Fulcrum Therapeutics

Nasdaq FULC

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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**

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

Discovery efforts validated by two clinical programs

Strong cash position with **runway into 2026**

Founded in 2015

IPO in 2019

Ticker: FULC

Robust Small Molecule Pipeline Across Multiple Rare Diseases

Indication	Asset / MOA	Preclinical	Phase 1	Phase 2	Phase 3
Clinical Programs					
FSHD	**Losmapimod** (DUX4 Reduction)				
SCD	**Pociredir** (HbF Induction)				
Discovery Programs					
Blood Disorders					
Muscle Disorders					
Collaborations					
Cardiomyopathies Bristol Myers Squibb™					

FSHD: Facioscapulohumeral muscular dystrophy; HbF: Fetal hemoglobin; SCD: Sickle cell disease

LOSMAPIMOD

for Facioscapulohumeral Muscular Dystrophy (FSHD)

Fast Track Designation

Orphan Drug Designation

Fulcrum Therapeutics

FSHD: Debilitating Disease With No Approved Therapies

The Disease

Chronic, progressive genetic muscular disorder characterized by significant muscle cell death and fat infiltration into muscle tissue

Debilitating Symptoms

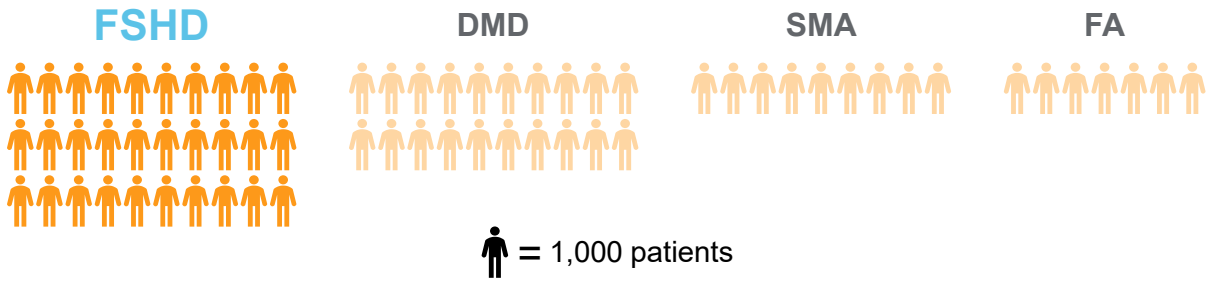
- Significant impairment of upper extremity function and mobility
- Many patients unable to work or live independently
- Approximately 20% of affected individuals become wheelchair-bound

Treatment Options

No approved therapies for FSHD

Population

Second most common adult muscular dystrophy affecting approximately 30,000 individuals in the US*



Disease Progression

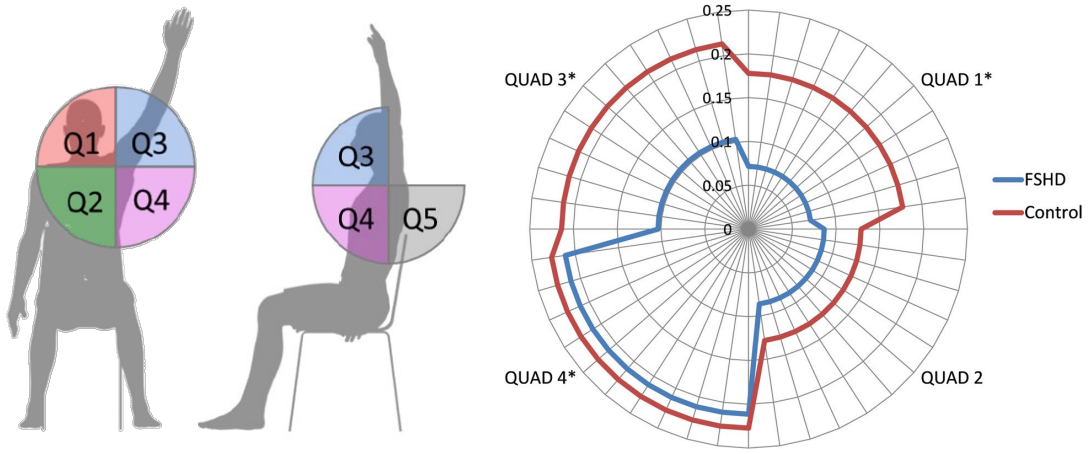
Implementing innovative clinical outcome measures and metrics is necessary to quantify disease progression

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

FSHD: Facioscapulohumeral muscular dystrophy; DMD: Duchenne muscular dystrophy, SMA: Spinal muscular atrophy; FA: Friedreich's ataxia
Hamel and Tawil, Neurologic Clinics, 2020; Himeda and Jones, Annual Review of Genomics and Human Genetics, 2019; Lally et al., Orphanet J Rare Dis, 2017; NORD; MDA.
*Calculated based on prevalence rate 1:8,000 – 1:20,000 in Jia et al, 2021, Neuromuscular Disorders; assuming 333 million US population

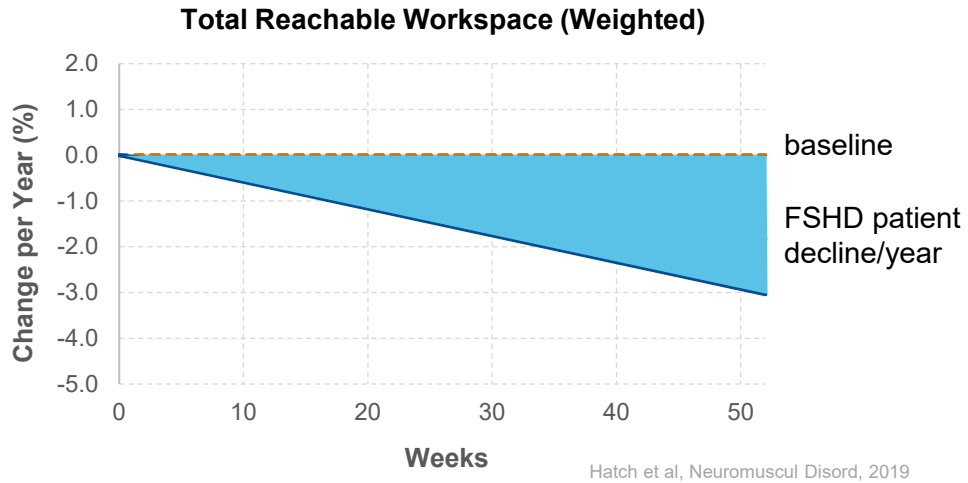
Reachable Workspace Enables Quantification of Disease Progression

RWS measures global upper extremity function



Han et al, Muscle Nerve, 2015

FSHD natural history demonstrates a ~3% RWS decline year over year



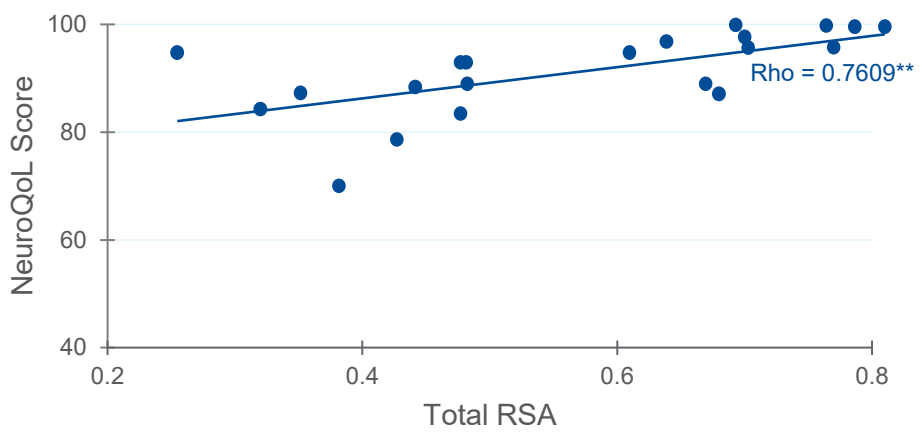
Hatch et al, Neuromuscul Disord, 2019

- Reachable Workspace (RWS) is a quantification of upper limb motion utilizing a contactless sensor-based system
- RWS is evaluated using a series of protocol-directed arm motions (with and without weights) assessing Relative Surface Area (RSA) across five quadrants (Q1-Q5)
- RSA has been shown to correlate 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 a FSHD patient population* exhibited annual declines in RWS of ~3% (measured Q1-Q4) compared to baseline

RWS: Reachable workspace. Han et al, Muscle Nerve, 2014; Han et al, Muscle Nerve, 2015; Hatch et al, AAN Annual Meeting, 2022; Hatch et al, Neuromuscul Disord, 2019; Kurillo et al, Technol Health Care, 2013; Mellion et al, AAN Annual Meeting, 2022
*N=16 patients

RWS correlates to FSHD Patient-reported Outcomes such as Neuro-QoL-Upper Extremity in Natural History Studies



Summed score of all 20 NeuroQoL-UE questions

Spearman Correlation Coefficients for Reachable Workspace to NeuroQoL-UE

	Total RSA	P-value
NeuroQoL-UE Raw	0.7609	0.0001

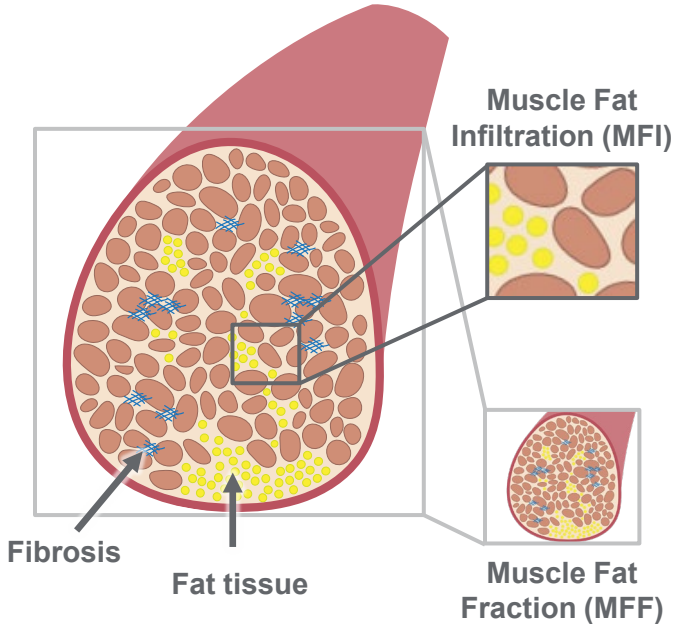
Hatch et al, Muscle Nerve, 2021

UE: Upper Extremity; RSA: Relative Surface Area; Hatch et al., Muscle Nerve, 2021.

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

Dystrophic Skeletal Muscle Tissue in FSHD

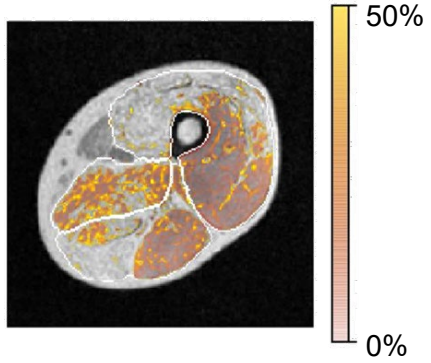
Tissue infiltration contributes to the loss of function by altering biomechanical properties



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

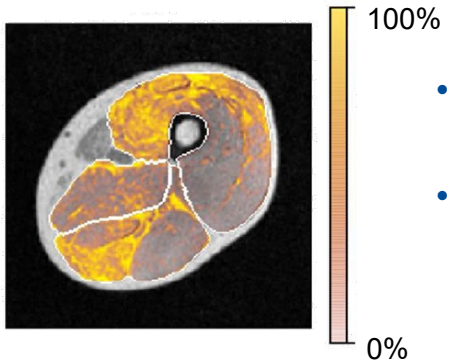
18 muscles are analyzed bilaterally (36 total muscles analyzed)

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

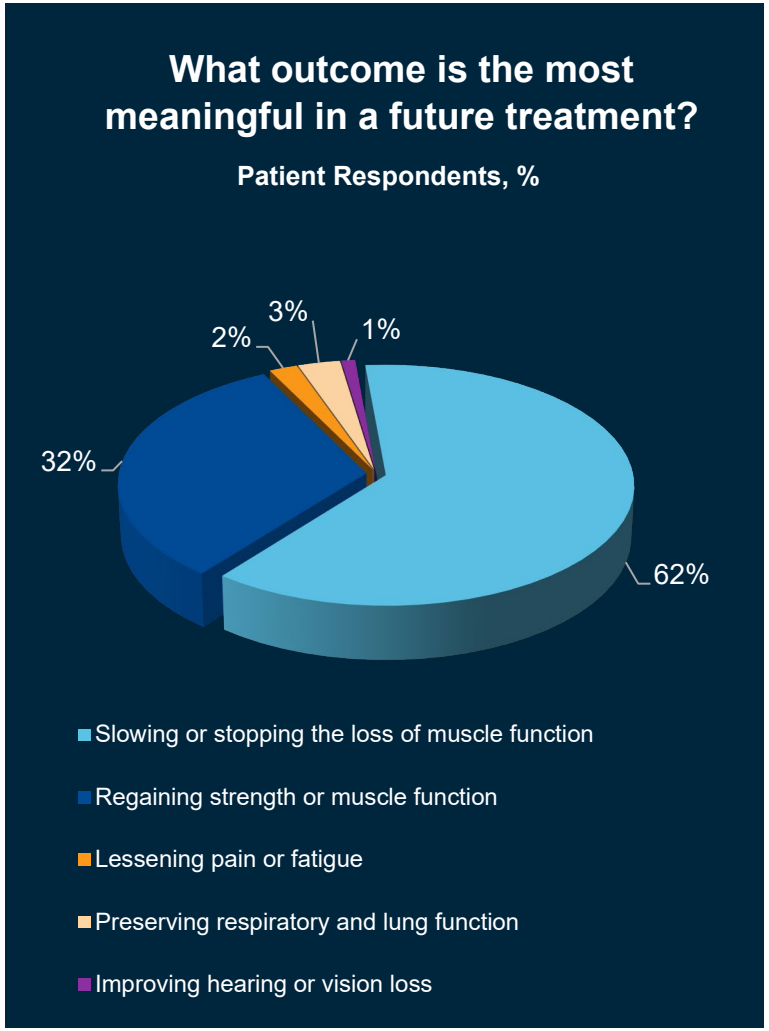
Muscle Fat Fraction (MFF)



- 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

MFF: Muscle Fat Fraction; MFI: Muscle Fat Infiltration; MRI: Magnetic Resonance Imaging. Mellion, Tawil, et. al. Neurology. 2022; Mellion, Widholm, et. al. Neurology. 2022.

Unmet Need for Safe and Effective Drug That Slows Disease Progression



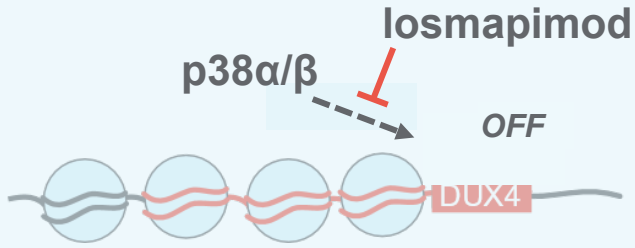
*"I would like to see something that would **stop progression** of the disease"*
– 26-year-old woman with FSHD

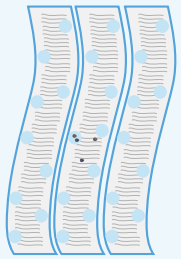
*"…if we had a therapy that at minimum **slowed the progression…** we would be able to guide and plan for what her future looks like."*
– Mother of young girl with FSHD

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

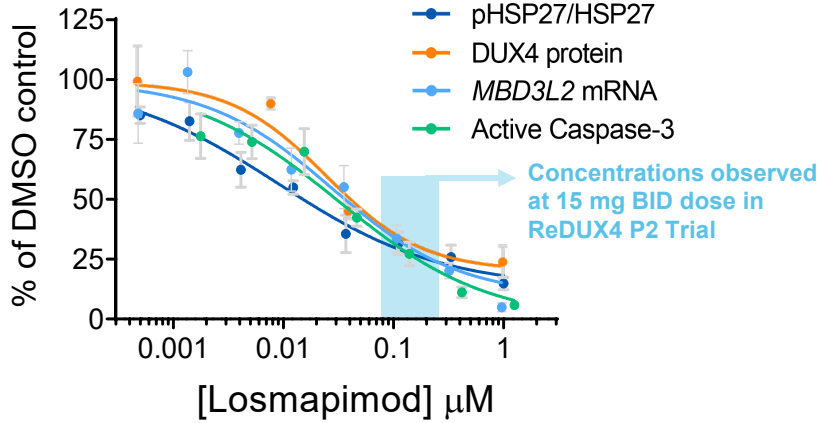
Arjomand J, et al. Facioscapulohumeral muscular dystrophy (FSHD) voice of the patient report. Published November 5, 2020. Accessed March 1, 2021

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

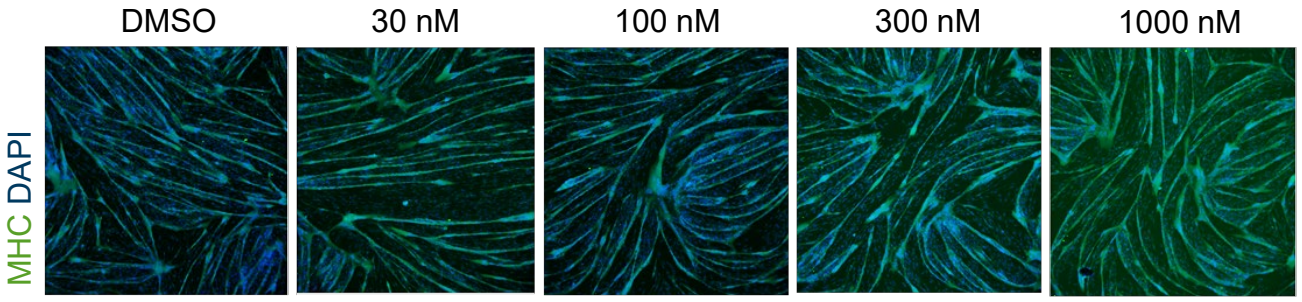




Losmapimod Reduces Aberrant DUX4 and Downstream Gene Expression



No changes in differentiation



Mahadevan. Science. 2010; Rojas, et al. J Pharmacol Exp Ther. 2020.
HSP27: substrate of p38 MAP kinase pathway; **MBD3L2**: DUX-4 target gene; **Caspase 3**: Indicator of cell Death

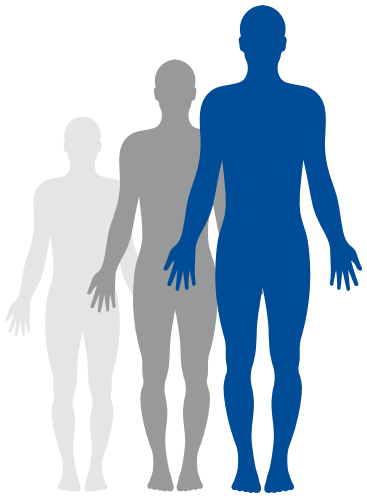
Fulcrum Therapeutics

ReDUX4: Phase 2 Trial Design

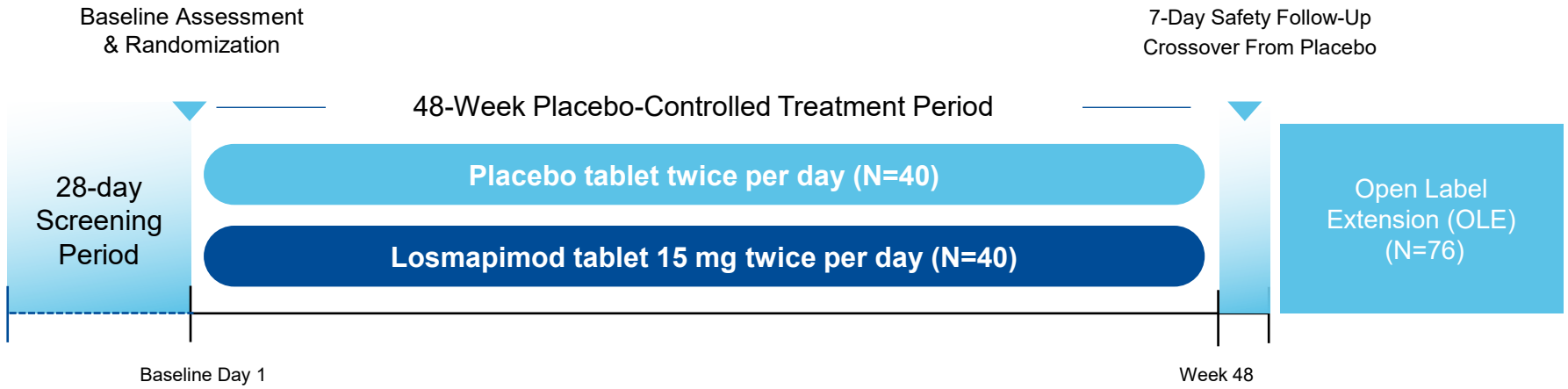
Study Population

ReDUX4:
~80 subjects, 18-65 years old

ReDUX4 OLE:
95% of participants continued



Study Design



Study Endpoints

Primary Endpoint

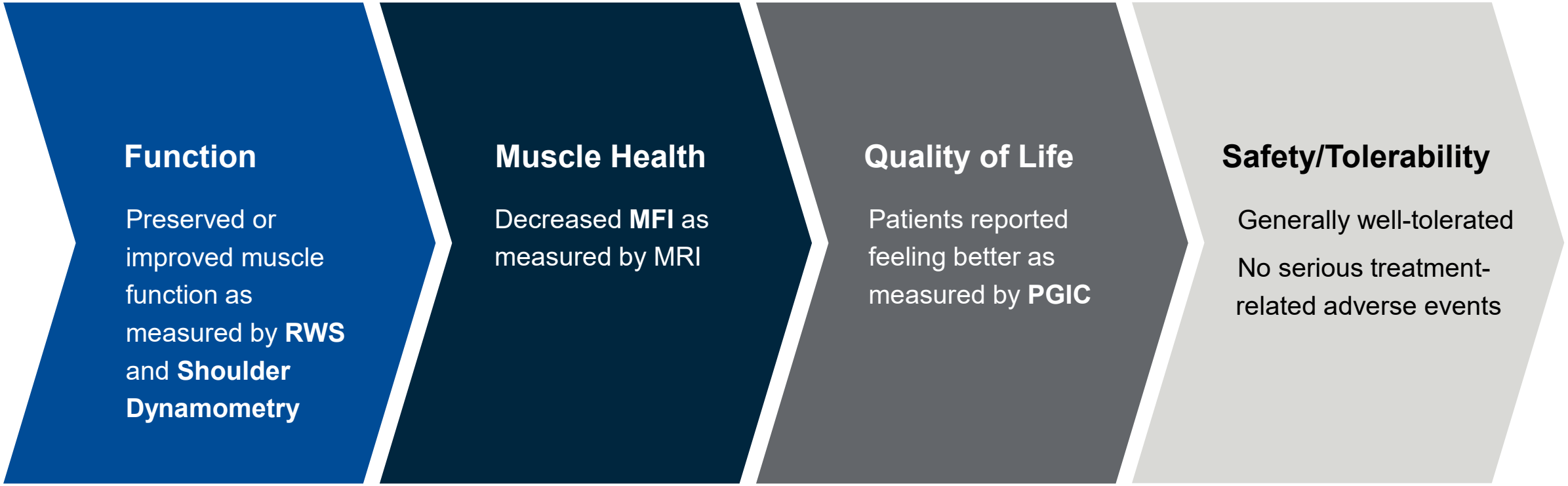
Change from baseline in DUX4 activity (muscle needle biopsy)

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 activity

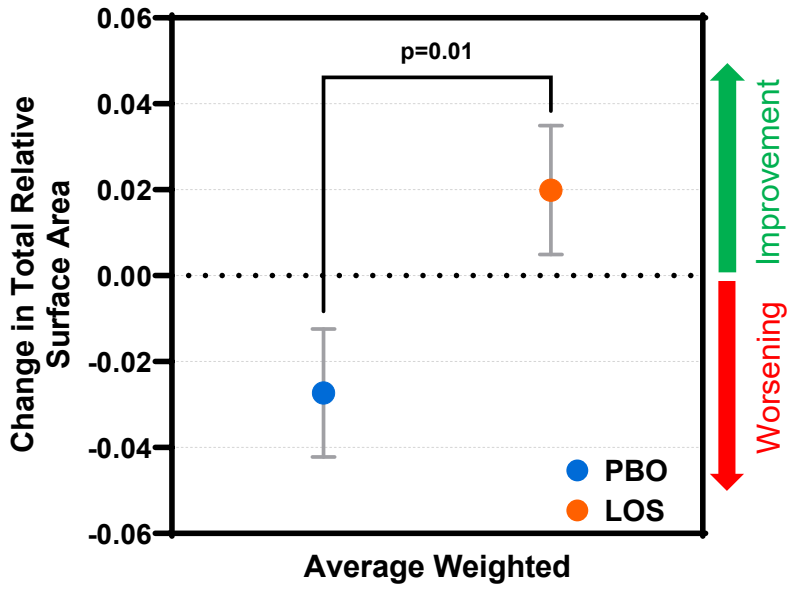
ReDUX4 Showed Clinical Benefits at Week 48



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

Losmapimod Demonstrated Significant Improvement in RWS Relative to Placebo with a Durability of Effect in Open Label Extension

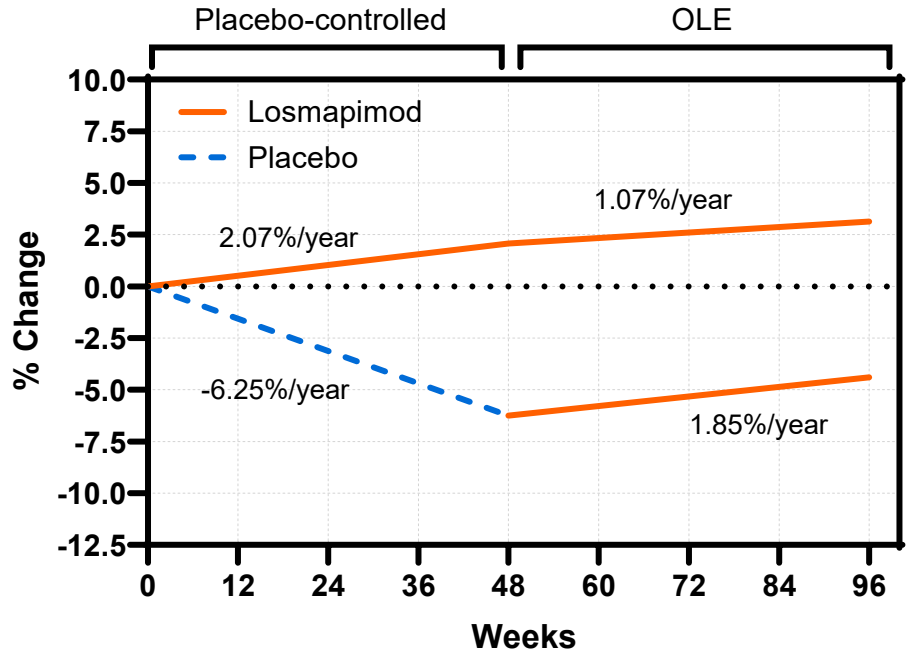
Change from Baseline in Average Total RSA (Q1-5) + Weight at 48 Weeks



Absolute Baseline Average Total RSA + Weight

	PBO	LOS
Baseline RSA (SE)	0.540 (± 0.038)	0.532 (± 0.036)

Annualized % Change of Average Total RSA (Q1-5) + Weight



	RCT (48 Weeks) LOS vs. PBO	OLE (96 Weeks) LOS vs. LOS
P-value*	0.04	0.80

Data from ReDUX4 trial and the ReDUX4 OLE trial; RSA: Relative surface area; OLE: Open label extension; PBO: placebo; LOS: losmapimod
*P-value of the difference in rate of change

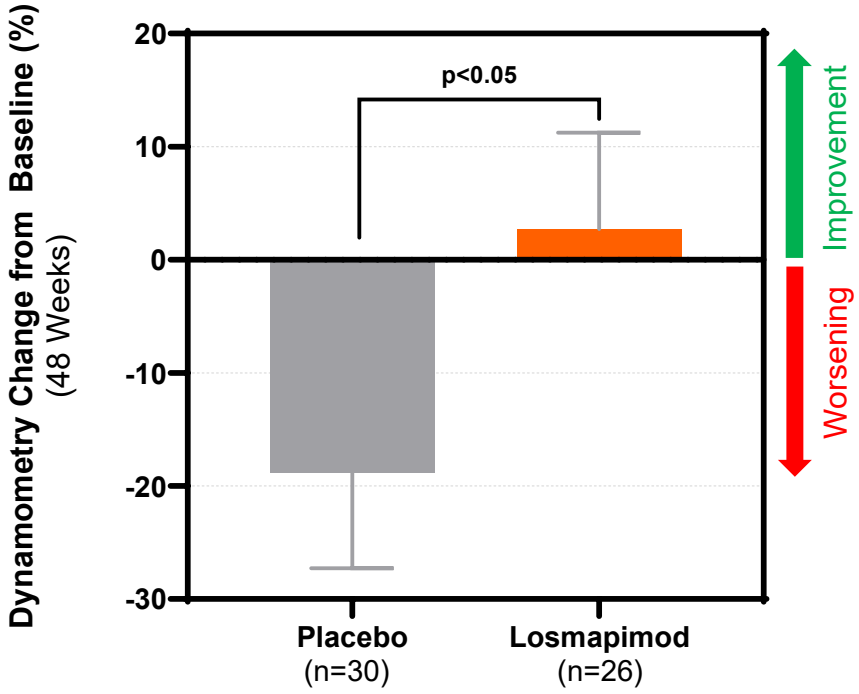
FULCRUM THERAPEUTICS

Fulcrum Therapeutics

Losmapimod Demonstrated Significant Improvement in Shoulder Abductors Dynamometry Relative to Placebo at 48 Weeks

UE muscle strength (as measured by dynamometry) is strongly correlated to UE function as measured by RWS

Shoulder Abductors Average Dynamometry of Both Arms



Correlation Between Reachable Workspace and Shoulder Abductor Dynamometry

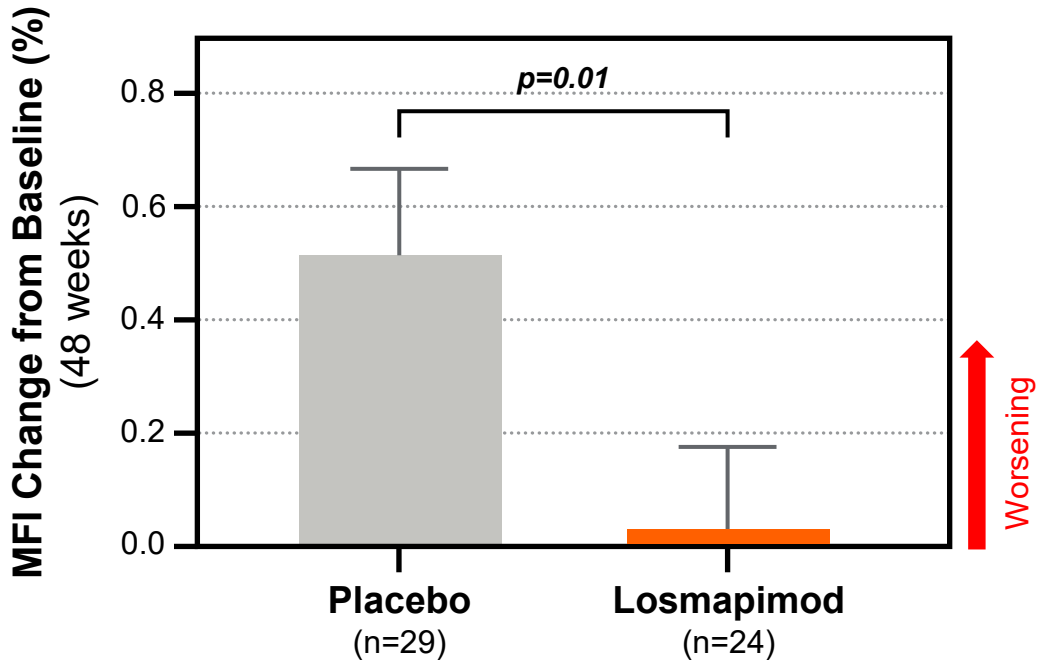
RSA vs. Dynamometry Shoulder Strength – 2-arm Average

	LOS (n=25)	PBO (n=29)	Total (n=54)
Spearman r (95% CI)	0.86 (0.70, 0.94)	0.86 (0.72, 0.93)	0.86 (0.77, 0.92)
p value	<0.0001	<0.0001	<0.0001

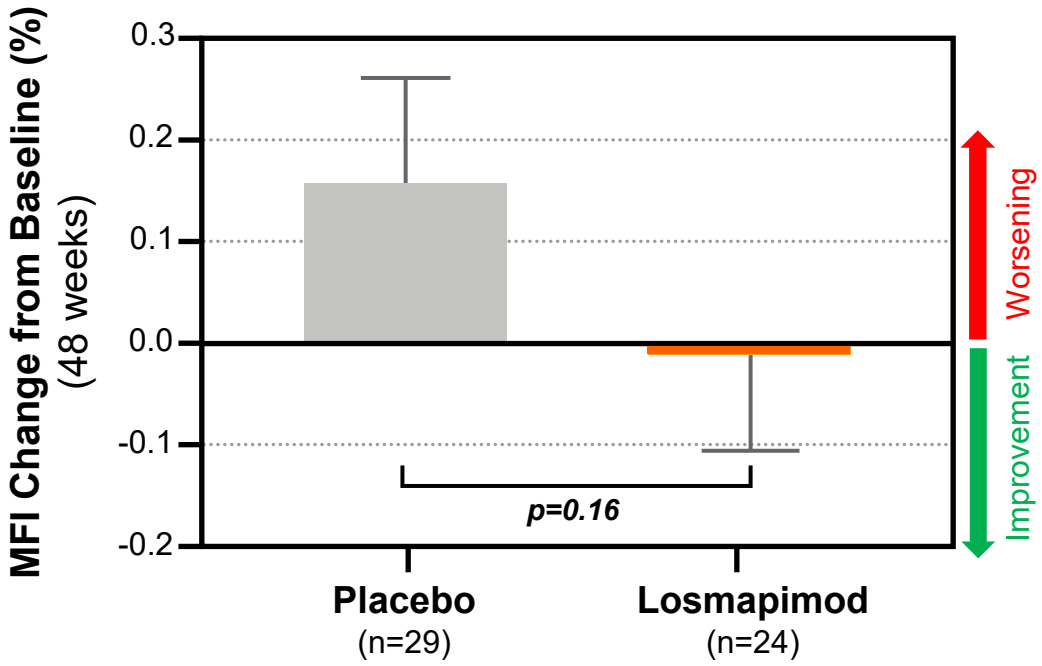
Data from ReDUX4 trial
LOS: losmapimod; UE: Upper extremity; PBO: Placebo; SE: Standard error; CI: Confidence interval; RWS: Reachable workspace; RSA: Relative surface area.

Losmapimod Improved or Maintained Muscle Health at 48 Weeks

Losmapimod slowed fat infiltration in intermediate muscles already affected by disease



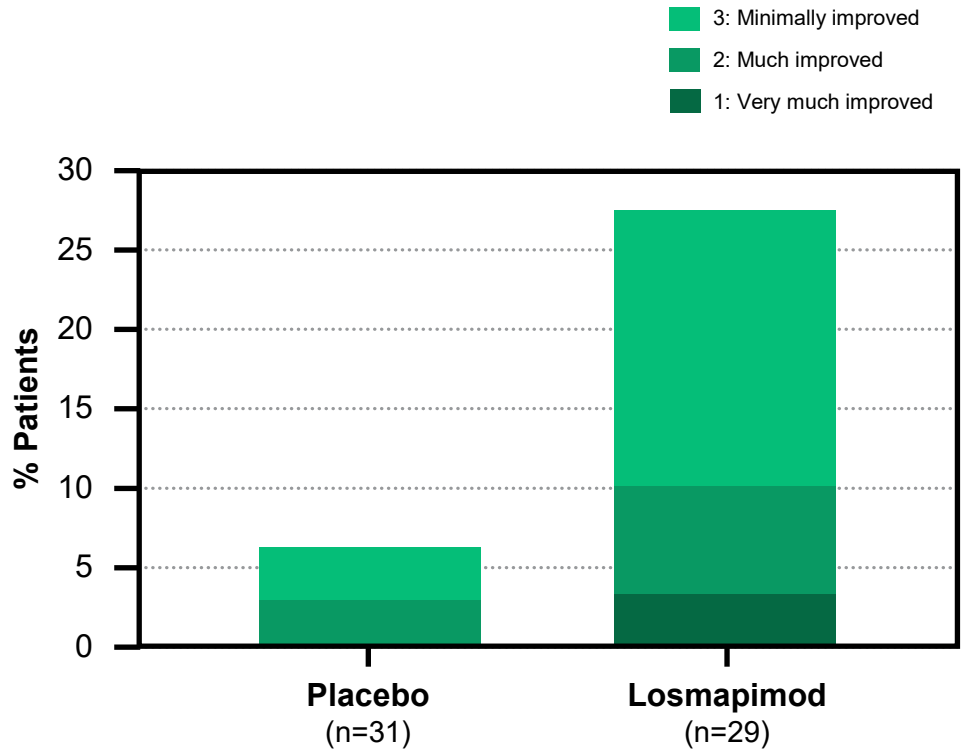
Losmapimod preserved health of normal-appearing muscles, limiting fat infiltration



