Fulcrum Therapeutics

Nasdaq FULC

March 2023

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Unlocking the Power of Small Molecules to Change the Course of Genetically Defined Rare Diseases

Diversified biotech developing oral small molecules designed to modify gene expression: **Two wholly owned programs in clinical development**

Losmapimod: **first-to-market** potential in facioscapulohumeral muscular dystrophy (FSHD); granted **Fast Track and Orphan Designations**

FTX-6058: potential **best-in class** oral small molecule HbF inducer for sickle cell disease (SCD); granted **Fast Track and Orphan Pediatric Designations**

Discovery engine validated by two clinical programs.

Strong cash position with **runway through mid-2025**

Founded in 2015

IPO in 2019

Ticker: FULC

U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023

Pipeline and Catalysts

Indication	Asset / Partner	Preclinical	Phase 1	Phase 2	Phase 3	2023 Catalysts
Wholly Owned Clinical Programs						
FSHD	Losmapimod (Oral DUX4 Reducer)					Complete enrollment in 2H'23
SCD	FTX-6058 (Oral HbF Inducer)					
Wholly Owned Discovery Programs						
Blood Disorder						
Neurologic Disorder						
Muscle Disorder						
Collaborations						
Cardiomyopathies	Bristol Myers Squibb™					

MoA: mode of action; U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023

LOSMAPIMOD

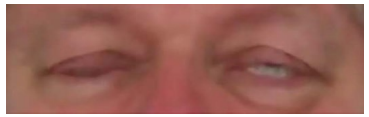
for Facioscapulohumeral Muscular Dystrophy (FSHD)

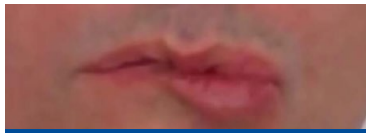
Fast Track Designation

Orphan Drug Designation

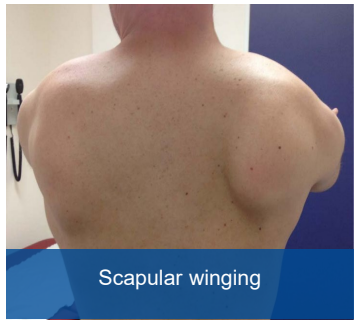
Fulcrum Therapeutics

About FSHD: Debilitating Disease With No Approved Therapies

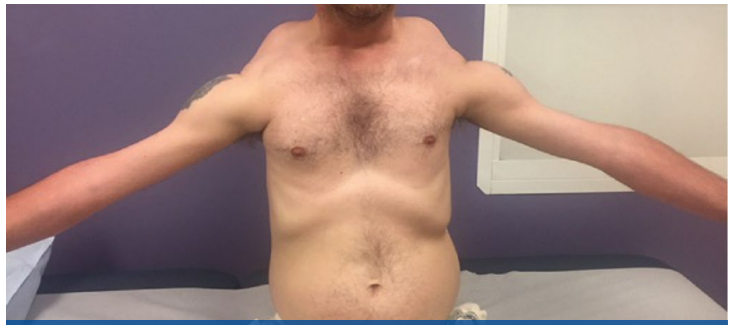




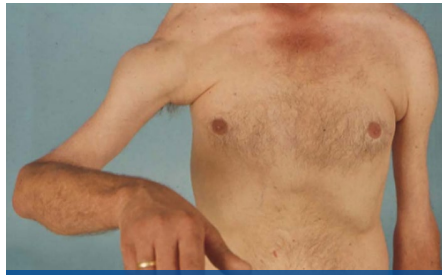
Facial weakness



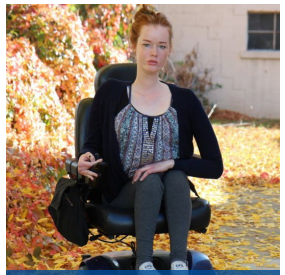
Scapular winging



Impaired ability to raise arms caused by scapular elevation



Wasting of muscles in chest, shoulders, and upper arms; Protuberant abdomen



Wheelchair dependence

- Chronic, progressive genetic muscular disorder characterized by significant muscle cell death and fat infiltration into muscle tissue
- Second most common adult muscular dystrophy affecting approximately 30,000 individuals in the US*
- Significant impairment of upper extremity function and mobility
- Approximately 20% of affected individuals become wheelchair-bound
- Many patients unable to work or live independently

Implementing innovative clinical outcome measures and metrics is necessary to quantify disease progression

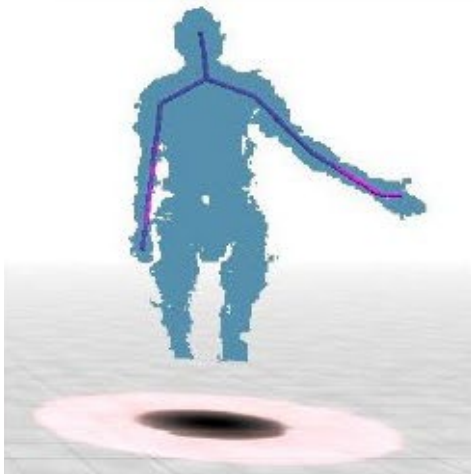
- Reachable workspace (RWS): Measure of disease progression
- Muscle fat infiltration (MFI): Measure of muscle health

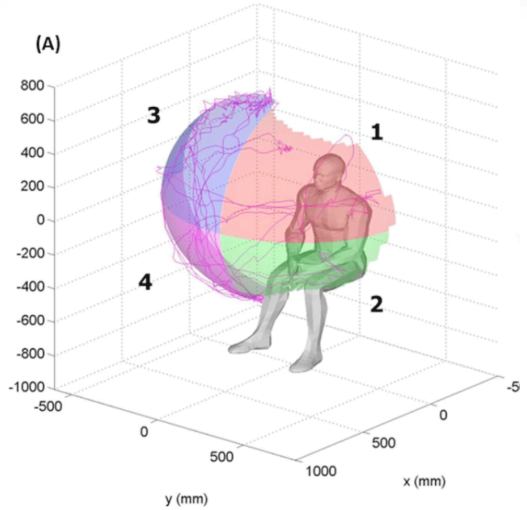
Hamel and Tawil, Neurologic Clinics, 2020; Himeda and Jones, Annual Review of Genomics and Human Genetics, 2019
*Calculated based on prevalence rate 1:8,000 – 1:20,000 in Jia et al, 2021, Neuromuscular Disorders; assuming 333 million US population

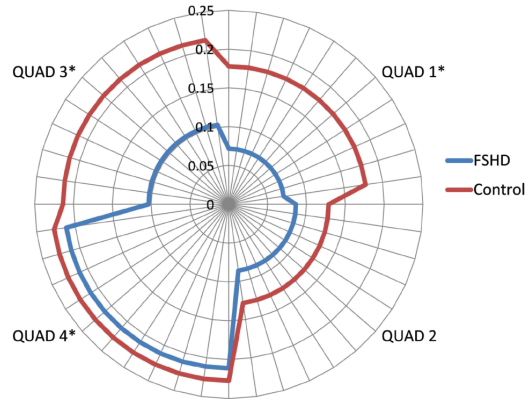
Reachable Workspace Enables Quantification of Disease Progression

- Quantitative and sensitive to disease progression
- Contactless sensor-based system with analysis and visualization software to quantify upper limb motion
- Demonstrated sensitivity to change in FSHD and in Duchenne/Becker muscular dystrophy
- RWS is correlated with abilities to perform activities of daily living (eating, self-care)

Arm movement protocol → Kinect sensor detected arm motion → RWS measures global upper extremity function → Absolute surface area measured with RWS





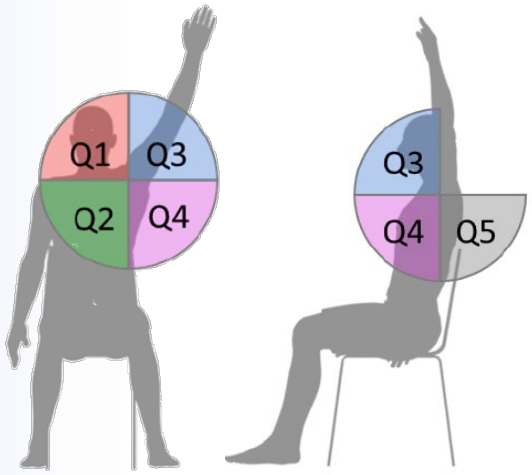


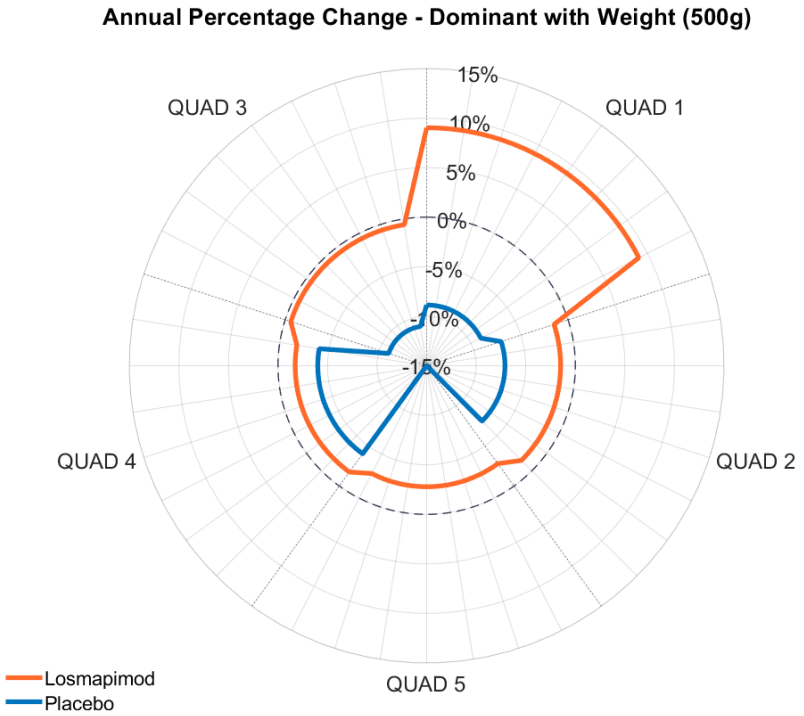
RWS: Reachable workspace. Kurillo et al, Technol Health Care, 2013; Han et al, Muscle Nerve, 2014; Han et al, Muscle Nerve, 2015; AAN 2022 Annual Meeting abstract

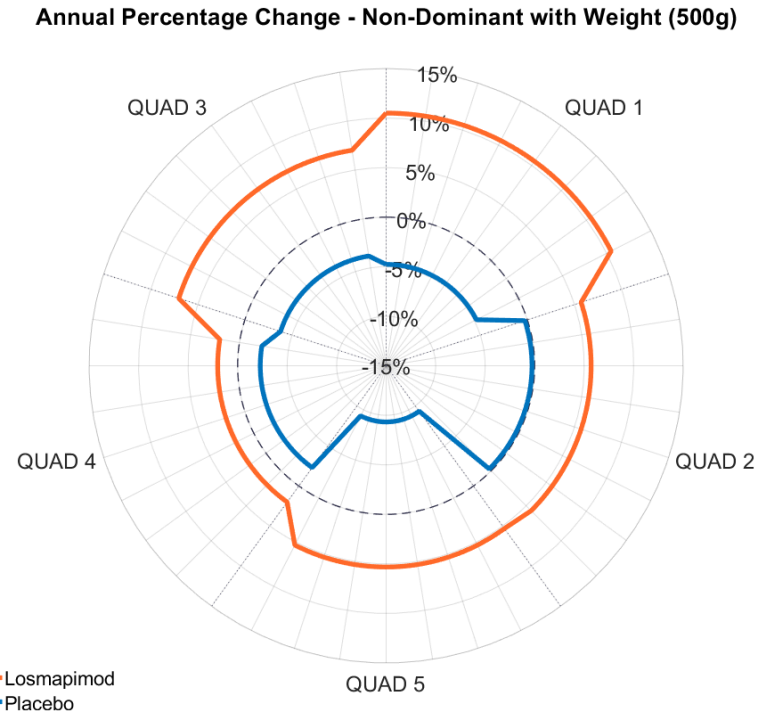
Function

Patients Treated with Losmapimod Experienced Numerical Benefit Over Placebo Across All Quintants*

- Losmapimod patients lost no more than 5% of weighted RWS in any direction, and in many cases experienced improvement
  - Numerical benefit versus placebo was observed in both dominant and non-dominant arms



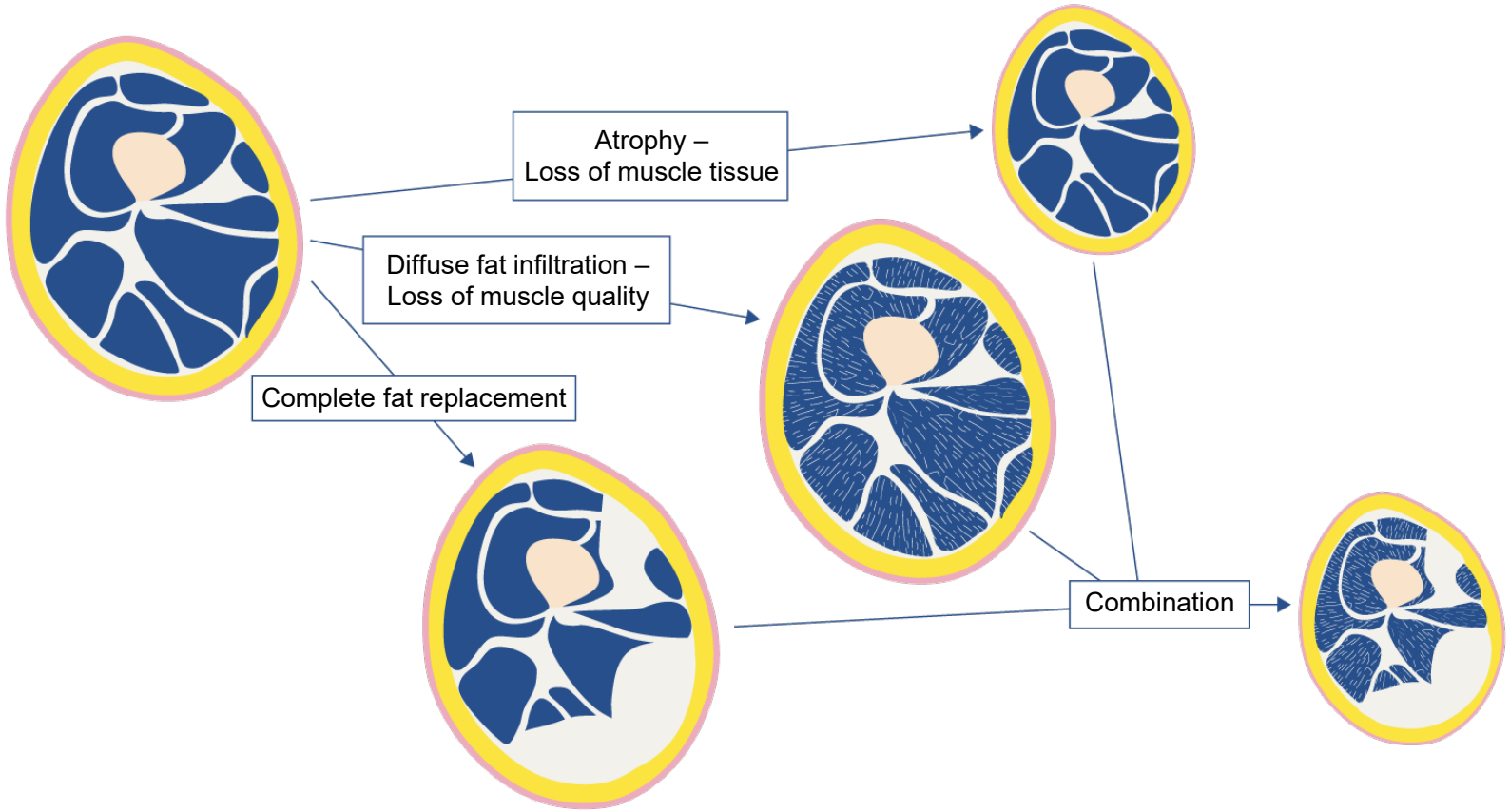




*Study not powered to detect differences between losmapimod and placebo groups for individual quintants

Muscle Fat Infiltration Measures Muscle Health

FSHD progression affects muscles in multiple ways



MFI evaluated by whole-body musculoskeletal MRI and composite assessments

Whole-muscle MRI captures intra- and intermuscular heterogeneity

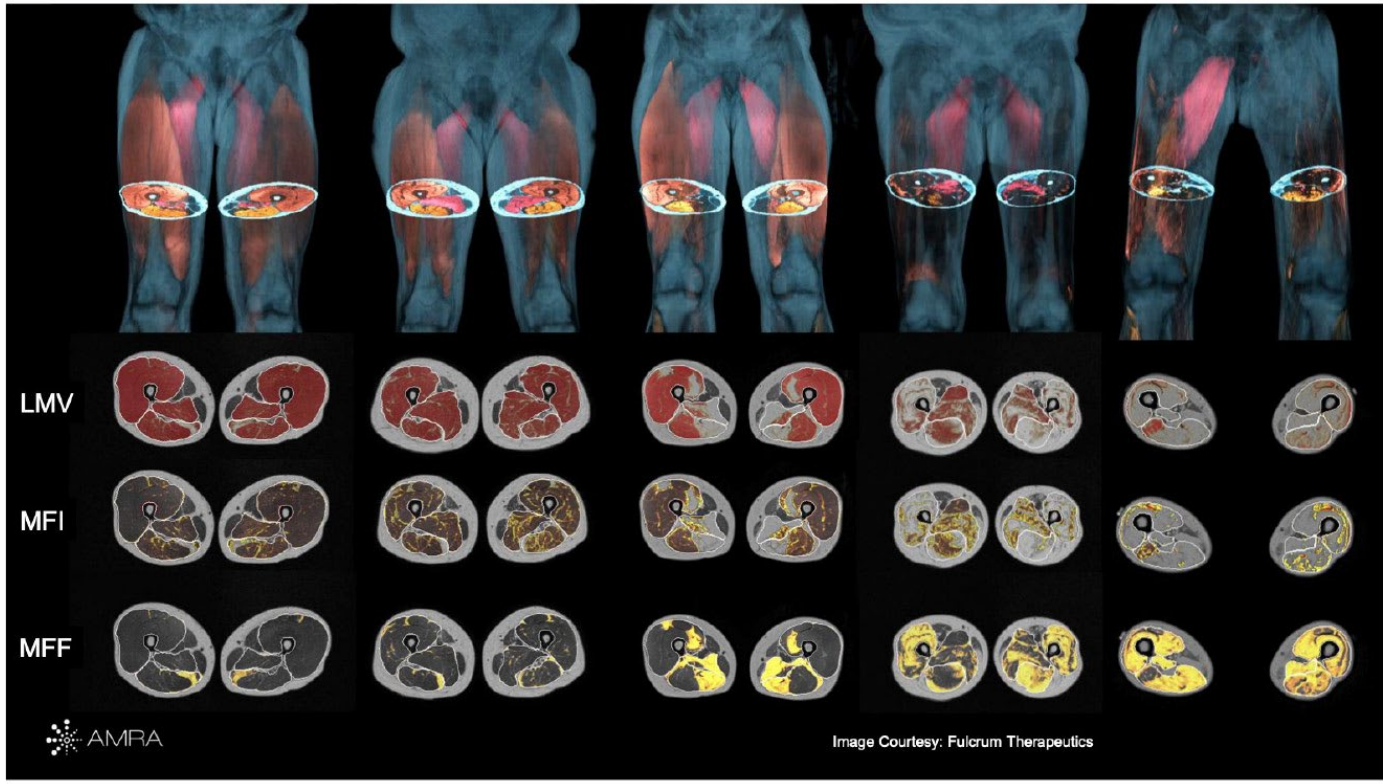
Allows for both holistic and quantitative assessment of muscle health

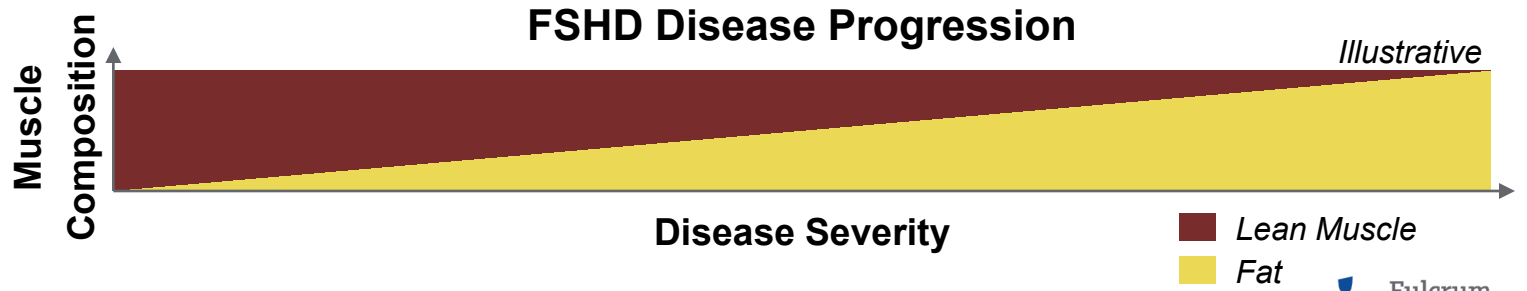
Fulcrum presentation in collaboration with AMRA Medical:1821-FSH-301 IM NA 05-06 May 2022; MFI: muscle fat infiltration

MRI-derived Muscle Categorization Enables Assessment of Muscle Health

108 Individual muscle

measurements are collated into composite scores





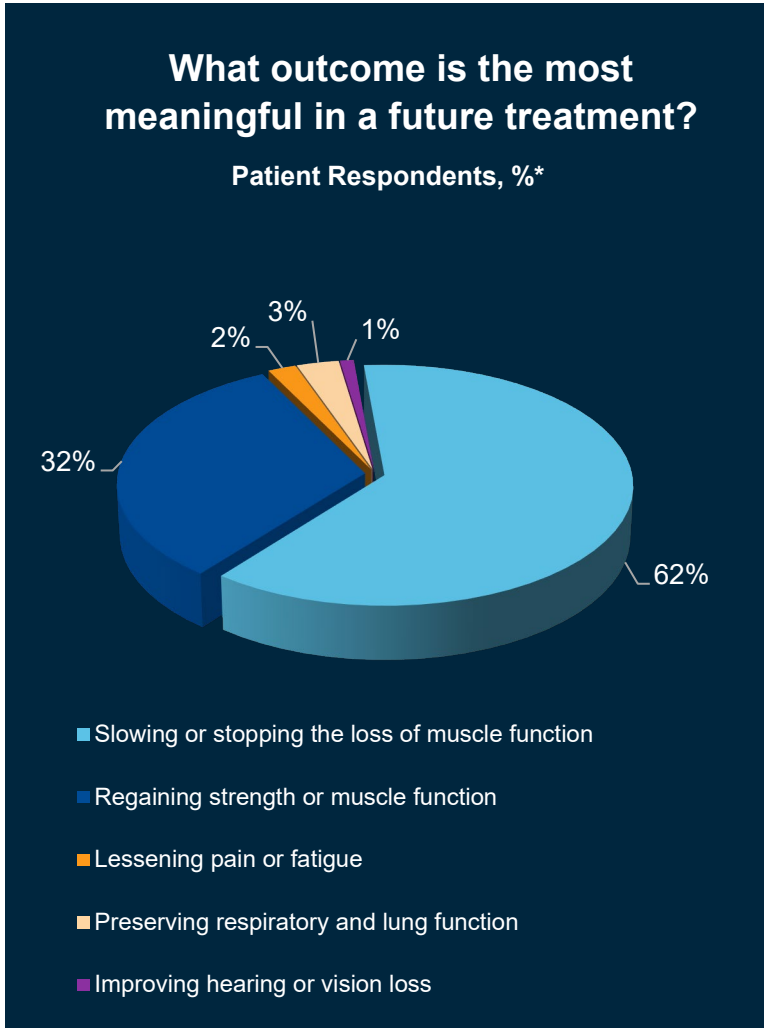
Fulcrum presentation in collaboration with AMRA Medical:1821-FSH-301 IM NA 05-06 May 2022
MRI: magnetic resonance imaging; LMV: Lean muscle volume; MFI: muscle fat infiltration: MFF: Muscle fat fraction

Unmet Need for Safe and Effective Drug That Slows Disease Progression

*"I would like to see something that would **stop progression** of the disease"*
– 26-year-old woman with FSHD

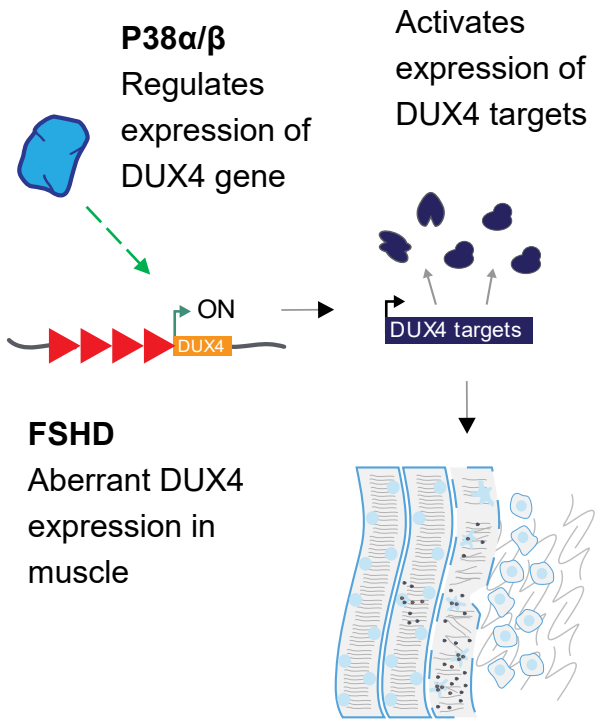
*"…if we had a therapy that at minimum **slowed the progression…** we would be able to guide and plan for what her future looks like."*
– Mother of young girl with FSHD

*"losing my **independence** is probably the most frightening and helpless feeling I have ever had" –*
50-year-old man with FSHD



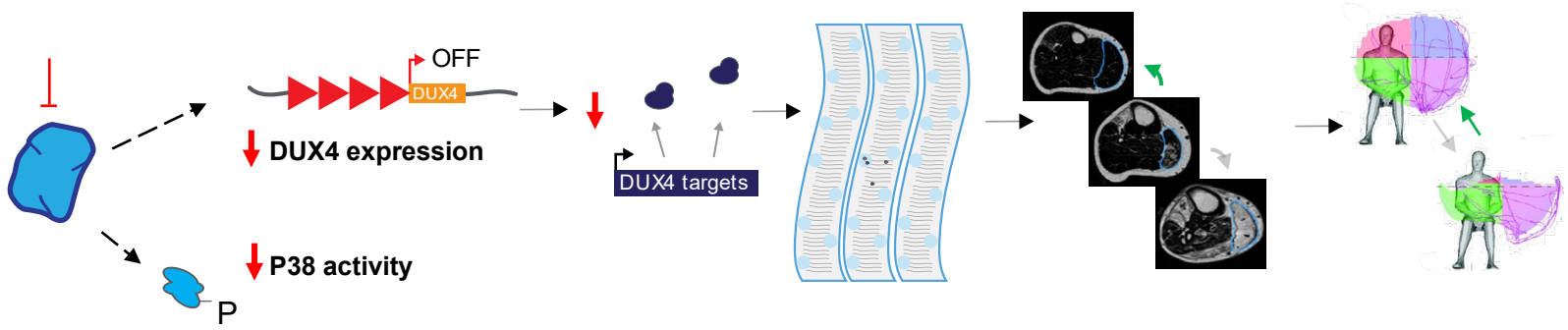
Arjomand J, et al. Facioscapulohumeral muscular dystrophy (FSHD) voice of the patient report. Published November 5, 2020. Accessed March 1, 2021
* Short of a cure, what outcome is the most meaningful to you in a future treatment? % of patient respondents for each answer choice.

Losmapimod Inhibits DUX4 Driven Gene Expression and Muscle Cell Death



Aberrant DUX4 expression and activity causes muscle cell death and fat infiltration

p38α/β inhibition reduces DUX4 expression



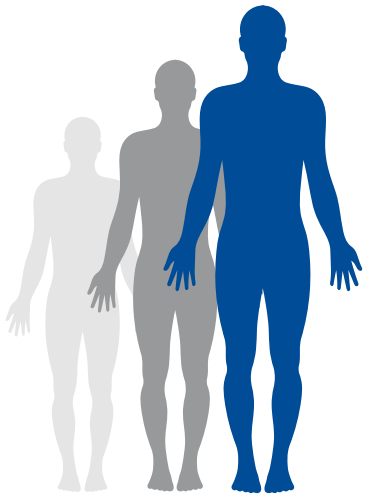
Reduction of DUX4 expression and activity results in slowing of fiber loss and downstream fatty replacement thus preventing muscle damage and loss of function

ReDUX4: Phase 2 Trial Design

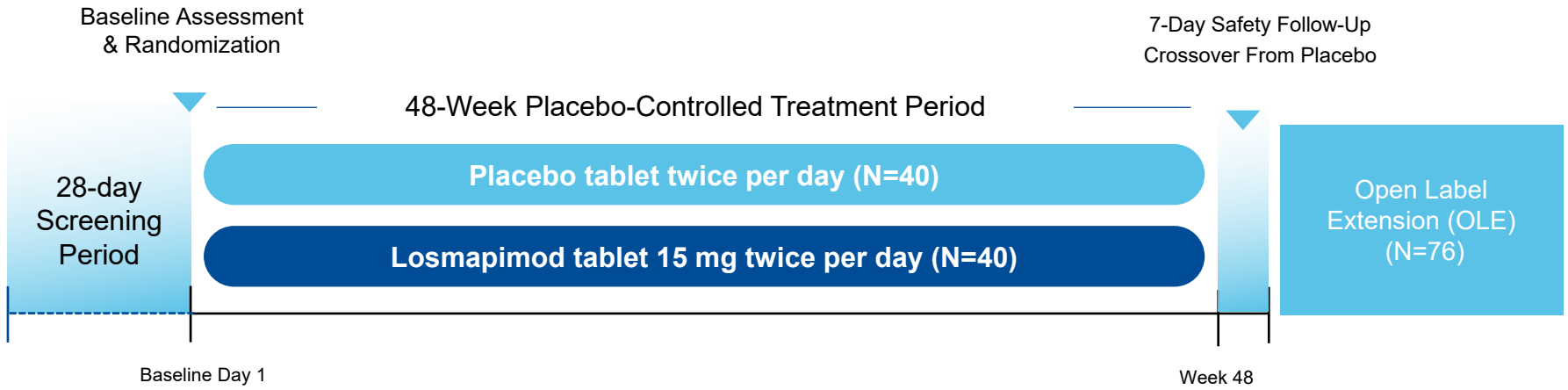
Study Population

ReDUX4:
~80 subjects, 18-65 years old

ReDUX4 OLE:
95% of participants continued



Study Design



Study Endpoints

Primary Endpoint

Change from baseline in DUX4 activity (muscle needle biopsy)

Selected Secondary/Exploratory Endpoints

- Reachable Workspace (RWS)
- MRI Endpoints (MFI, MFF and LMV)
- Patients' Global Impression of Change (PGIC)
- Safety and tolerability

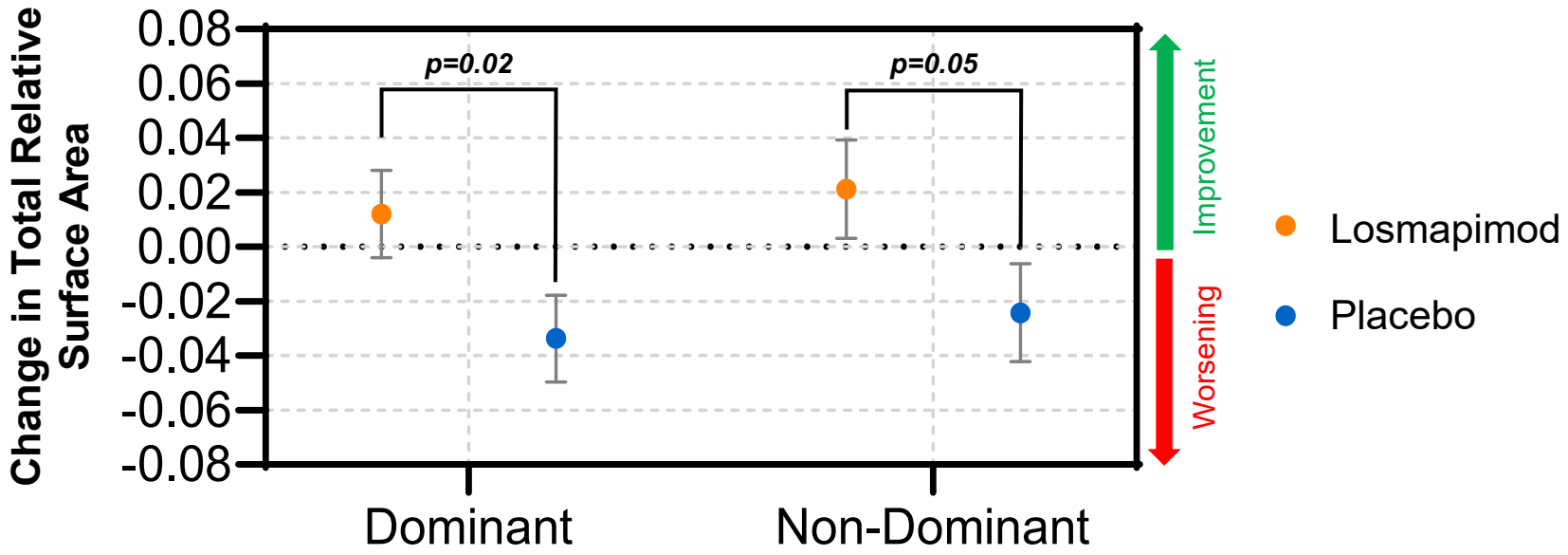
MFI: muscle fat infiltration; MFF: muscle fat fraction; LMV: lean muscle volume. Failed to meet primary endpoint of change in DUX4

ReDUX4 Showed Clinical Benefits at Week 48

RWS: reachable workspace; MFI: muscle fat infiltration; PGIC: patients' global impression of change

Losmapimod Demonstrated Significant Improvement in Reachable Workspace Relative to Placebo at 48 Weeks

RWS Using 500 g Weight at 48 Weeks



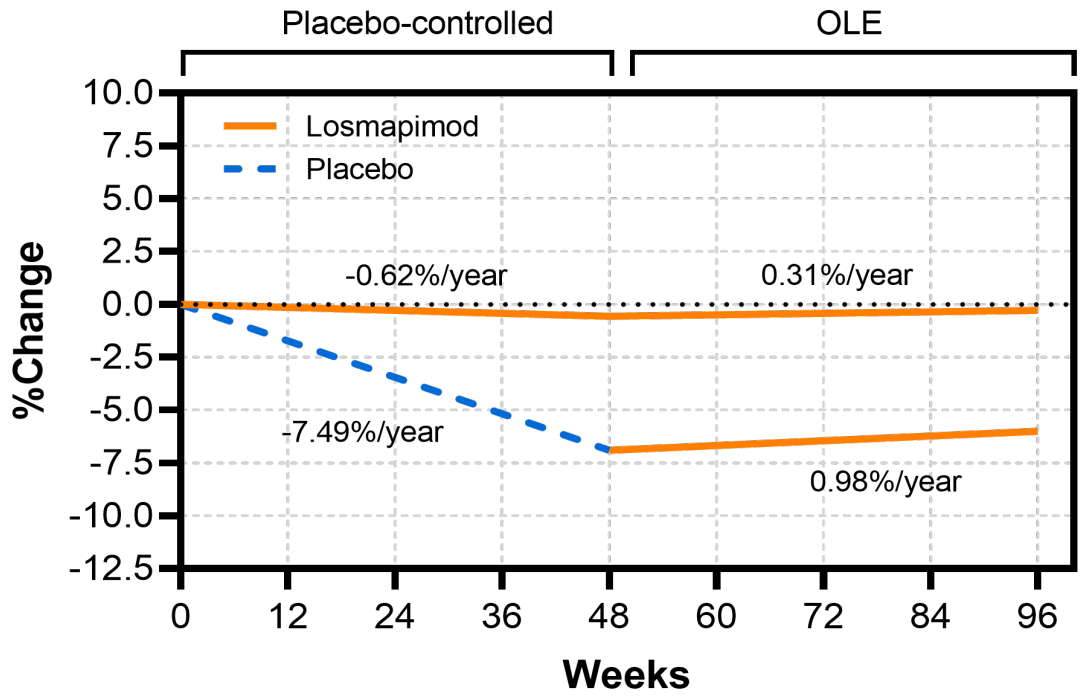
Data from ReDUX4 trial

RWS: Reachable workspace

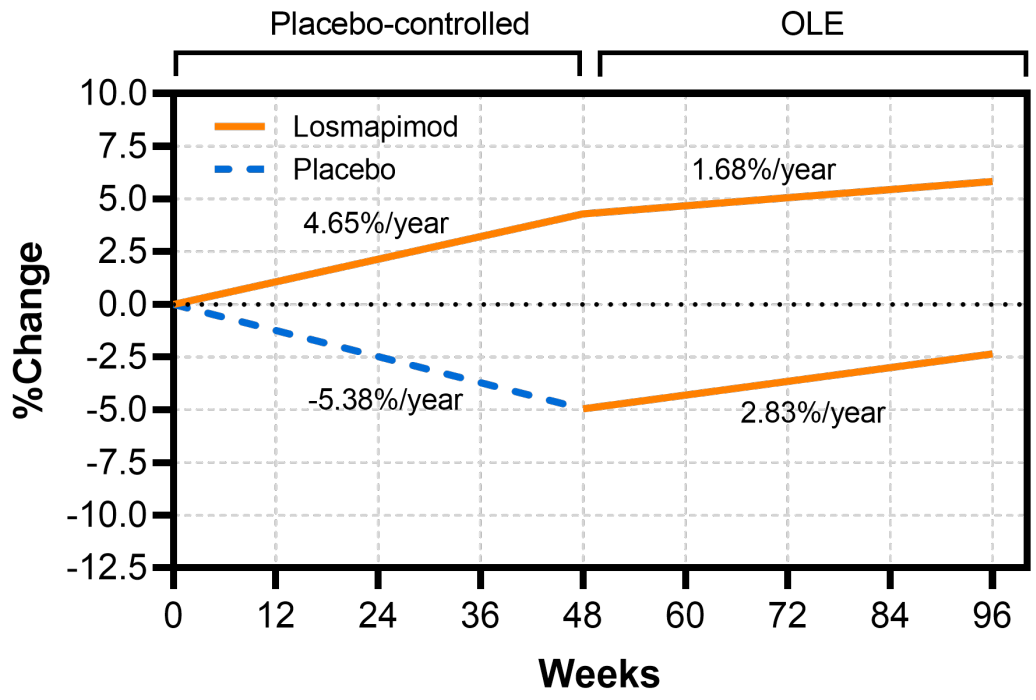
Open Label Extension Demonstrated Maintenance of Treatment Effect

96-week OLE results demonstrate durability of effect in treatment arm and stabilization in cross-over arm

Dominant Arm Total RSA+ Weight



Non-Dominant Arm Total RSA+ Weight

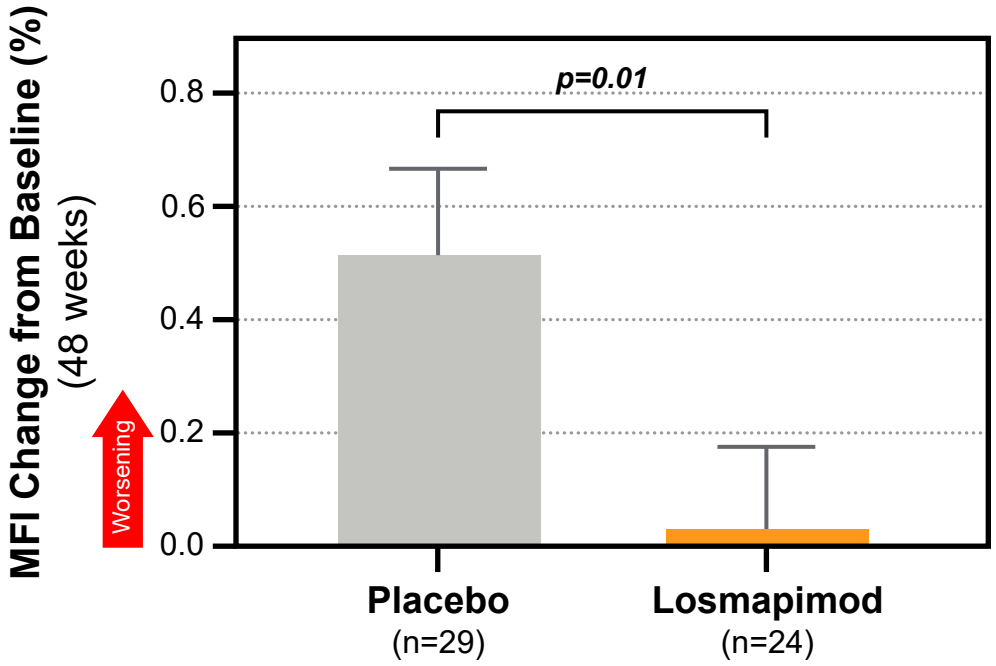


Data from ReDUX4 trial and the ReDUX4 OLE trial

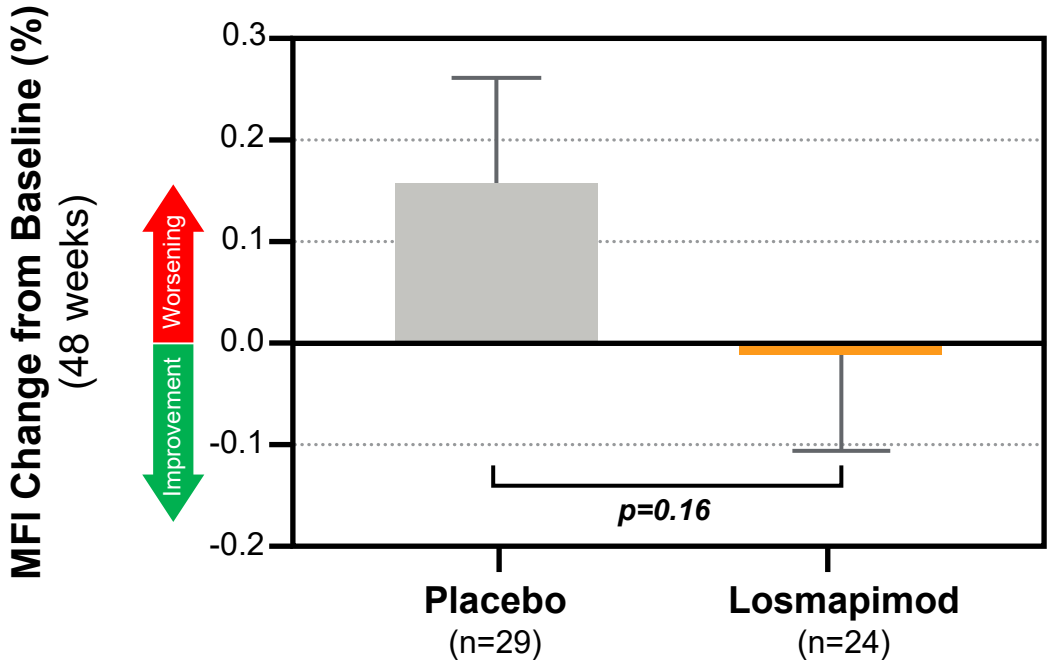
RSA: relative surface area; OLE: open label extension; PBO: placebo; LOS: losmapimod

Losmapimod Improved or Maintained Muscle Health at 48 Weeks

Losmapimod slowed fat infiltration in muscles already affected by disease



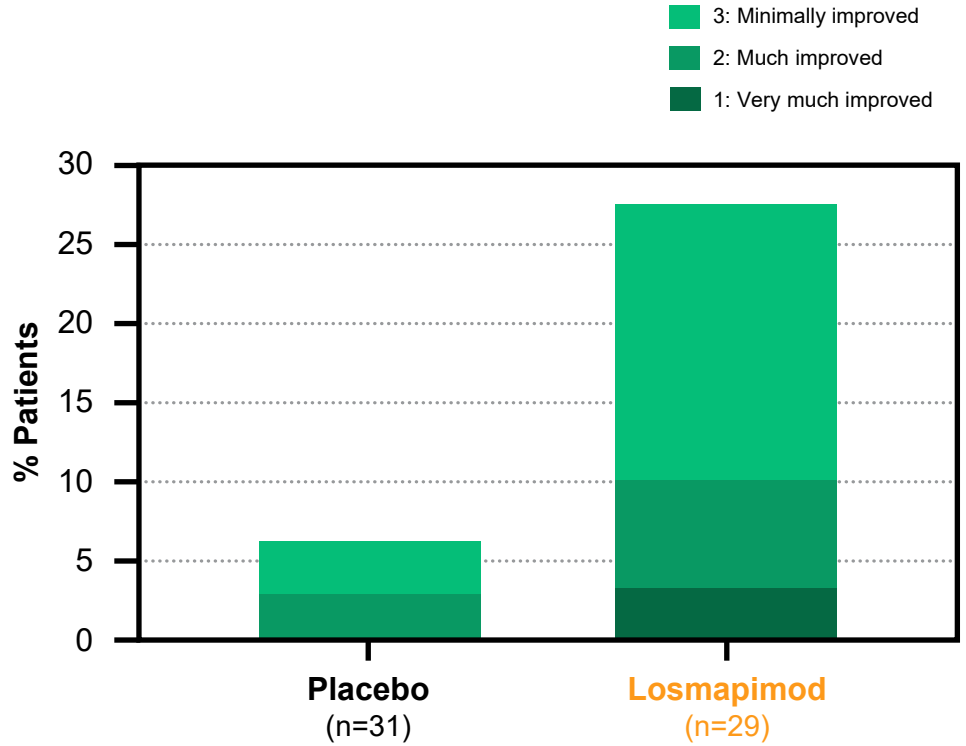
Losmapimod preserved health of normal-appearing muscles, limiting fat infiltration



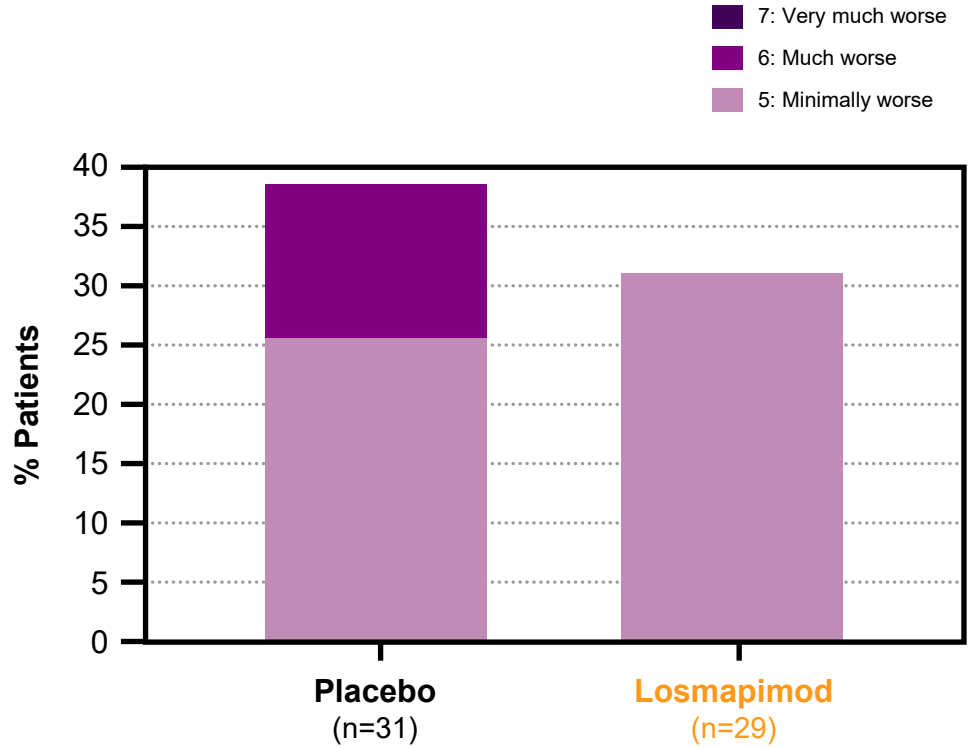
Data from ReDUX4 trial
MFI: muscle fat infiltration

Losmapimod-treated Patients Reported Feeling Better at 48 Weeks

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

Losmapimod Was Generally Well-tolerated with No Serious Treatment-related Adverse Events

01 Majority of treatment-emergent adverse events (TEAEs) were mild or moderate

02 No TEAE led to treatment discontinuation or study withdrawal

03 No significant changes in vital signs, laboratory studies, or electrocardiogram were observed

04 Majority of TEAEs assessed as unlikely related or not related to study drug

05 Most common AEs: fall, procedural pain, back pain, and headache

06 Majority of AEs resolved with continued dosing

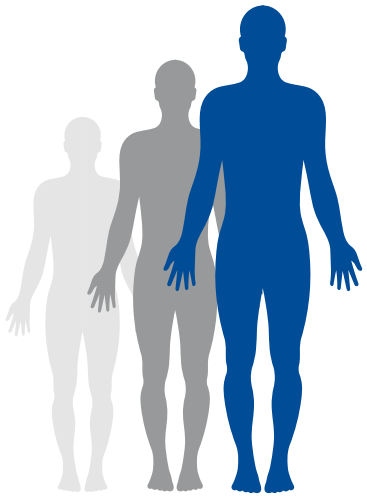
07 Observed safety and tolerability data are consistent with prior losmapimod experience in **>3,600** clinical study participants

Data from ReDUX4 trial.

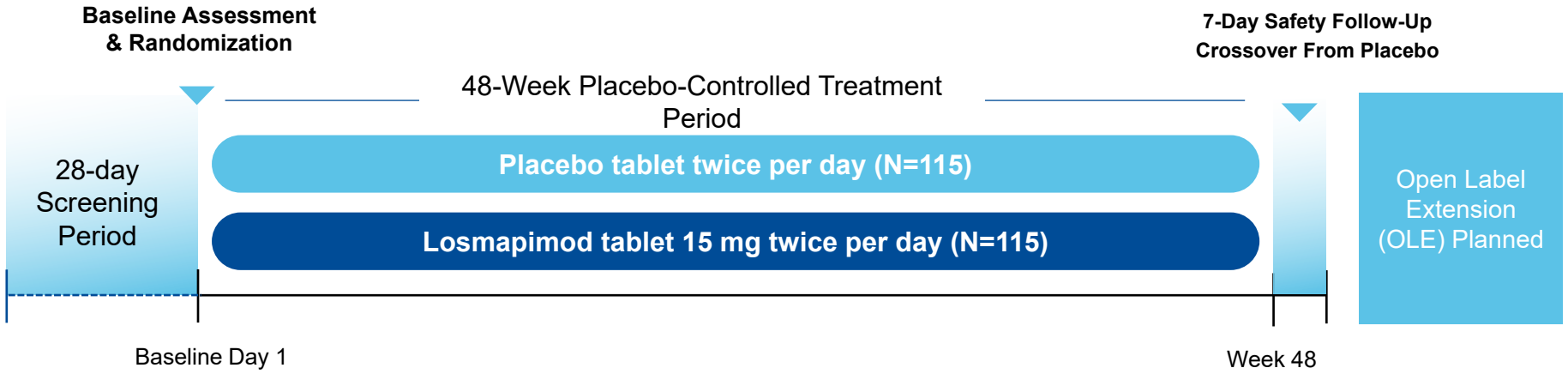
REACH: Global Phase 3 Trial of Losmapimod in FSHD

Study Population

Enrollment ongoing:
~230 participants, 18-65 years old



Study Design



Study Endpoints

Primary

RWS quantification of total relative surface area with 500g wrist weight in dominant arm

Secondary

- MFI
- Neuro-QoL Upper Extremity
- PGIC
- Safety and tolerability

Selected Exploratory

- Healthcare utilization questionnaire
- EQ-5D questionnaire

RWS: reachable workspace; MFI: muscle fat infiltration; PGIC: patients' global impression of change

Losmapimod: First-to-Market Potential in FSHD

No approved therapy for FSHD patients

- Second most common adult muscular dystrophy
- Affects approximately 30,000 people in the US

First-to-market potential

- Oral small molecule to reduce DUX4 gene expression
- Positioned to become first-to-market therapeutic for untreated patient population

Disease modifying potential

- Potential patient benefit in measures of function and patient reported outcomes
- Potential to preserve muscle health
- Favorable safety profile in over 3,600 patients across multiple studies

Development path forward

- Phase 3 registrational REACH trial ongoing
- FDA Fast Track and Orphan Drug designations
- Method of use patent into 2038

Hamel and Tawil, Neurologic Clinics, 2020

FTX-6058

for Sickle Cell Disease

Fast Track Designation

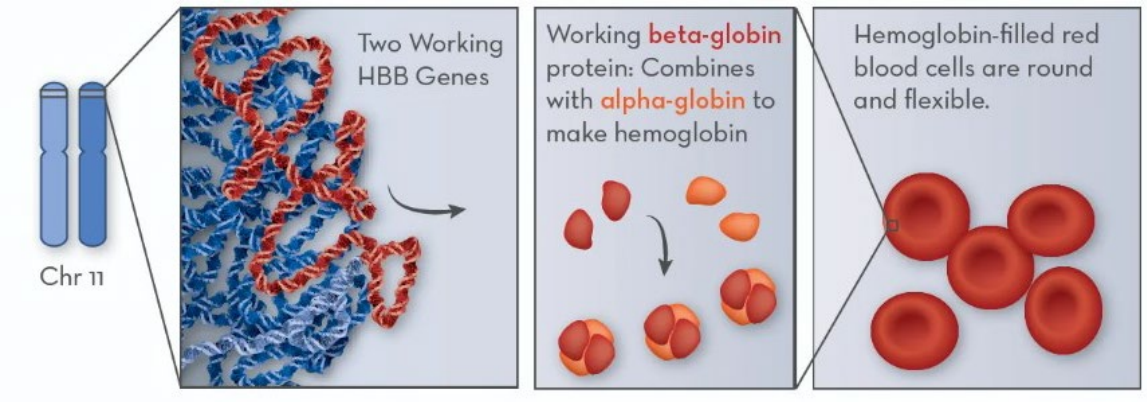
Orphan Pediatric Designation

Fulcrum Therapeutics

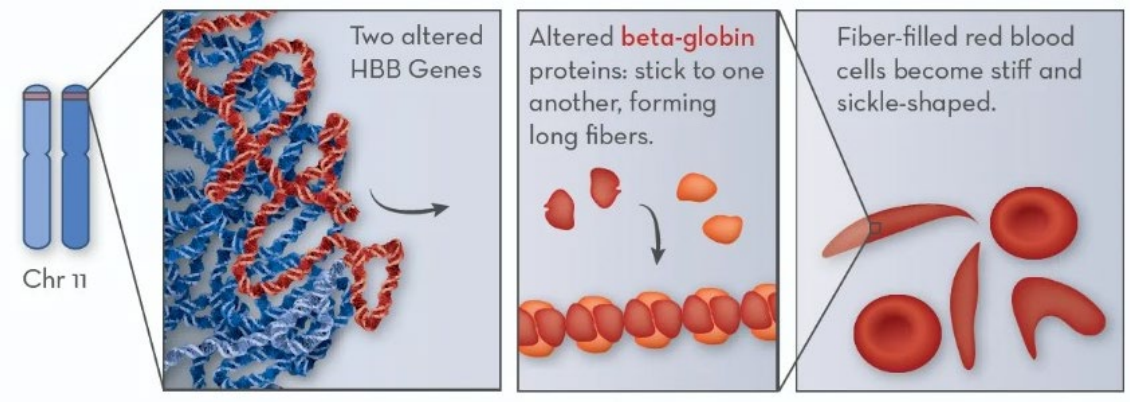
About Sickle Cell Disease

- Genetic disorder caused by mutation in the hemoglobin-beta (HBB) gene
- Mutation results in abnormal sickle-shaped red blood cells (RBC)
- Debilitating symptoms:
  - Vaso-occlusive crises (VOCs)
  - Other complications including stroke, neuropathy, and acute chest syndrome (ACS)
  - Anemia/hemolysis
  - Morbidity and mortality
- US prevalence estimated at ~100,000

