapeutics