



Fulcrum
Therapeutics

 Nasdaq FULC

July 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 clinical programs**



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 Designations**



Discovery engine validated by two clinical programs.

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

Founded in 2015

IPO in 2019

Ticker: FULC

Pipeline

Indication	Asset / Partner	Preclinical	Phase 1	Phase 2	Phase 3
Clinical Programs					
FSHD	Losmapimod (Oral DUX4 Reducer)				
SCD	FTX-6058 (Oral HbF Inducer)	*			
Discovery Programs					
Blood Disorder					
Neurologic Disorder					
Muscle Disorder					
Collaborations					
Cardiomyopathies	Bristol Myers Squibb™				

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

FSHD: Facioscapulohumeral muscular dystrophy; HbF: Fetal hemoglobin; SCD: Sickle cell disease; DBA: Diamond-blackfan anemia.

Q2 2023 Updates

Losmapimod FSHD

- Screening is closed for the Phase 3 REACH pivotal trial in patients with Facioscapulohumeral Muscular Dystrophy
- Expect to report topline data for REACH in the fourth quarter of 2024

FTX-6058 Sickle Cell Disease

- On February 23, 2023, the FDA placed the IND for FTX-6058 on a full clinical hold
- Interactions with the FDA to resolve the clinical hold are ongoing

Fulcrum Corporate

- Appointed Alan A. Musso as Chief Financial Officer
- Cash runway into mid-2025

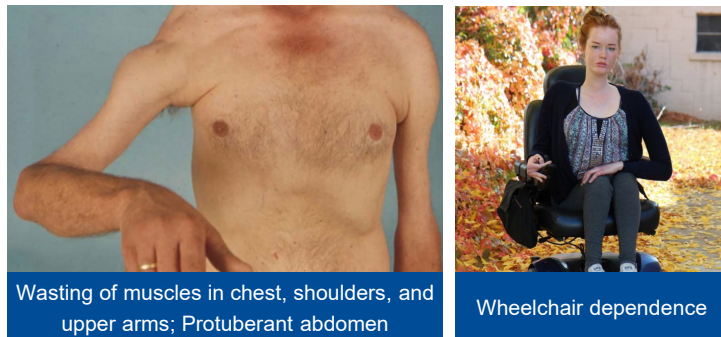


LOSMAPIMOD

for Facioscapulohumeral
Muscular Dystrophy (FSHD)

Fast Track Designation
Orphan Drug Designation

About FSHD: Debilitating Disease With No Approved Therapies



- 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
- Many patients unable to work or live independently
- Approximately 20% of affected individuals become wheelchair-bound

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

Reachable Workspace Enables Quantification of Disease Progression

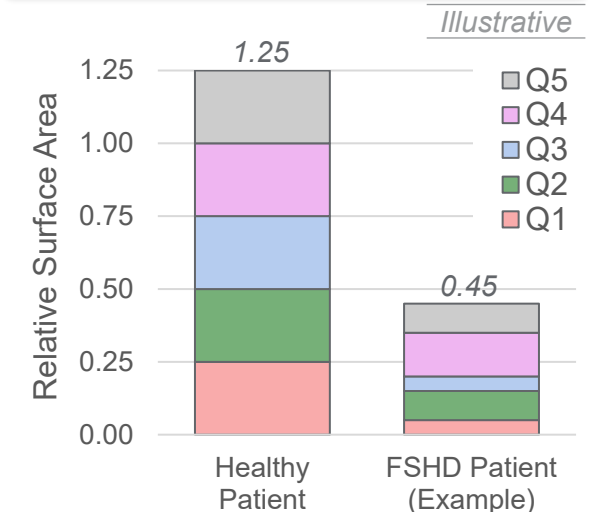
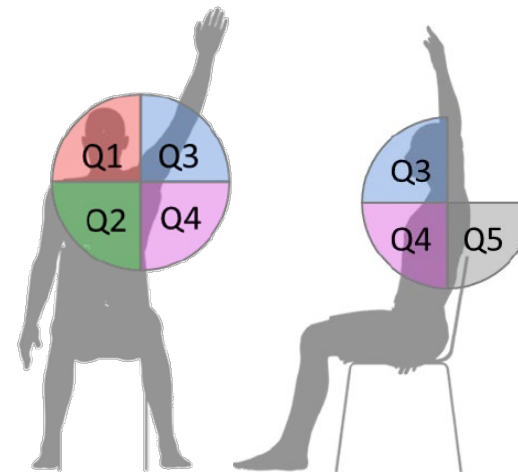
- RWS utilizes a contactless sensor-based system with analysis and visualization software to quantify upper limb motion
- RWS is measured across five quintants (Q1-Q5) that correlates with abilities to perform activities of daily living (e.g., eating, self-care)
- Demonstrated sensitivity to disease progression in FSHD and in Duchenne/Becker muscular dystrophy
 - A longitudinal study in an all-comer FSHD patient population exhibited annual declines in RWS of 2 – 3% (measured Q1-Q4) compared to baseline

Arm movement protocol

Sensor detected arm motion

RWS measures global upper extremity function

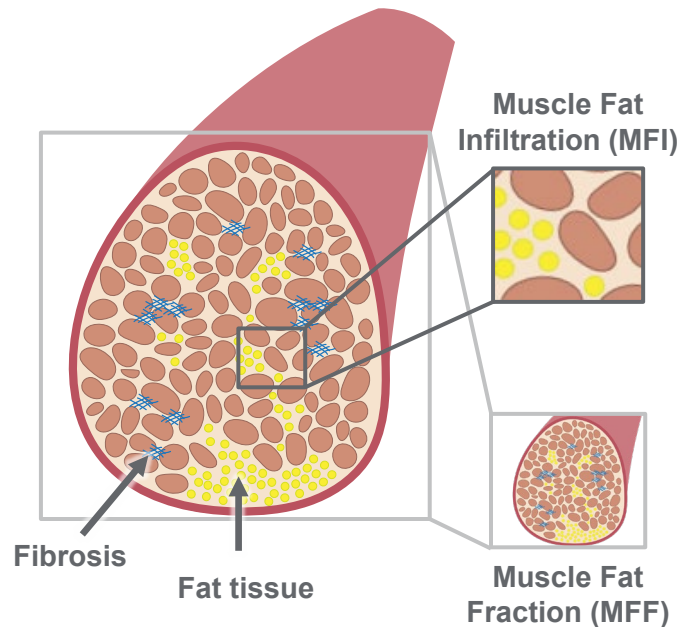
Relative surface area measured with RWS



Whole Body Musculoskeletal MRI Enables Assessment of Muscle Health and Dystrophic Progression

Dystrophic Skeletal Muscle Tissue in FSHD

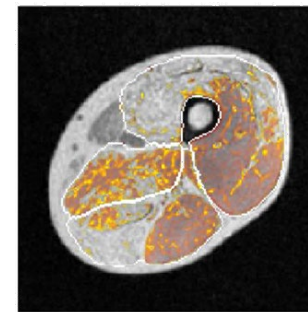
Tissue infiltration contributes to the loss of function by altering biomechanical properties



Whole Body MRI Provides a Holistic and Quantitative Assessment of Muscle Quality and Health

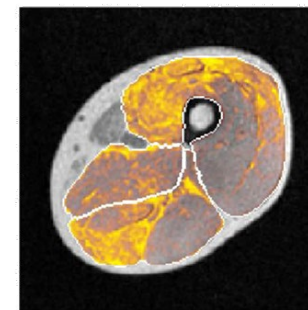
18 muscles are analyzed bilaterally (36 total muscles analyzed)

Muscle Fat Infiltration (MFI)



- Measurement of the diffuse fatty infiltration in the muscle
- MFI is an indicator of muscle quality and sensitive to early muscle fat replacement

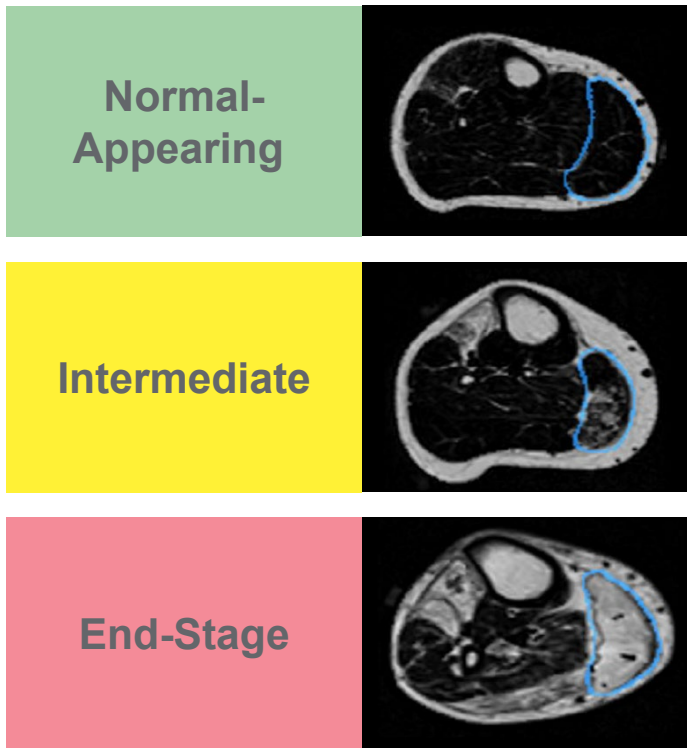
Muscle Fat Fraction (MFF)



- Measurement of the overall amount of fat within the muscle
- MFF is an indicator of FSHD-affected muscles with a strong correlation to clinical function / disability

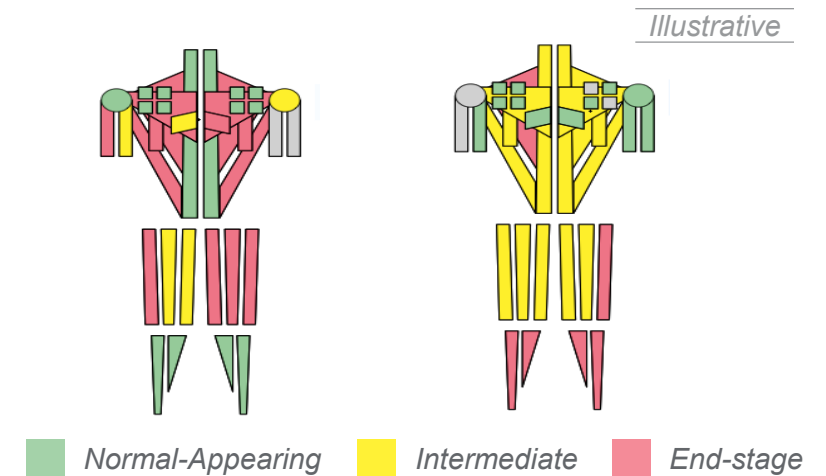
Muscle Categorization by Whole Body MRI Captures FSHD Disease Heterogeneity and Identifies Muscles for Clinical Endpoint Evaluation

Muscle Categorization Based on MFI and MFF Measurements



- Muscles do not appear to be affected by disease; minimal to no fat deposits
- MFI < 10%; MFF < 50%
- Muscles clearly affected by disease, but not so severely to have lost all function
- MFI ≥ 10%; MFF < 50%
- Muscles severely affected and replaced with fat; likely to have lost most function
- MFF ≥ 50%

Illustrative Application of Muscle Categorization to FSHD Patients



- FSHD progression across the 36 assessed muscles is variable, resulting in meaningful inter- and intra-patient heterogeneity
- Intermediate muscles are utilized for clinical evaluation due to likelihood of progression

Unmet Need for Safe and Effective Drug That Slows Disease Progression



Facioscapulohumeral
Muscular Dystrophy (FSHD)

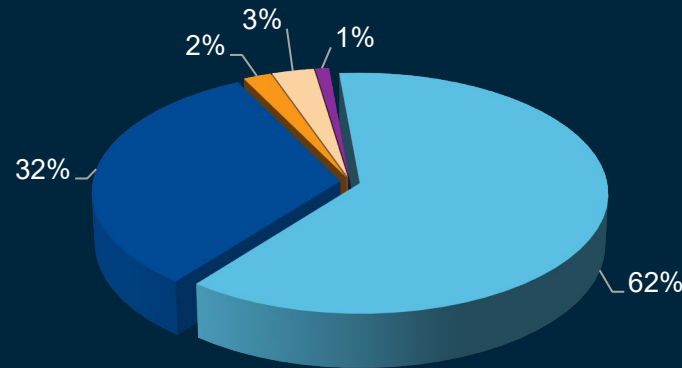
VOICE OF THE PATIENT REPORT

Externally Led
Patient-Focused
Drug Development
Meeting

*This report is dedicated to the individuals
who courageously shared their stories.*

What outcome is the most meaningful in a future treatment?

Patient Respondents, %



- Slowing or stopping the loss of muscle function
- Regaining strength or muscle function
- Lessening pain or fatigue
- Preserving respiratory and lung function
- Improving hearing or vision loss



*“I would like to see something that
would **stop** progression of the
disease”*

– 26-year-old woman with FSHD

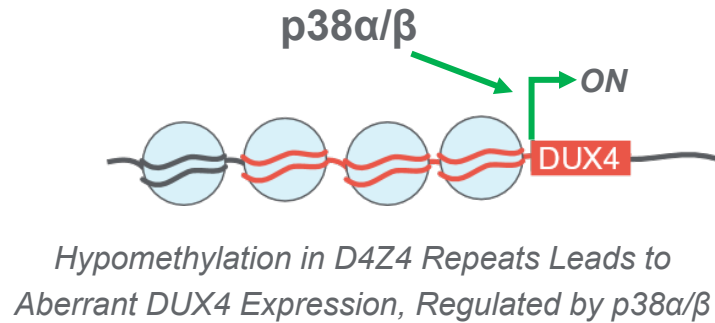
*“...if we had a therapy that at
minimum **slowed the progression...**
we would be able to guide and plan
for what her future looks like.”*

– 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

Losmapimod Inhibits DUX4 Driven Gene Expression and Muscle Cell Death in FSHD Patients

FSHD

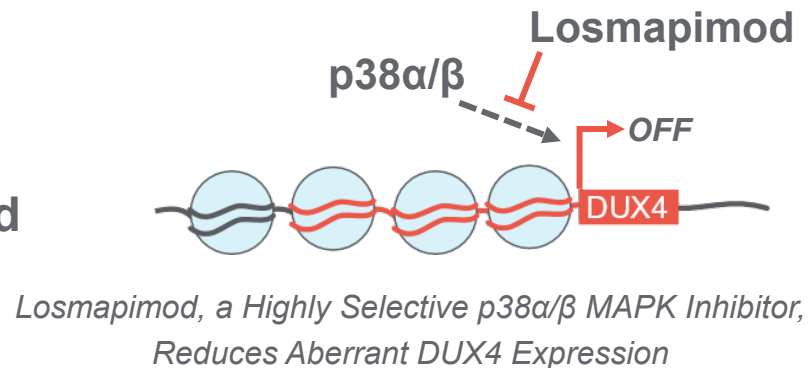


DUX4-driven Gene Expression

DUX4 Activity Causes Muscle Cell Death and Fat Infiltration



Losmapimod in FSHD



~~DUX4-driven Gene Expression~~

Reduced DUX4 Transcription Leads to Slower Cell Death and Fat Infiltration



ReDUX4: Phase 2 Trial Design

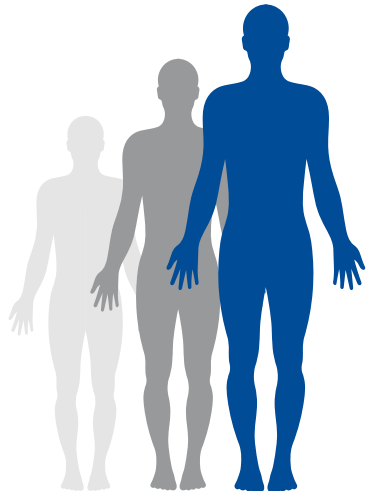
Study Population

ReDUX4:

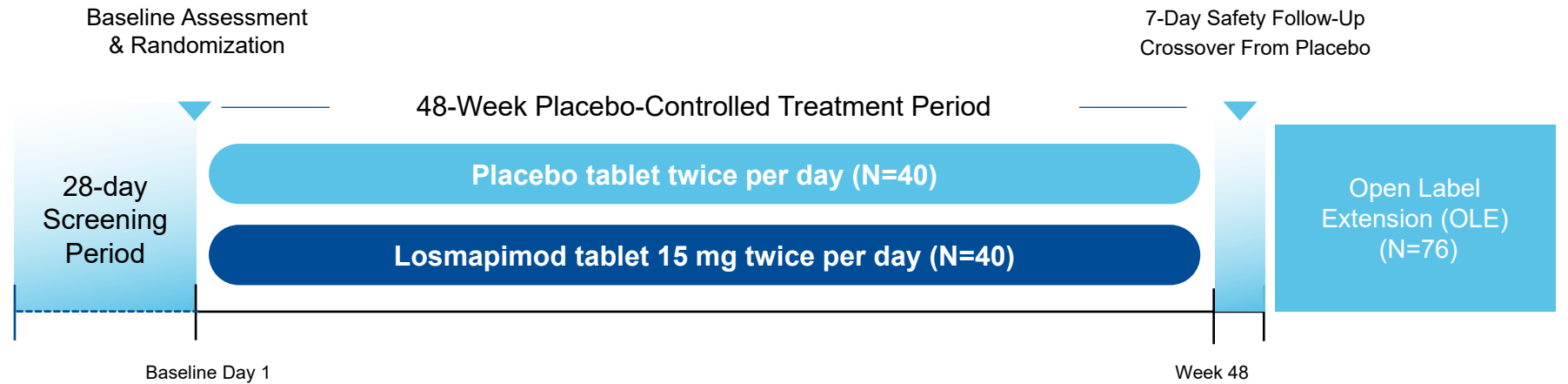
~80 subjects, 18-65 years old

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

ReDUX4 Showed Clinical Benefits at Week 48

Function

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

Muscle Health

Decreased **MFI** as measured by MRI

Quality of Life

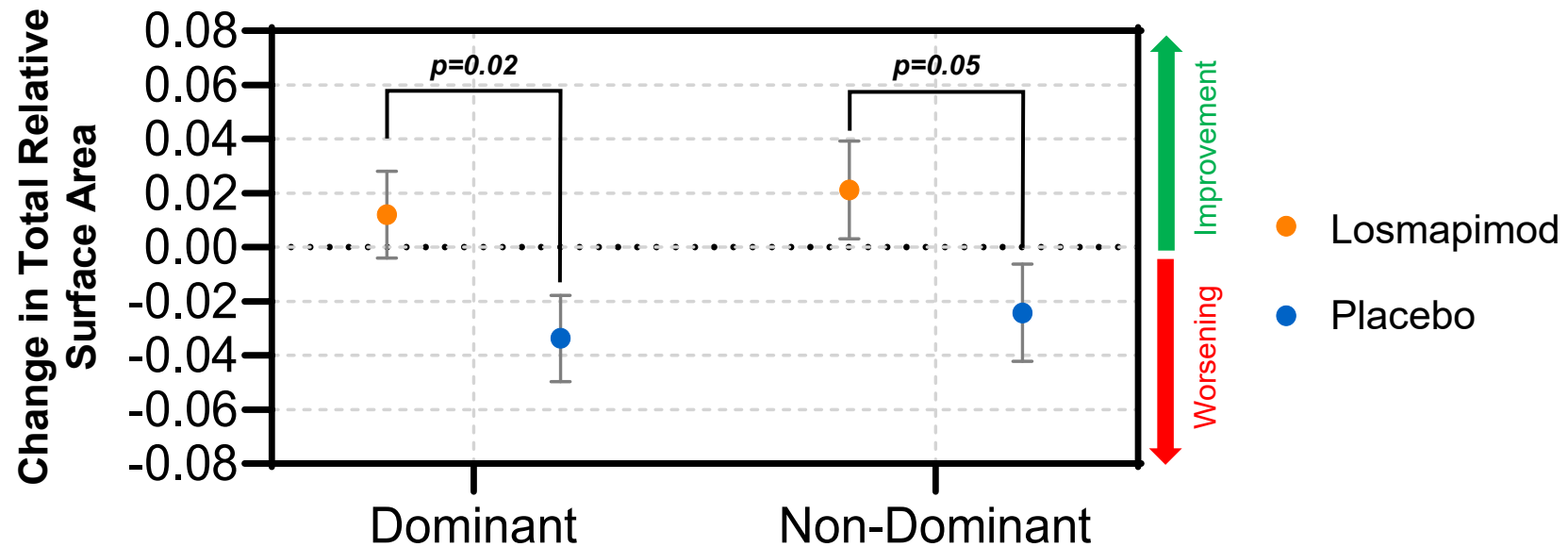
Patients reported feeling better as measured by **PGIC**

Safety/Tolerability

Generally well-tolerated
No serious treatment-related adverse events

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

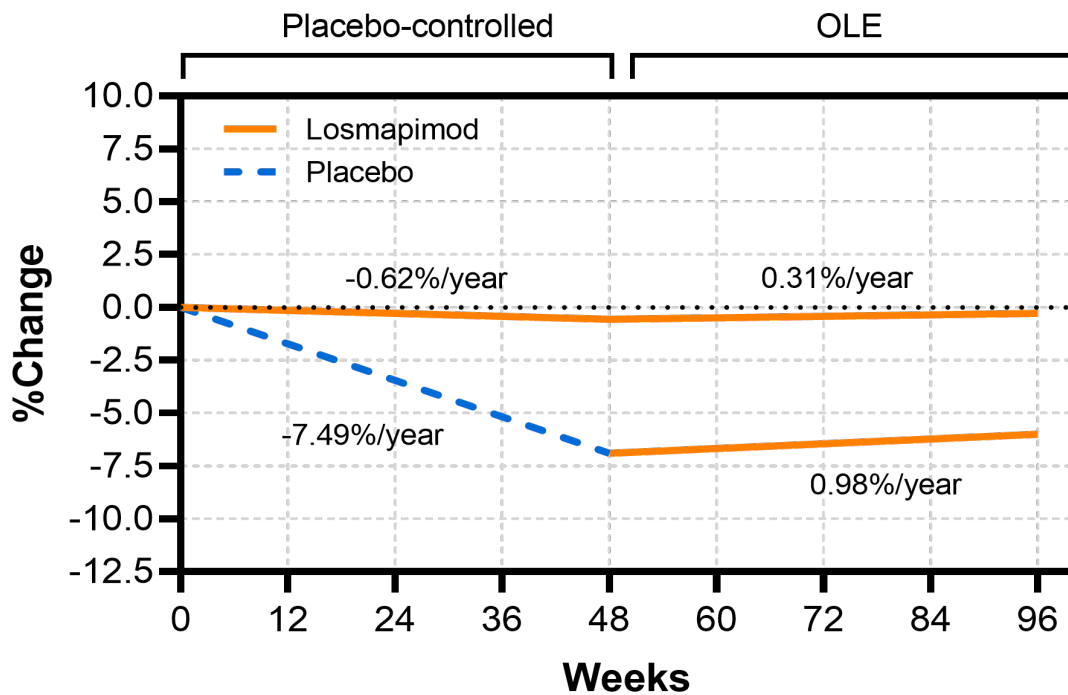
RWS Using 500 g Weight in Dominant & Non-Dominant Arm at 48 Weeks



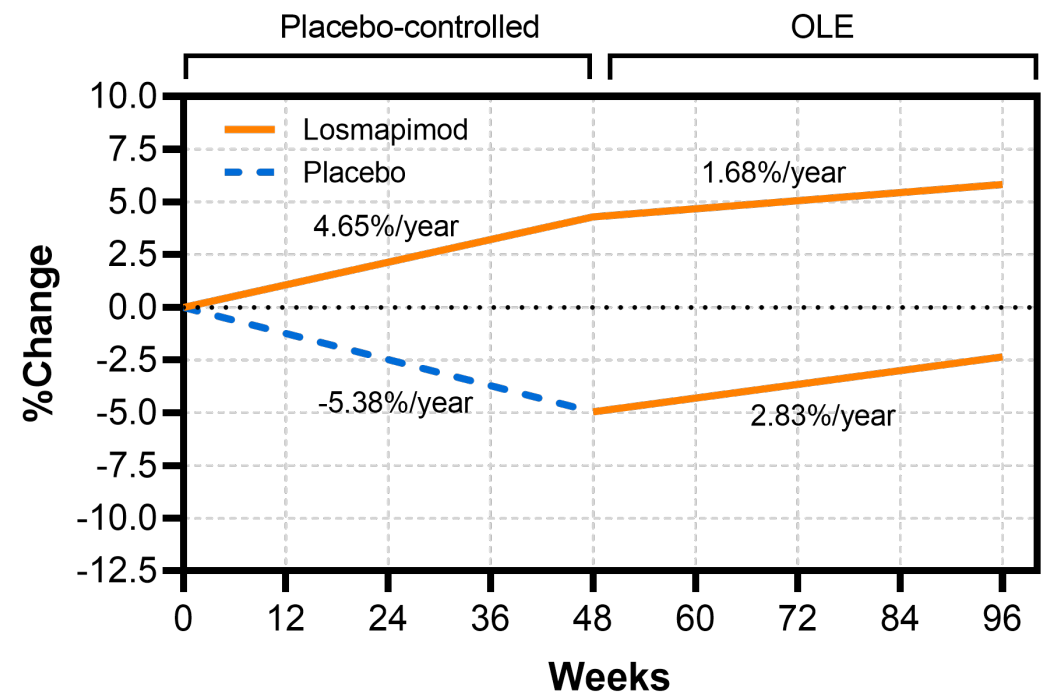
Open Label Extension Demonstrated Maintenance of Treatment Effect

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

Dominant Arm Total RSA + Weight



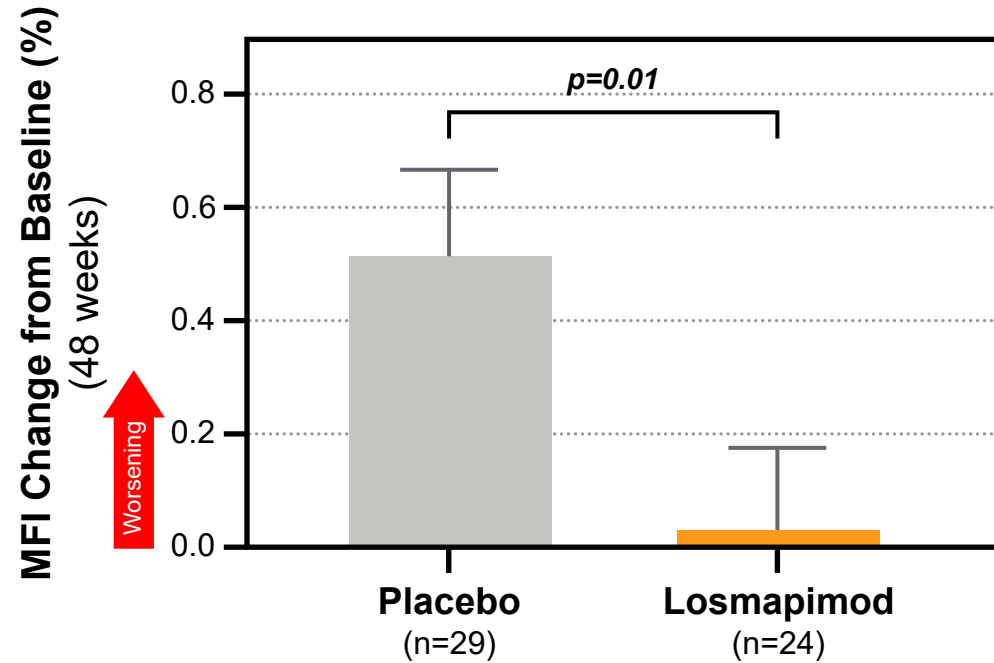
Non-Dominant Arm Total RSA + Weight



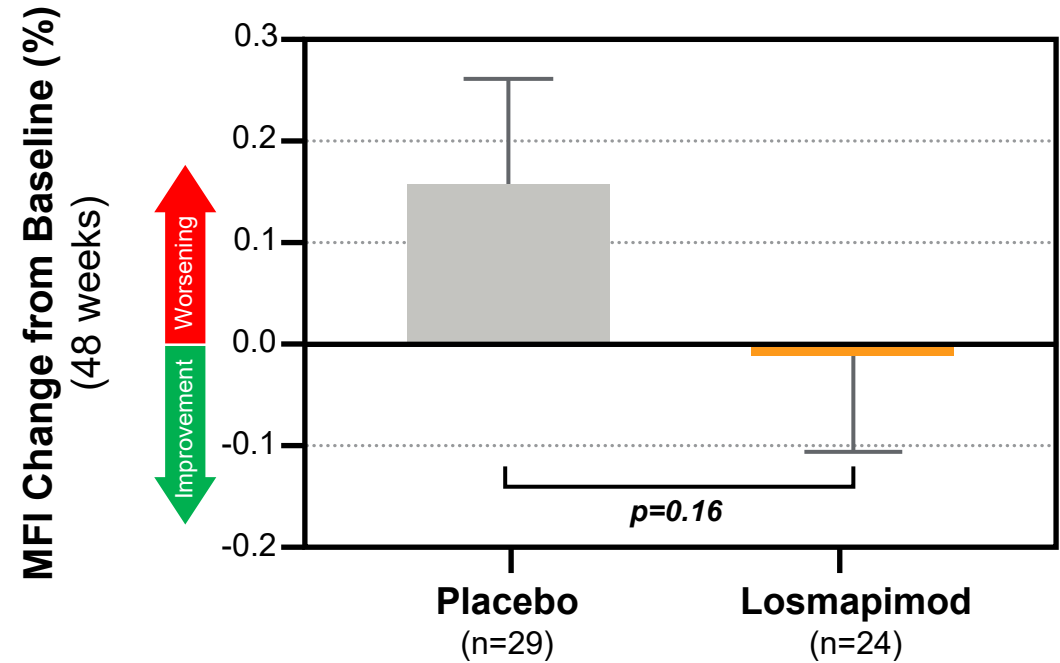
Data from ReDUX4 trial and the ReDUX4 OLE trial
 RSA: relative surface area; OLE: open label extension; PBO: placebo; LOS: losmapimod

Losmapimod Improved or Maintained Muscle Health at 48 Weeks

Losmapimod slowed fat infiltration in intermediate muscles already affected by disease



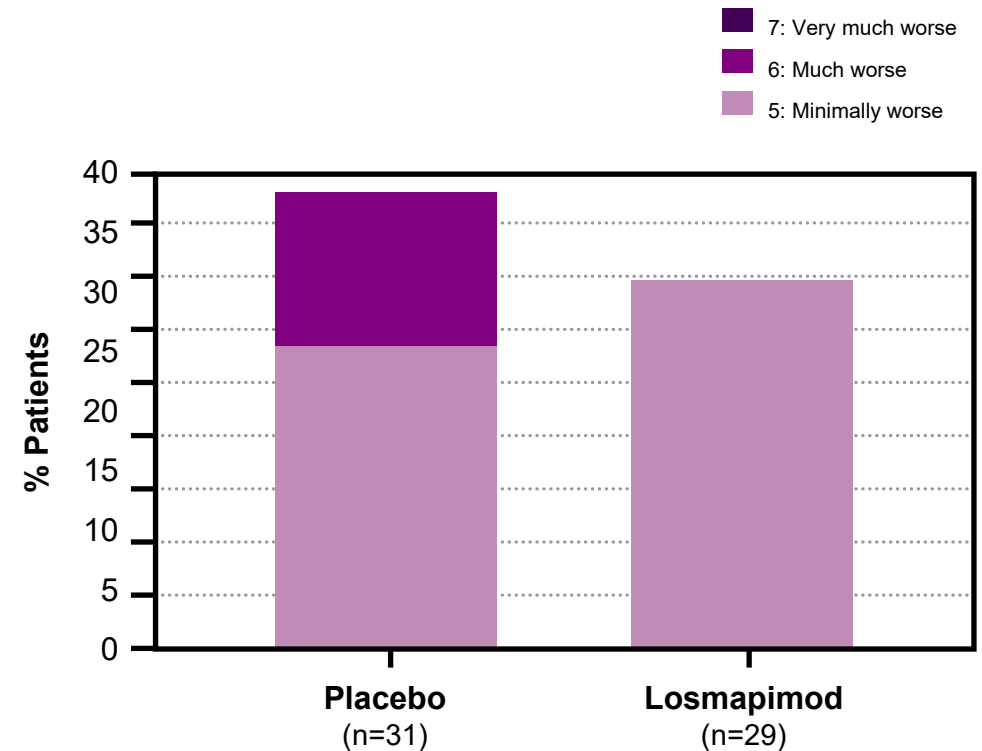
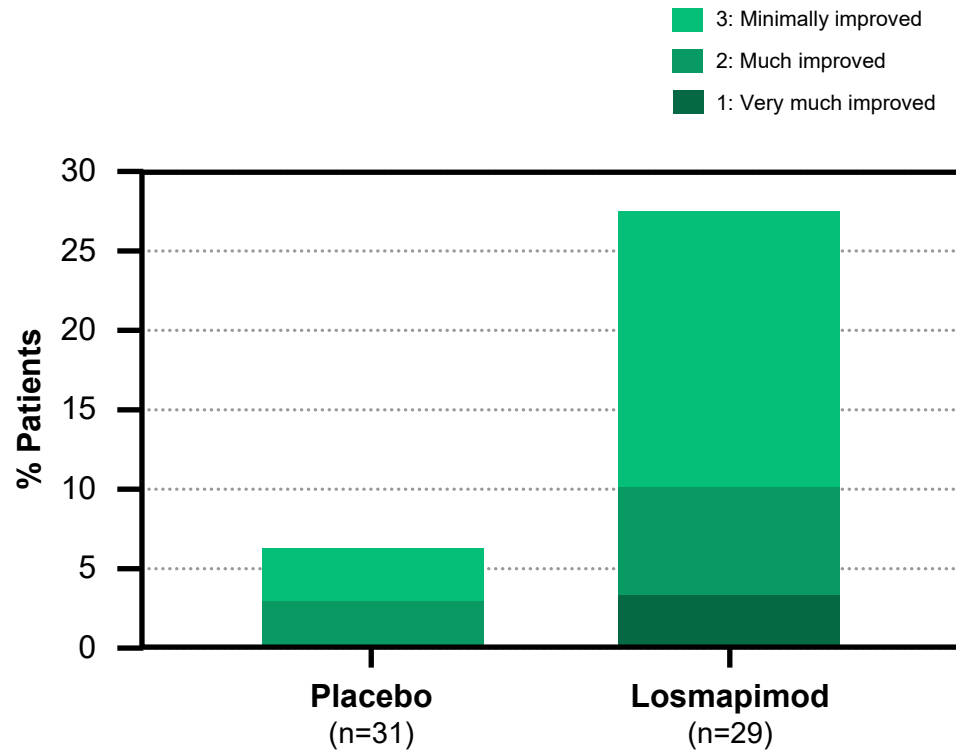
Losmapimod preserved health of normal-appearing muscles, limiting fat infiltration



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)

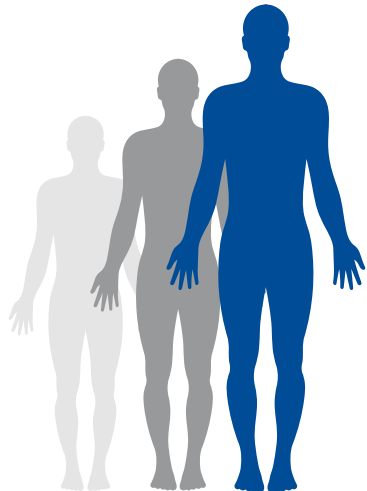
Losmapimod Was Generally Well-tolerated with No Serious Treatment-emergent Adverse Events

- 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

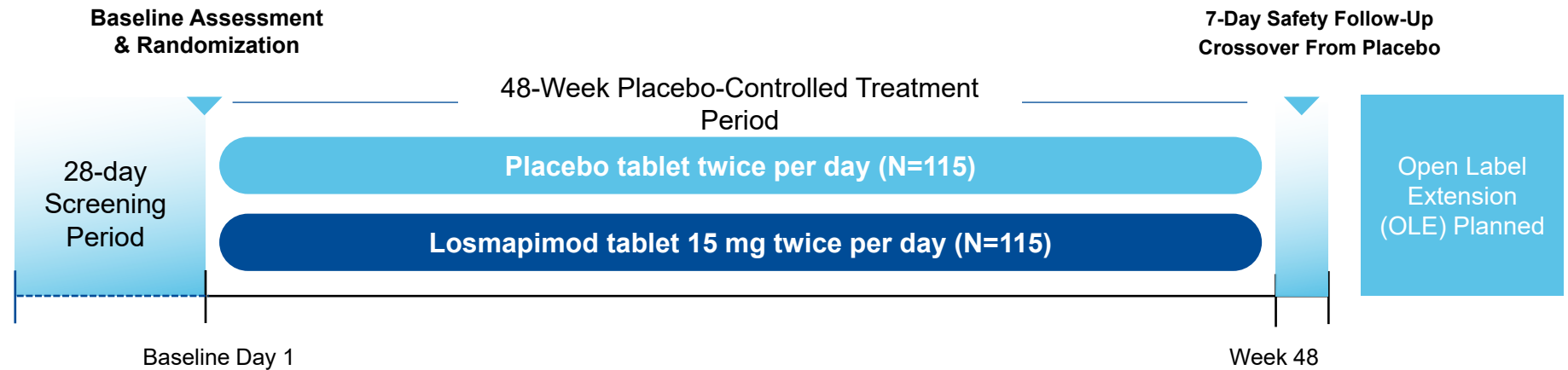
REACH: Global Phase 3 Trial of Losmapimod in FSHD

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

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

Exploratory

- Healthcare utilization questionnaire
- EQ-5D questionnaire

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



FTX-6058

for Sickle Cell Disease

Fast Track Designation
Orphan Pediatric Designation

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 rupture or block blood vessels

Debilitating Symptoms

- Vaso-occlusive crises (VOCs)
- Other complications, including stroke, neuropathy, and acute chest syndrome
- Anemia / hemolysis
- Morbidity and mortality

Global Impact



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)

Despite Therapeutic Options, Significant Unmet Need Remains for People Living With SCD




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

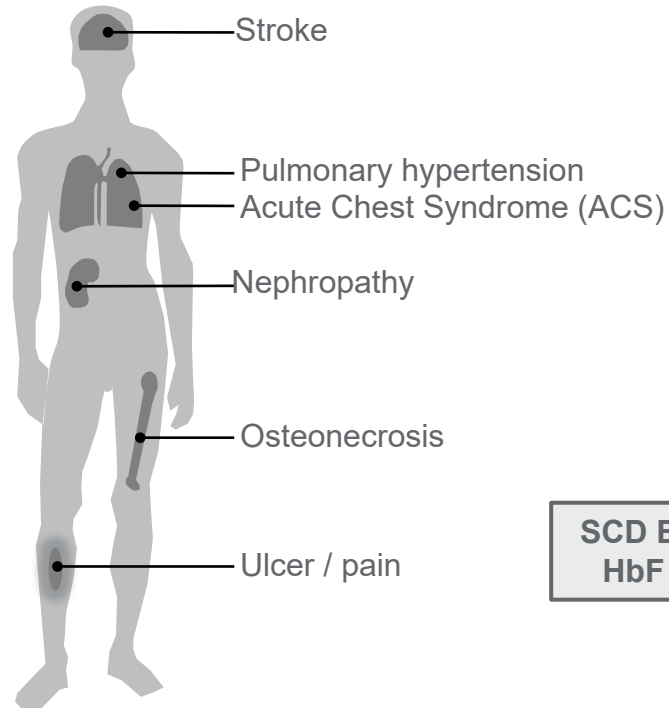
Increasing Fetal Hemoglobin

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

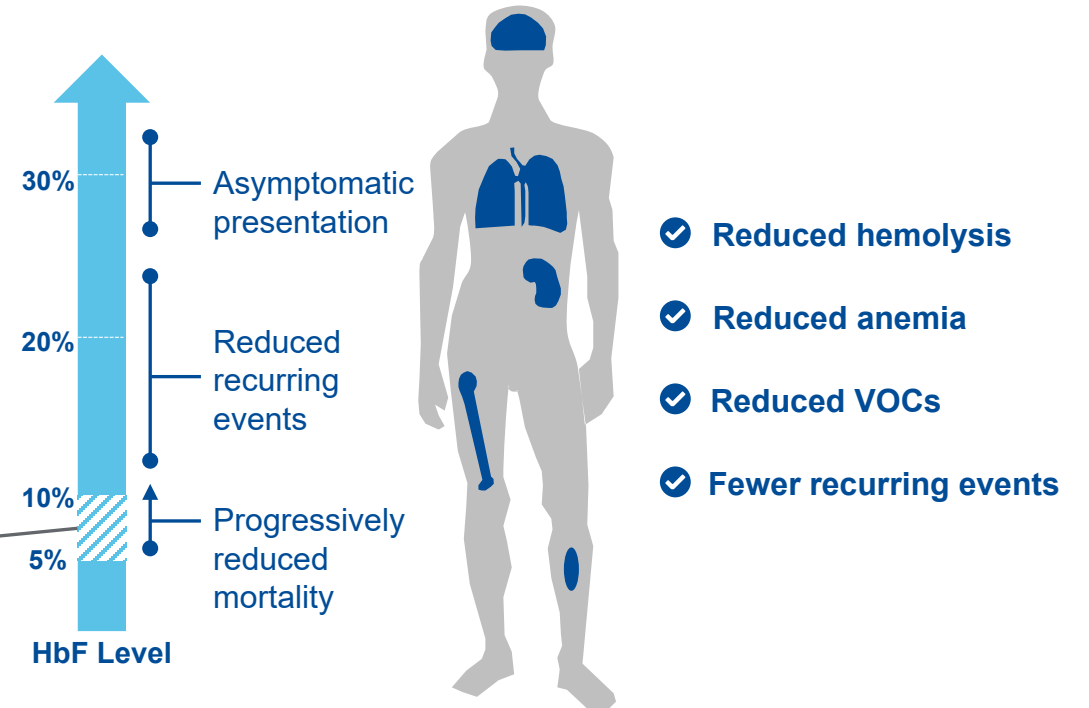
Higher HbF Levels Result in Reduced Symptomology in People Living with Sickle Cell Disease

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

Typical SCD Subject

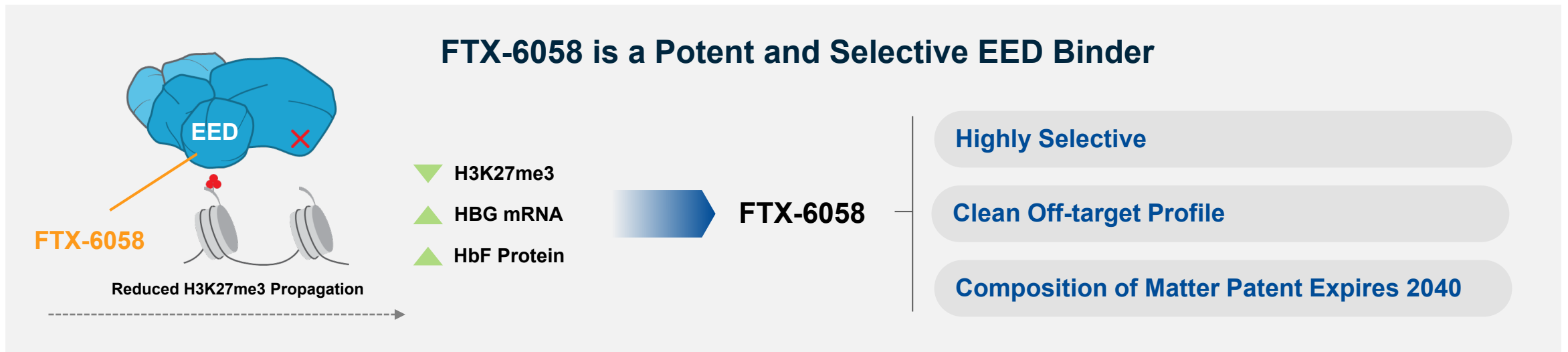


SCD Subject with High HbF Levels



By Raising HbF Levels, FTX-6058 Provides the Potential to Ameliorate Disease Pathology through Convenient Oral Dosing

Targeting EED Results in HbF Increases

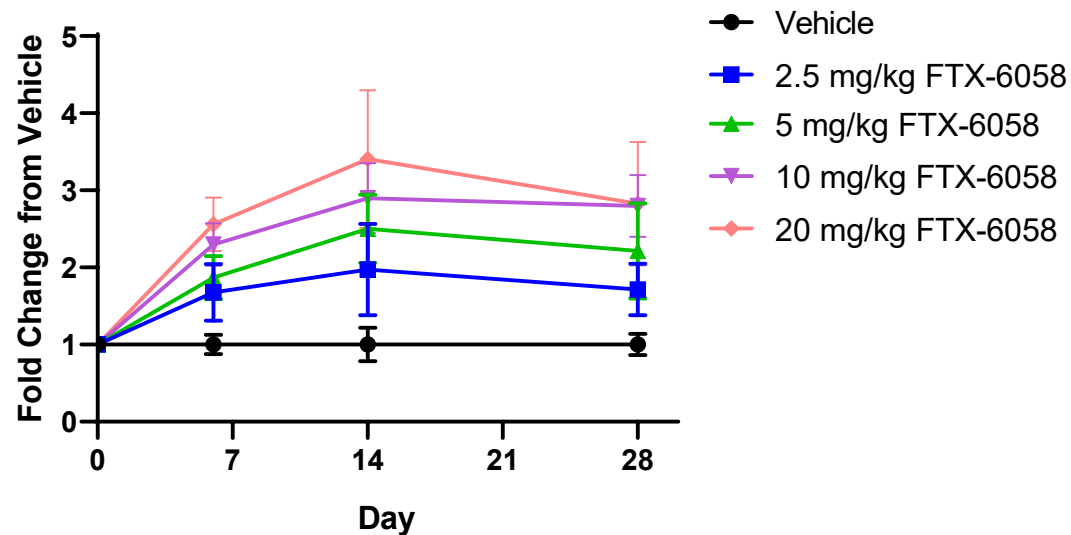


EED: Embryonic Ectoderm; HbF: Fetal hemoglobin; HBG: hemoglobin gene

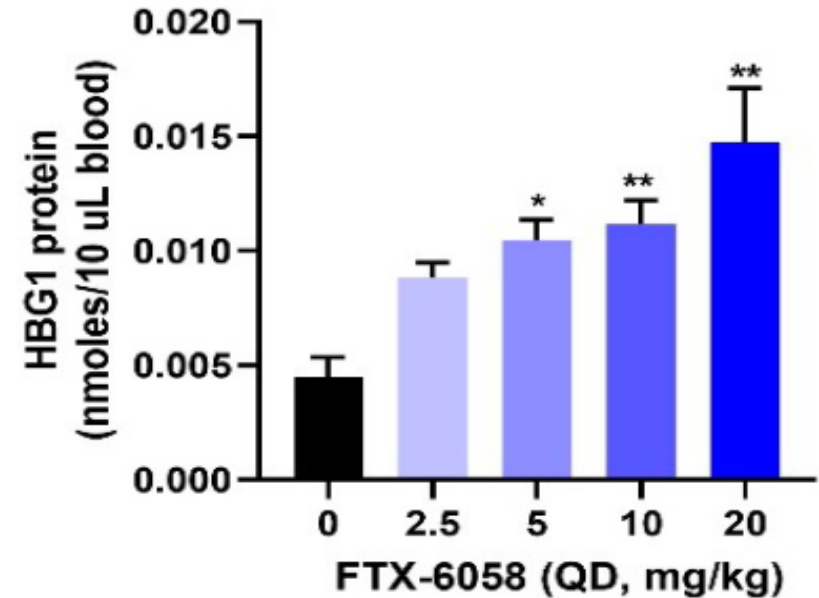
In vivo FTX-6058 Administration Results in Dose-dependent HbF Increases

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

HBG mRNA



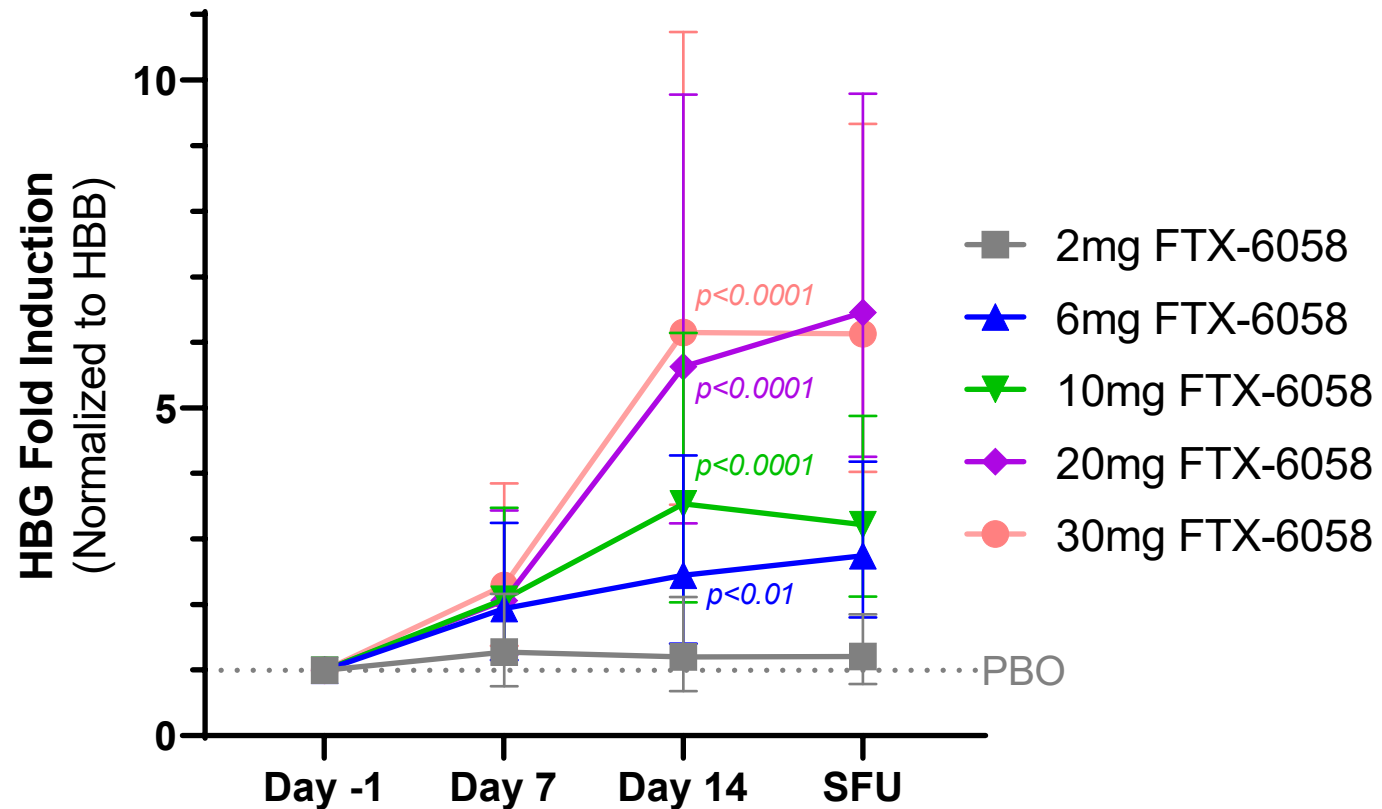
HBG1 protein (day 28)



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 in Healthy Volunteers

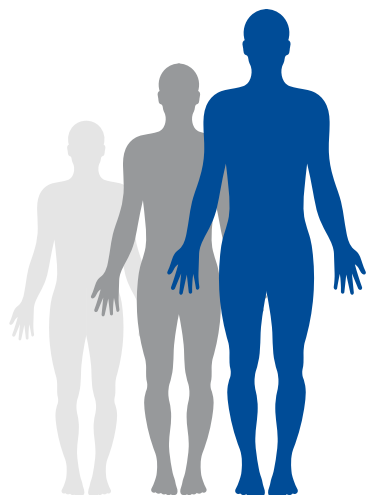


Safety follow-up (SFU) samples were collected 7 – 10 days post 14-day treatment period; PBO: placebo; Data presented as geometric LS mean ratio (to placebo) with 95% confidence interval; mixed-effects model for repeated measures (MMRM) analysis performed for Day 7 and Day 14; analysis of covariance (ANCOVA)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

Phase 1b Clinical Trial in SCD Subjects (FDA 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

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

HU: Hydroxyurea; VOC: Vaso-occlusive crisis; QOL: Quality of Life

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

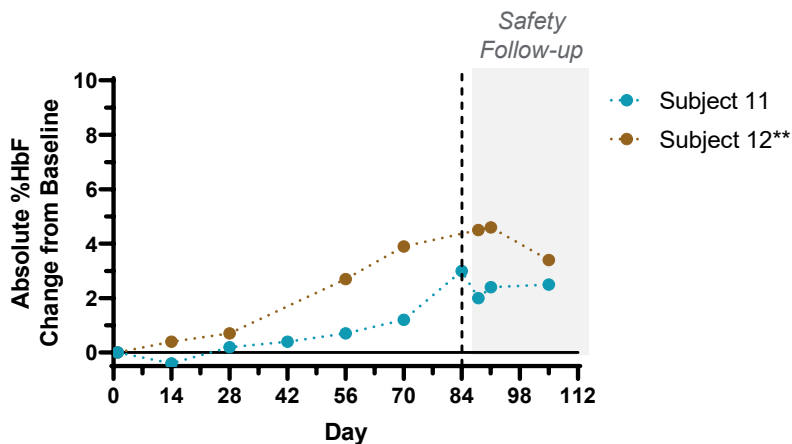
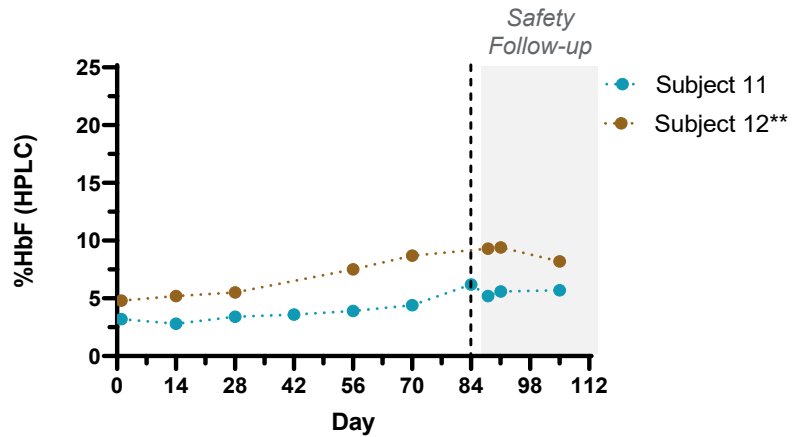
- All three were deemed not related to study drug by the investigators
- Two occurred in non-adherent patients (one of them being an SAE)
- The one reported SAE was with acute chest syndrome

No lab-related adverse events

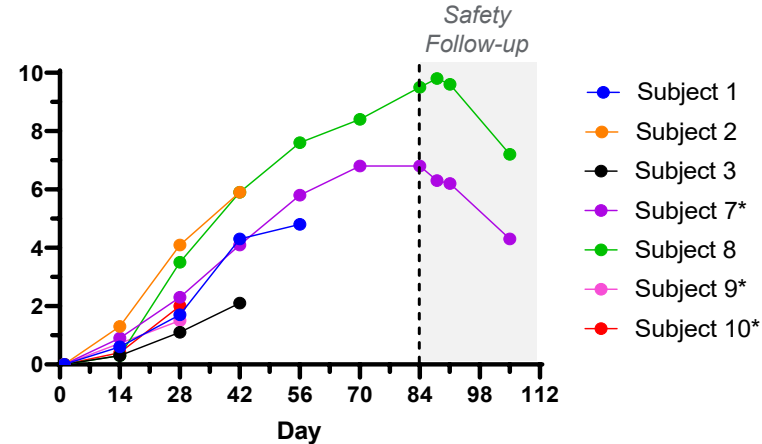
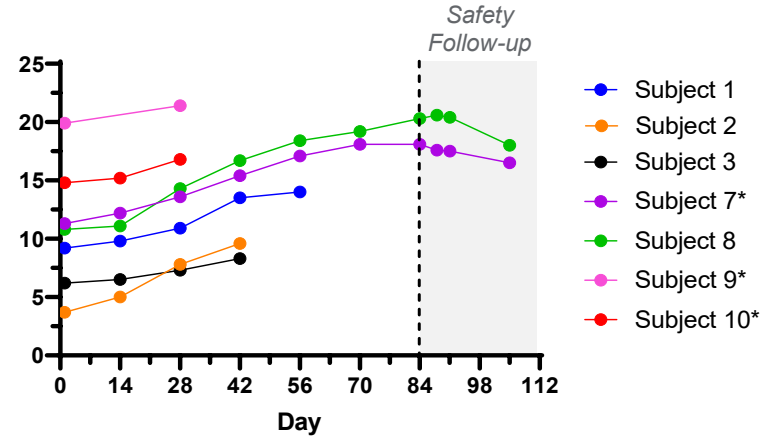
No discontinuations reported due to TEAE

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

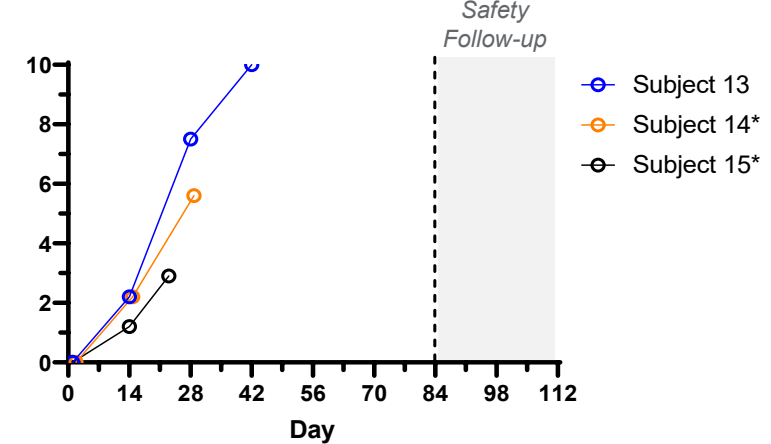
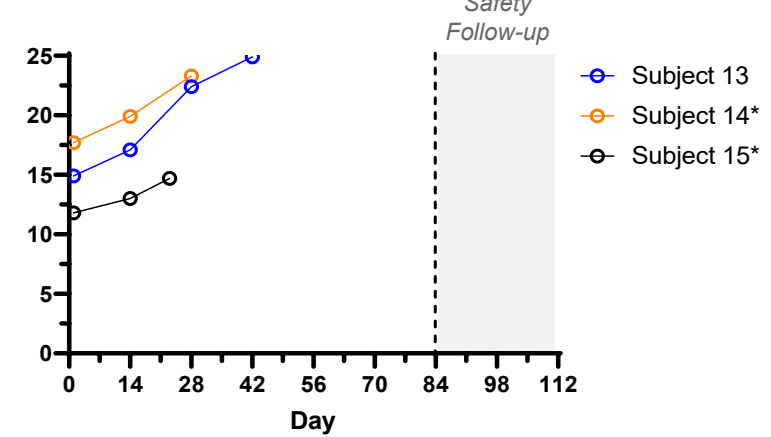
2mg



6mg



12mg



U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023. Safety data collection continued with data cutoff of March 3, 2023.

*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

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

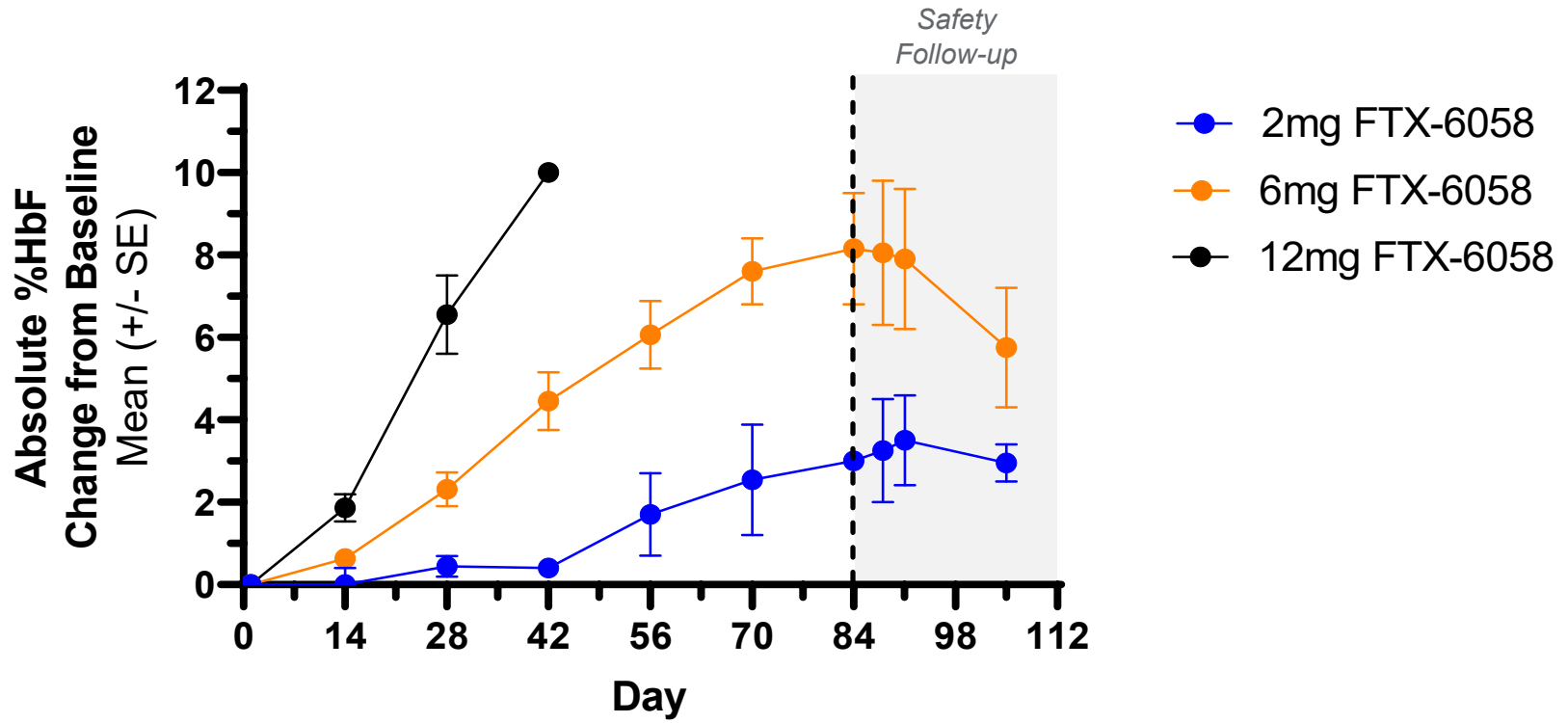
Subject	Dose	Confirmed treatment duration (days)	On-treatment analysis eligible**
1	6 mg	56	✓
2	6 mg	42	✓
3	6 mg	42	✓
4	6 mg	0	
5	6 mg	0	
6	6 mg	0	
7*	6 mg	84	✓
8	6 mg	84	✓
9*	6 mg	28	✓
10*	6 mg	28	✓
11	2 mg	84	✓
12	2 mg	84	✓
13	12 mg	51	✓
14*	12 mg	25	✓
15*	12 mg	22	✓
16	12 mg	4	

U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023. Safety data collection continued with data cutoff of March 3, 2023.

* 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

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

Absolute %HbF Change from Baseline

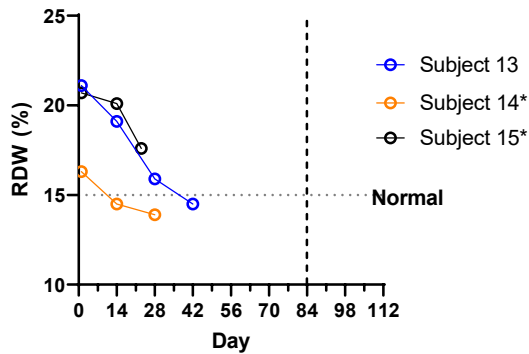
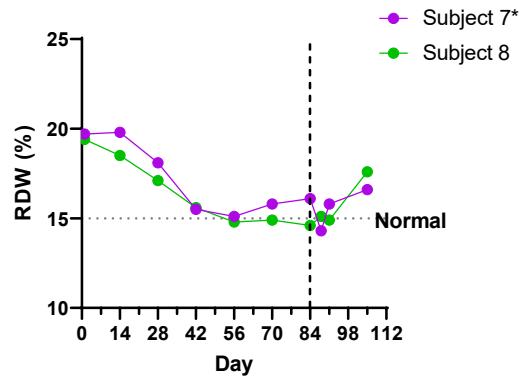


U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023. Safety data collection continued with data cutoff of March 3, 2023.

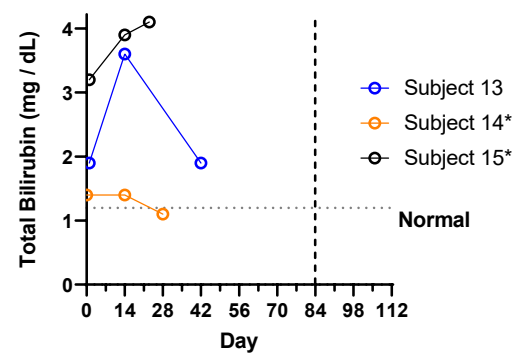
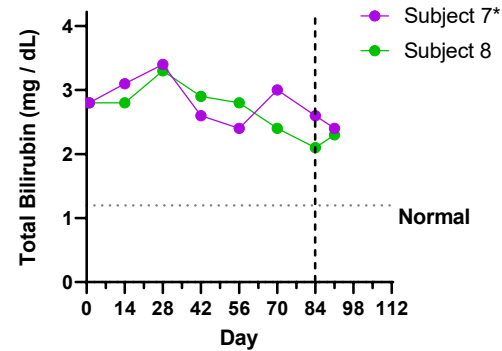
Note: Summary data includes both subjects on and off hydroxyurea; Subject 15 ceased dosing on Day 22 and therefore, was only included in the analysis up to Day 14

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

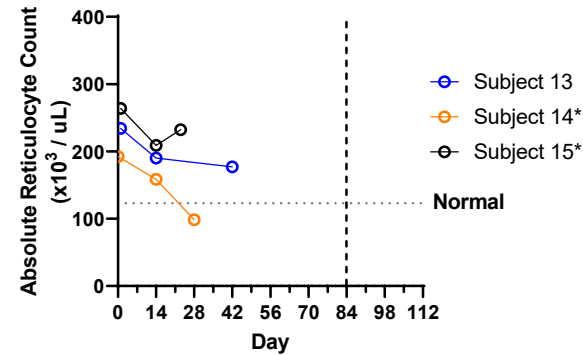
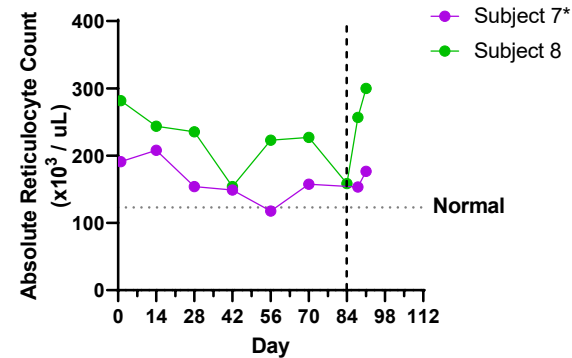
Red Cell Distribution Width (RDW)



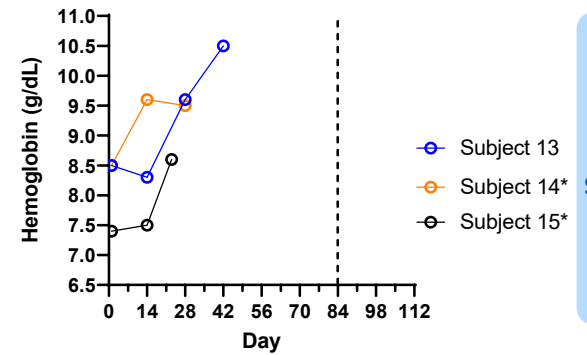
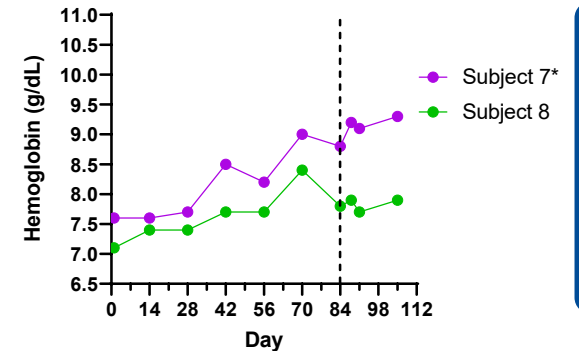
Total Bilirubin



Absolute Reticulocyte Count



Total Hemoglobin



Reductions in RDW indicate RBCs are becoming more uniform in shape

Bilirubin decreases indicate less hemolysis

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

U.S. FDA issued a full clinical hold for FTX-6058 on February 23, 2023. Safety data collection continued with data cutoff of March 3, 2023.

*Subjects on stable dose of hydroxyurea; Note: Subject 15 ceased dosing on Day 22

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

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HbF: fetal hemoglobin; HU: hydroxyurea

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

FDA Fast Track Designation

Composition of matter patent into 2040

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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

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THANK YOU