Healthy Person



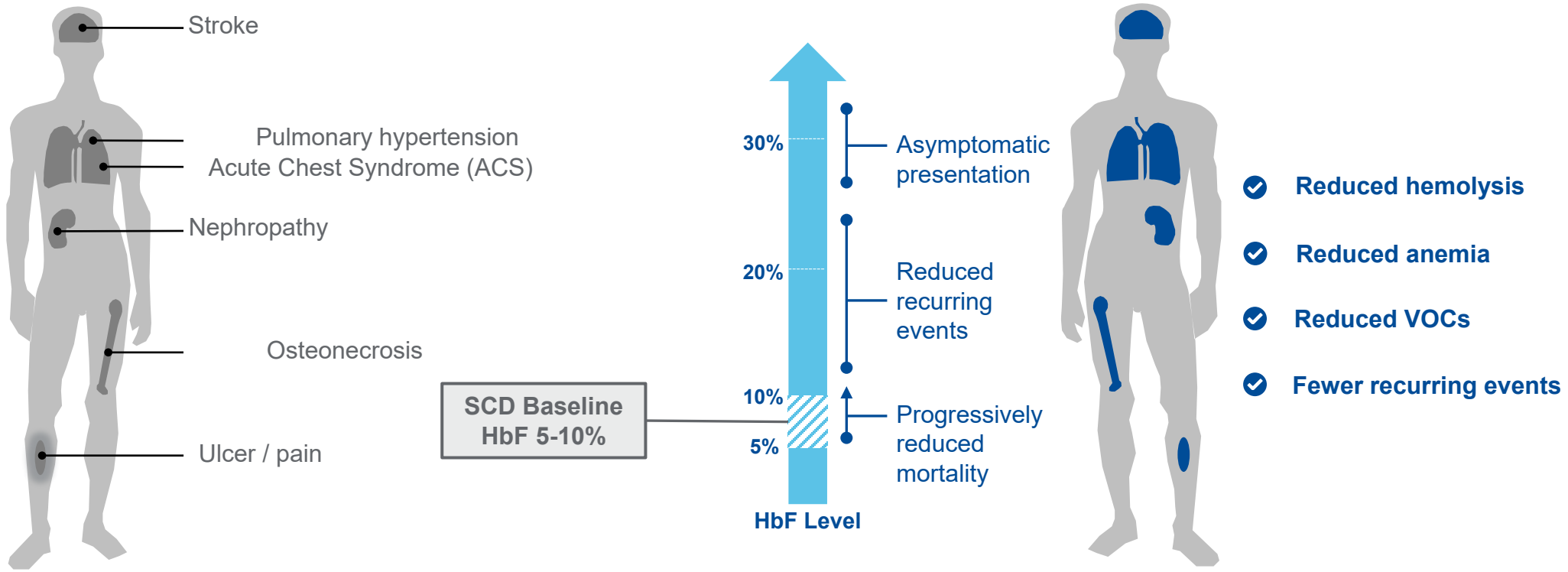
Person with Sickle Cell Disease



Sedrak and Kondamudi, StatPearls, last update August 29, 2022. Learn.Genetics, Hemoglobin Disorders: https://learn.genetics.utah.edu/content/genetics/hemoglobin, retrieved 12/24/2022

Higher HbF Levels Result in Reduced Symptomology in People Living with Sickle Cell Disease

Even incremental increases in HbF can lead to meaningful improvement in disease severity



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

FTX-6058: Potential Best-in-Class Therapeutic Profile

HbF Induction → **Physiologic Disease Modification**

Hydroxyurea, Gene Editing, FTX-6058

HbS Polymerization Inhibition

P-selectin Inhibition

Anemia Amelioration

Improved Disease Symptoms

FTX-6058: Best-in-Class Profile

Raises HbF level

Potential to ameliorate disease pathology

Convenient oral dosing

Potential to differentiate on safety and tolerability

HbF: fetal hemoglobin; HbS: sickle hemoglobin

FTX-6058

for Sickle Cell Disease

Preclinical and healthy volunteer data

Fulcrum Therapeutics

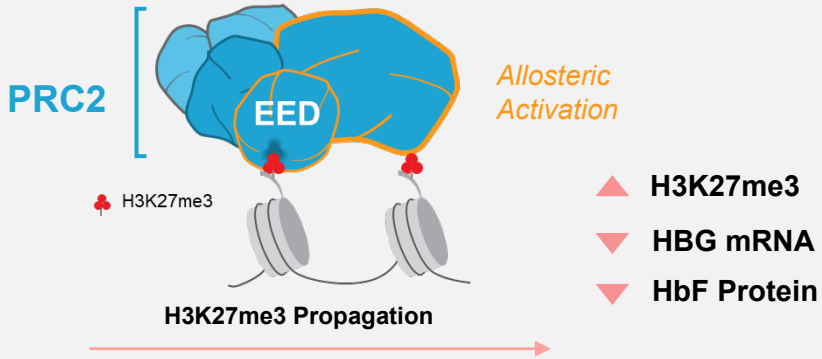
Targeting EED Results in HbF Increases

CRISPR + Compound Screening Engine
Experimentally screened candidate targets

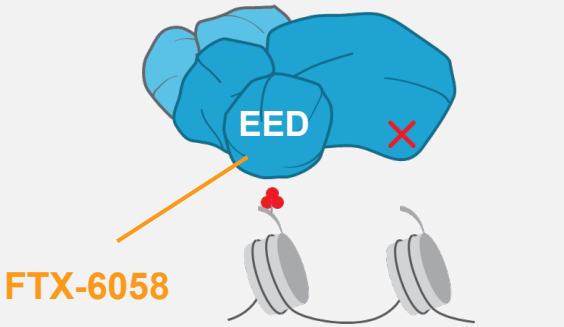
Computational Data Mining
Computationally mined candidate targets

Identified Targets that Regulate HbF

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



FTX-6058 is a Potent and Selective EED Binder



- H3K27me3 ▼
- HBG mRNA ▲
- HbF Protein ▲

FTX-6058

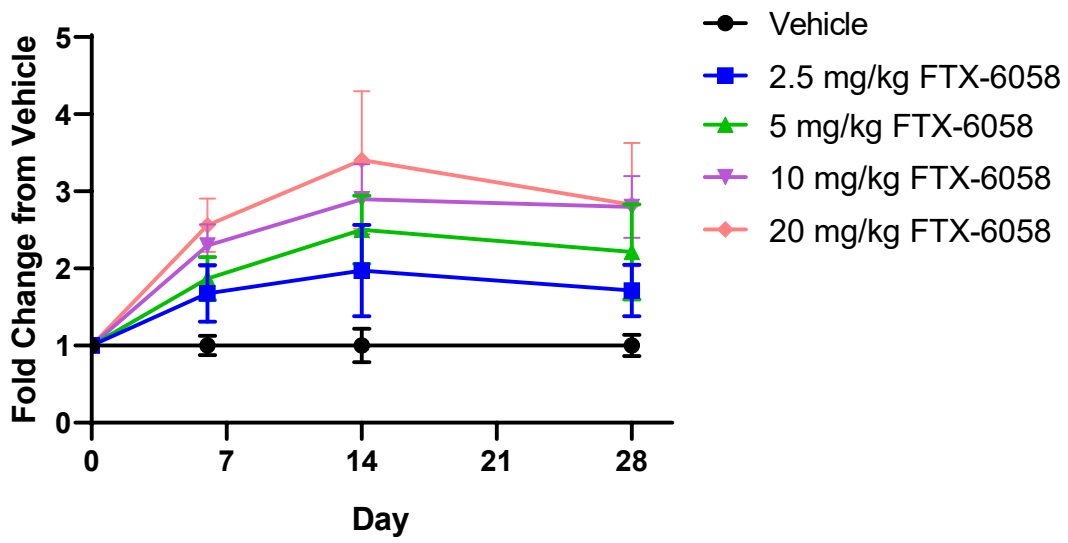
- **Highly Selective**
- **Clean Off-target Profile**
- **Composition of Matter Patent Expires 2040**

EED: Embryonic Ectoderm; HBG: hemoglobin gene

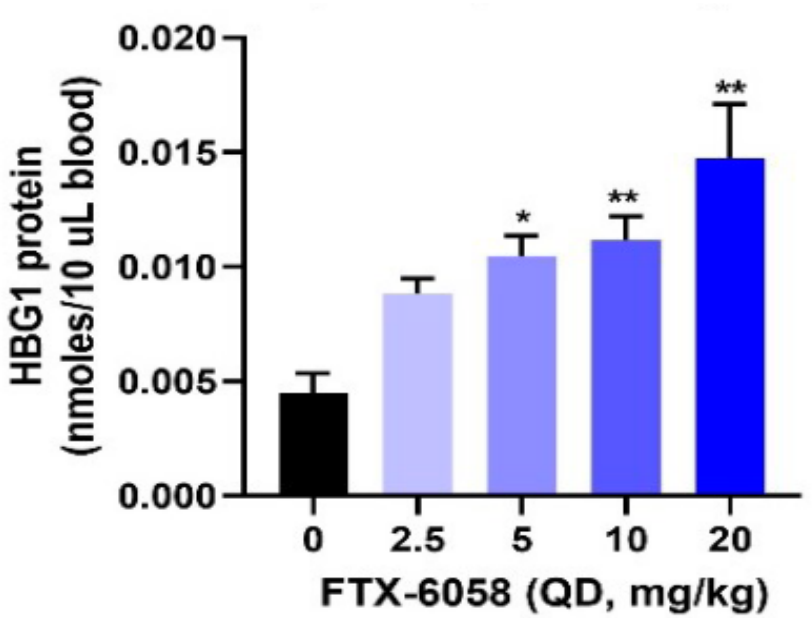
In vivo FTX-6058 Administration Results in Dose-dependent HbF Increases

Proof-of-mechanism data in Townes mouse models show dose-responsive mRNA and protein induction

HBG mRNA



HBG1 protein (day 28)

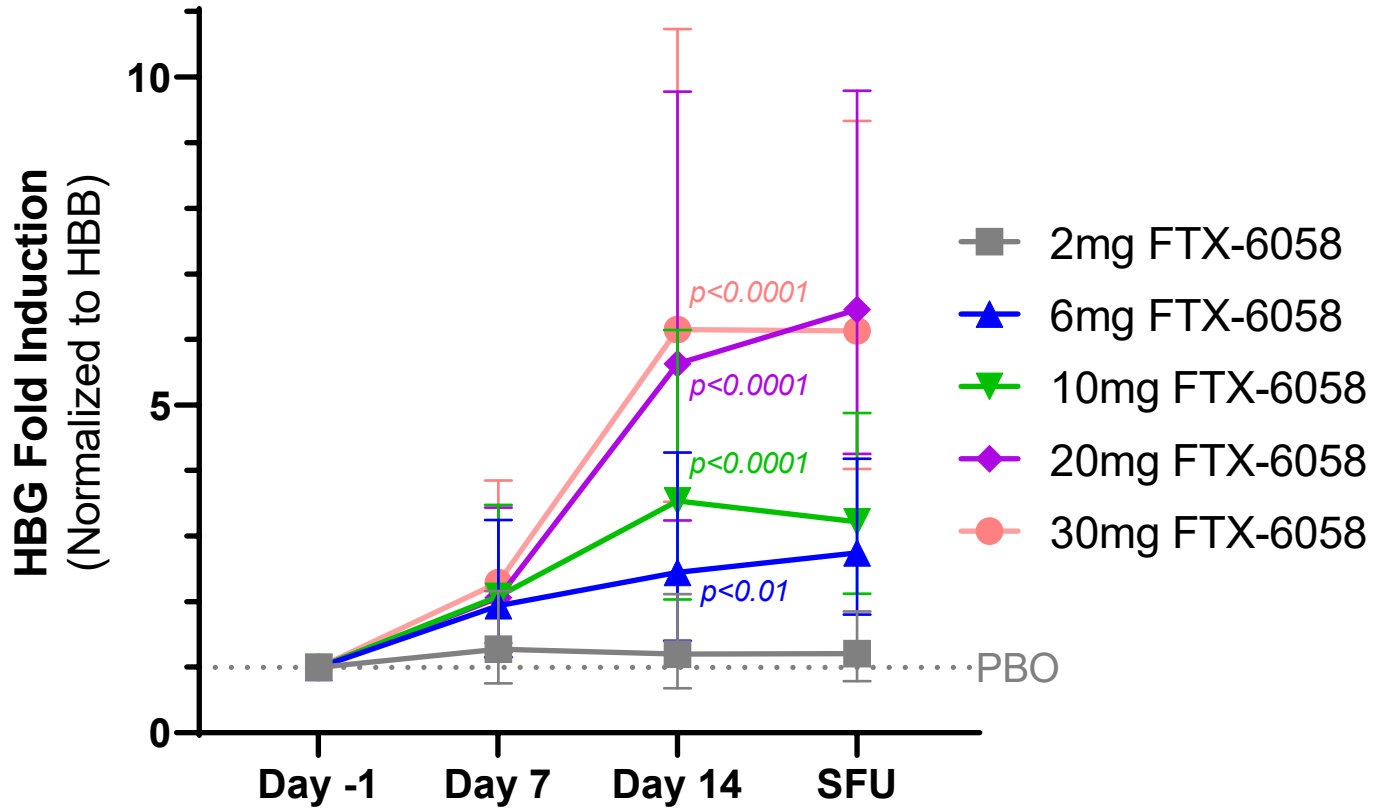


HBG1: Hemoglobin subunit gamma-1 : One-way ANOVA vs Vehicle. * $p < 0.05$, ** $p < 0.01$

Dose-dependent HBG mRNA Induction in Healthy Volunteers

Gamma Globin (HBG) mRNA Induction is both Time- and Dose-dependent in MAD Cohorts

HBG Fold Induction



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: hemoglobin gene; HBB: hemoglobin subunit beta gene

FTX-6058

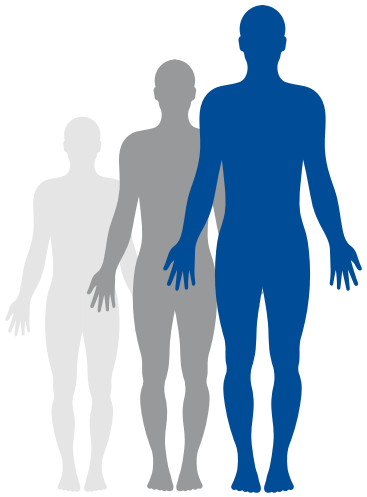
Phase 1b Clinical Trial
for Sickle Cell Disease

Fulcrum Therapeutics

Phase 1b Clinical Trial in SCD Subjects (Clinical Hold)

Study Population

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



Study Design

4-Week Treatment Period

Study Endpoints

Primary

Safety and tolerability

Pharmacokinetic measurements

Secondary

Change in %HbF protein
Change in reticulocytes
Red cell distribution width

Exploratory

Target engagement
Incidence of VOCs
Biomarkers of hemolysis
QOL measures
% F cells

HU: hydroxyurea; VOC: vaso-occlusive crisis; QOL: Quality of Life

SCD Phase 1b Demographics

	2 mg Cohort	6 mg Cohort	12 mg Cohort	Total
Number of subjects enrolled, n	2	10	3*	15
Average age, years (range)	37 (25, 48)	28 (21, 48)	32 (21, 43)	30 (21, 48)
Gender, Male (%)	1 (50%)	2 (20%)	2 (67%)	5 (33%)
Mean baseline HbF (range %)	4.0 (3.2, 4.8)	9.3 (3.7, 19.9)	14.8 (11.8, 17.7)	9.7 (3.2, 19.9)
Genotype, n (%)				
HbSS	2 (100%)	10 (100%)	3 (100%)	15 (100%)
HbSβ^0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
HbSβ$^+$	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hydroxyurea Utilization, n (%)	0 (0%)	3 (30%)	2 (67%)	5 (33%)

Mean baseline HbF of 9.7% is consistent with recent SCD clinical studies and published data

5 subjects were on hydroxyurea

All subjects enrolled to-date have the HbSS genotype

Data analysis cutoff : March 3, 2023; *A 4th subject was enrolled but withdrew after 4 days of treatment

FTX-6058 Was Generally Well Tolerated

15 Treatment Emergent Adverse Events (TEAEs) in 8/16 (50%) subjects

- 3/15 TEAEs reported as possibly related to study drug (headache, lip numbness, diarrhea)
  - All three were mild severity and non-serious

3/15 TEAEs characterized as VOCs (i.e., sickle cell anemia with crisis) per protocol definition

- All three were deemed not related to study drug by the investigators
- Two occurred in non-adherent patients (one of them being an SAE)
- The one reported SAE was with acute chest syndrome

No lab-related adverse events

No discontinuations reported due to TEAE

VOC: vaso-occlusive crisis; Data analysis cutoff : March 3, 2023

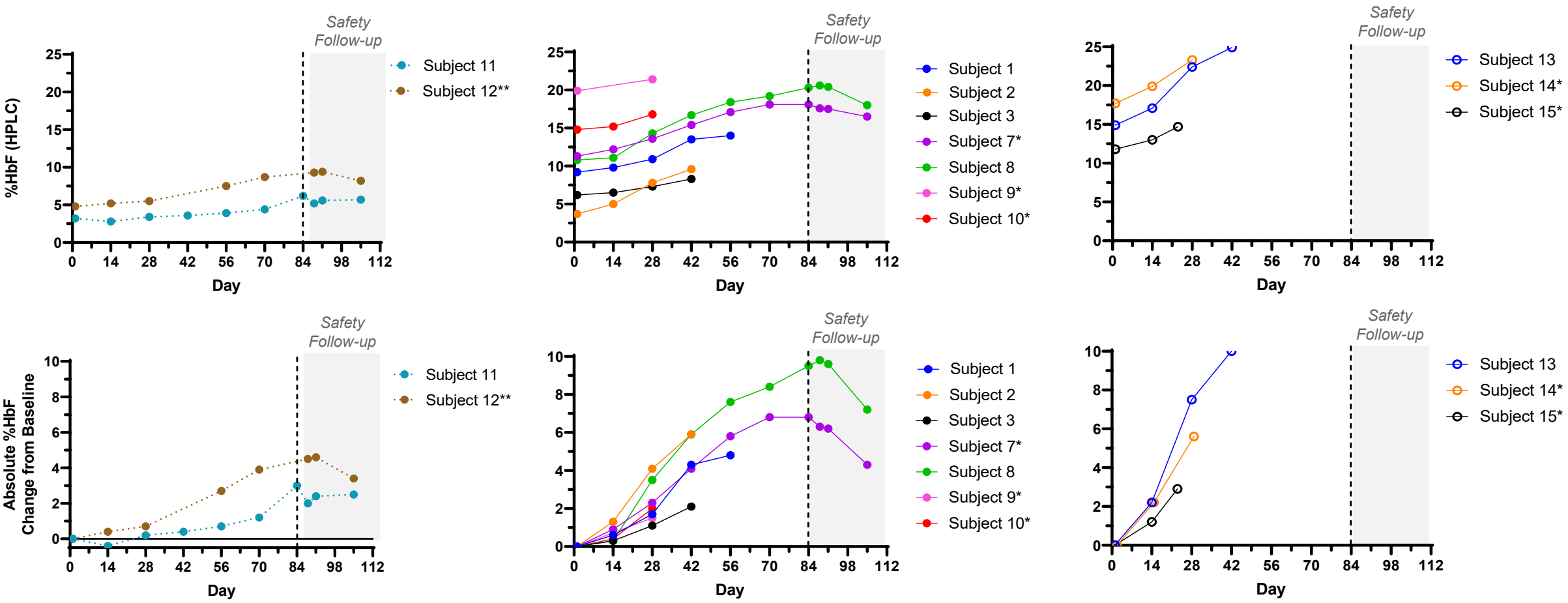
Instituted Observed Dosing and On-Treatment Analysis Following Initial Non-Adherence

Subject	Dose	Confirmed treatment duration (days)	On-treatment analysis eligible**
1	6 mg	56	✓
2	6 mg	42	✓
3	6 mg	42	✓
4	6 mg	0	
5	6 mg	0	
6	6 mg	0	
7*	6 mg	84	✓
8	6 mg	84	✓
9*	6 mg	28	✓
10*	6 mg	28	✓
11	2 mg	84	✓
12	2 mg	84	✓
13	12 mg	42	✓
14*	12 mg	28	✓
15*	12 mg	22	✓
16	12 mg	0	

* Subjects concurrently receiving hydroxyurea
** On-treatment analysis eligible requires detectable drug levels (PK) and drug accountability/subject interview
Confirmed treatment duration days are consecutive days of dosing starting on first day of dosing
Orange box indicates subjects enrolled after observed dosing initiated

FTX-6058 Appears to Have a Dose Dependent, Clinically Relevant and Consistent Increase in HbF

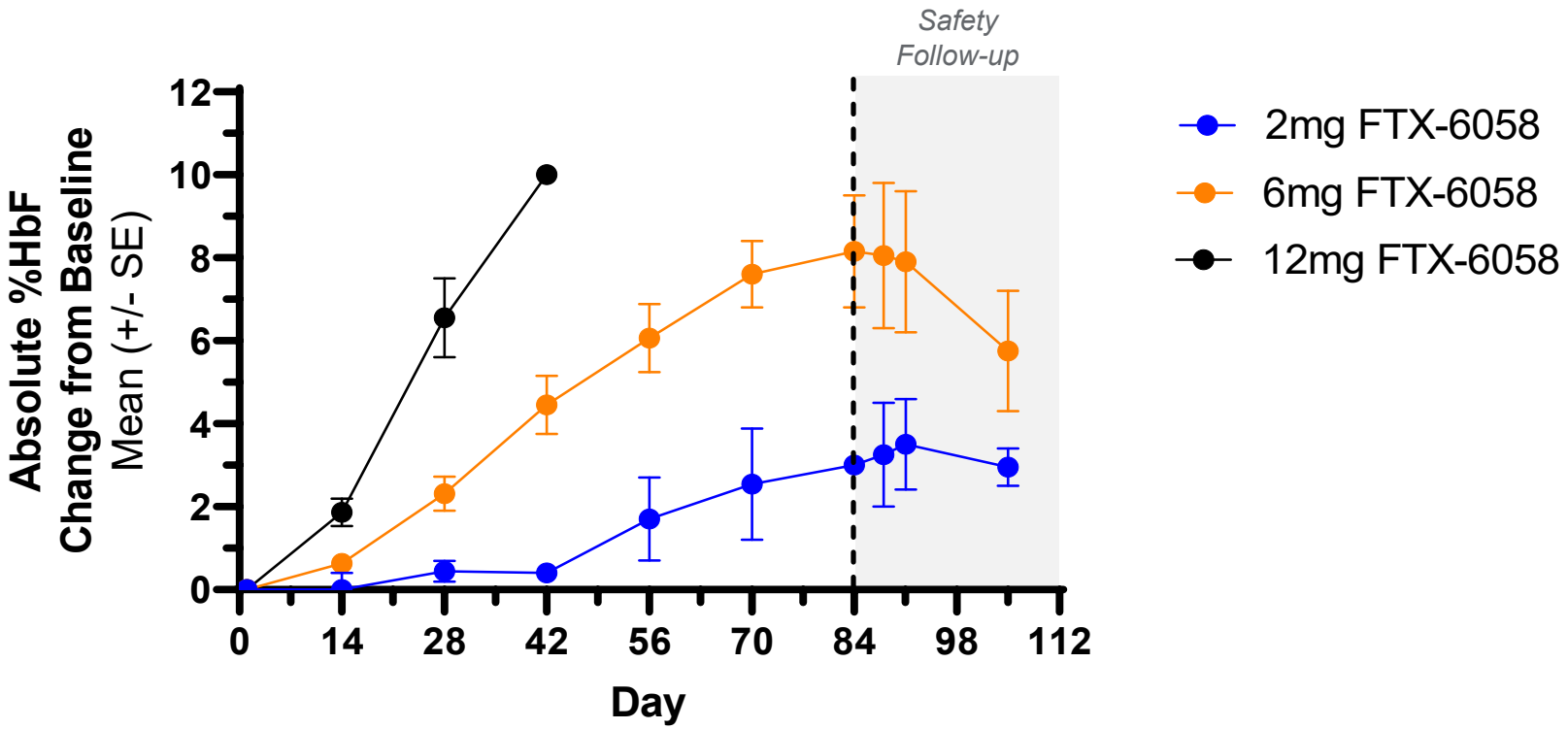
2mg | **6mg** | **12mg**



*Subjects on stable dose of hydroxyurea; Note: Subject 15 ceased dosing on Day 22
** Day 42 and day 84 data not available for subject 12; samples were received by the lab outside of stability window
Data cutoff as of March 3rd, 2023

Initial FTX-6058 Data Demonstrates Dose-dependent Increases in HbF

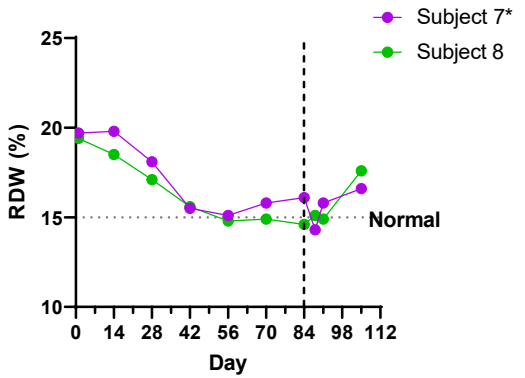
Absolute %HbF Change from Baseline

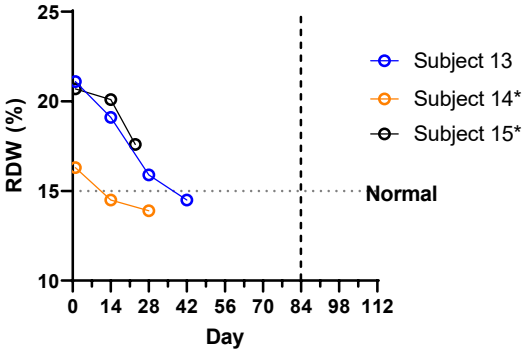


Note: Summary data includes both subjects on and off hydroxyurea; Subject 15 ceased dosing on Day 22 and therefore, was only included in the analysis up to Day 14
Data cutoff as of March 3rd, 2023

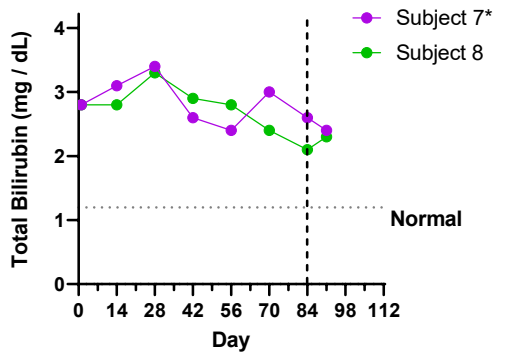
Initial Data from 6 mg and 12 mg FTX-6058 Demonstrates Improvements in Biomarkers of Hemolysis

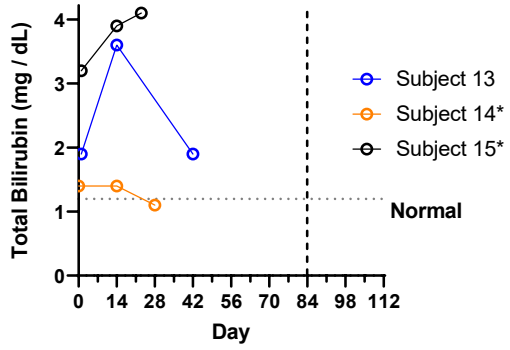
Red Cell Distribution Width | **Total Bilirubin** | Absolute Reticulocyte Count | Total Hemoglobin



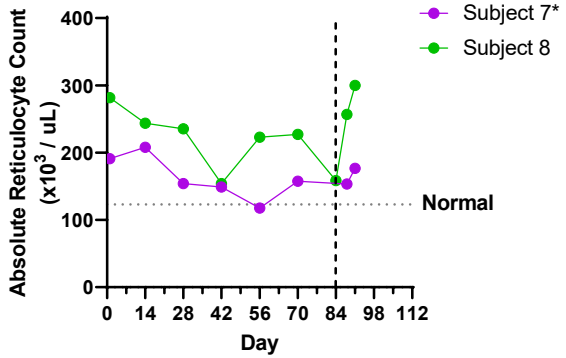


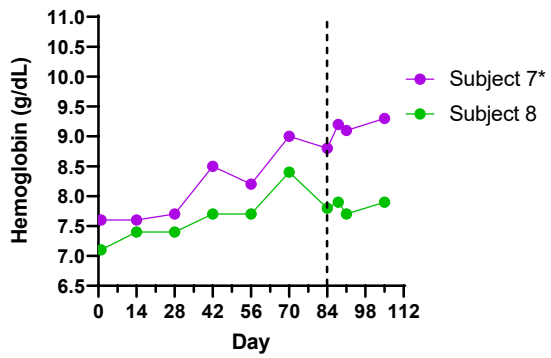
Reductions in RDW indicate RBCs are becoming more uniform in shape



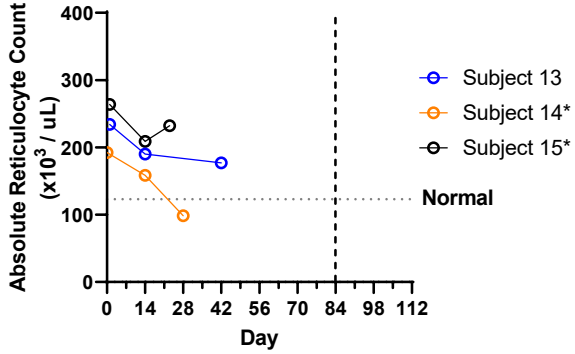


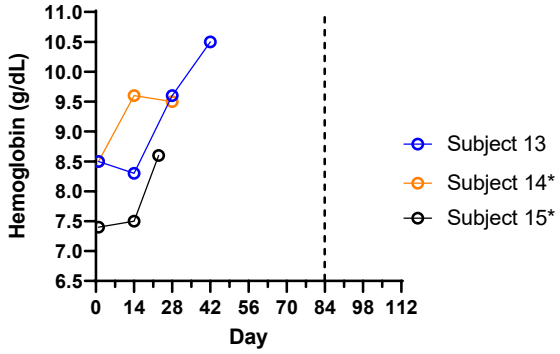
Bilirubin decreases indicate less hemolysis





6 mg





12 mg

Reductions in reticulocytes and increases in total hemoglobin indicate less anemia and healthier bone marrow function

*Subjects on stable dose of hydroxyurea; Note: Subject 15 ceased dosing on Day 22
Data analysis cutoff as of March 3rd, 2023

FULCRUM THERAPEUTICS

Fulcrum Therapeutics

FTX-6058 Demonstrates Best-in-Class Potential

Healthy volunteer mRNA data indicate higher levels of HbF induction are possible

- To date, all patients on treatment have responded
- Levels of HbF increase are clinically relevant among patients both on HU and off HU
- Consistency of response demonstrated across patients, independent of baseline HbF
- Dose response at 2 mg, 6 mg, and 12 mg
- Overall FTX-6058 was generally well-tolerated

Data analysis cutoff : March 3, 2023
HbF: fetal hemoglobin; HU: hydroxyurea

Next Steps: Complete Phase 1b to Enable Registrational Dose Selection

Amend Protocol and Increase Number of Sites:
Streamline PK Collection and Reduce Patient Burden

→ Accelerate Enrollment

Optimize Treatment Effect:
Continue Dose Escalation to 12 mg

→ Completion of Phase 1b

Refine PK / PD Model:
Select Optimal Therapeutic Dose

→ Dose Selection for Next Phase

U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023

FTX-6058: Differentiated HbF Inducer with Best-in-Class Potential

Persistent unmet need

SCD is a severe disorder (estimated US SCD population is ~100,000)

Approximately 200,000 annual emergency department visits related to SCD

Best-in-class potential

Oral small molecule hemoglobin F (HbF) inducer

Potential to be broadly protective of SCD symptomology

Demonstrated proof-of-concept

Dose responsive target engagement and HbF increase*

Robust HbF increases in adherent patients, on and off hydroxyurea*

Development path forward

Completion of Phase 1b to enable registrational dose selection

FDA Fast Track Designation

Composition of matter patent into 2040

* Data analysis cutoff : March 3, 2023; Sedrak and Kondamudi, StatPearls, last update August 29, 2022; Hussain et al, Am J Prev Med, 2010

U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023

Summary: Diversified, Differentiated Pipeline of Clinical Assets

Losmapimod well-positioned to be first-to-market for patients living with FSHD

Enrollment for REACH Phase 3 trial to be completed in 2H 2023

FTX-6058 has best-in-class potential for SCD

Well-positioned to deliver on goals

Cash runway through mid 2025

U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023

Fulcrum Therapeutics

THANK YOU