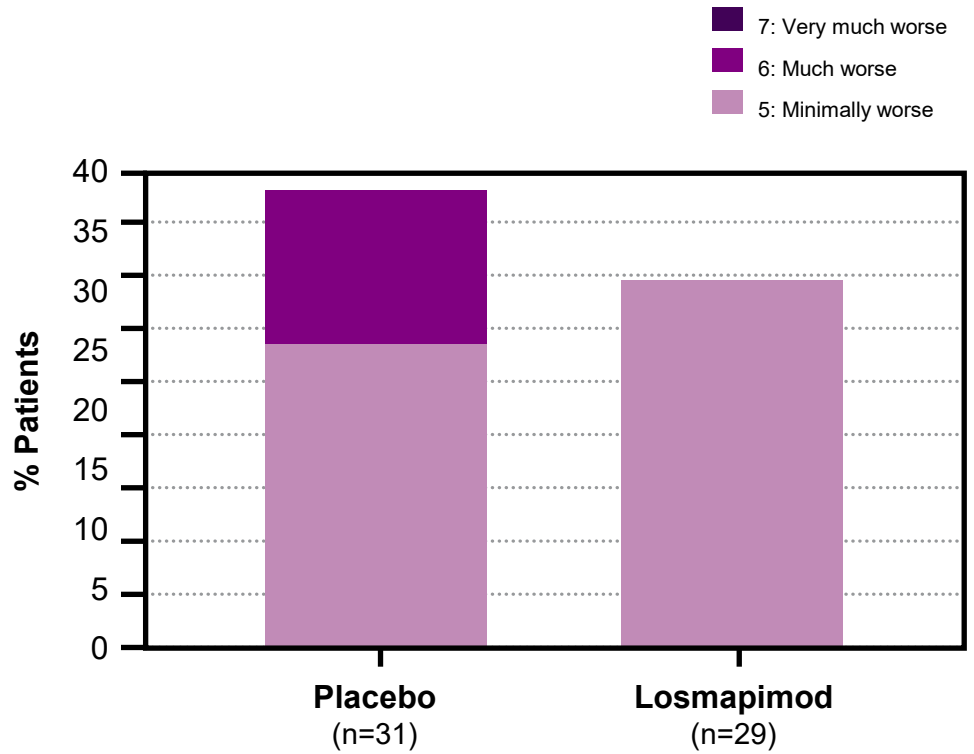
Data from ReDUX4 trial
MFI: muscle fat infiltration

Losmapimod Improved Patient-reported Outcomes 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 (ReDUX4 – Placebo Controlled Period)

Number of Patients with:	Losmapimod (n=40) n (%)	Placebo (n=40) n (%)
Any TEAE	29 (72.5)	23 (57.5)
Any treatment-related TEAE	9* (22.5)	2 (5.0)
Any serious adverse event (SAE)	2** (5.0)	0
Any TEAE leading to treatment discontinuation	0	0
Any TEAE leading to death	0	0
AE by Maximum Severity		
Mild	18 (45.0)	15 (37.5)
Moderate	9 (22.5)	8 (20.0)
Severe	2 (5.0)	0
Most Common AEs		
Fall	6 (15.0)	2 (5.0)
Procedural pain	2 (5.0)	3 (7.5)
Back pain	2 (5.0)	3 (7.5)
Headache	2 (5.0)	5 (12.5)

- Majority of treatment-emergent adverse events (TEAEs) were mild or moderate
- Majority of TEAEs not related or unlikely related to study drug
- No deaths or subject discontinuations due to TEAEs
- No significant changes in vital signs, laboratory studies or EKG
- Observed safety and tolerability data are consistent with prior losmapimod experience in **>3,600** clinical study participants

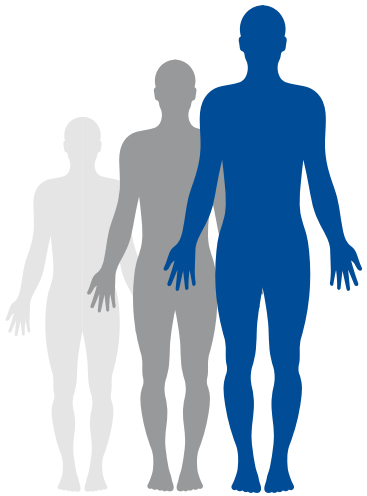
*9 subjects in the losmapimod group had TEAEs considered possibly related to study drug, the most frequent of which were dyspepsia, rash, and alanine aminotransferase increase (each occurred in 2 participants)
**Three serious adverse events (SAEs), post-op wound infection, alcohol poisoning, and a suicide attempt, were reported in 2 participants in the losmapimod group. All SAEs were severe and assessed as unrelated to study drug

Data from ReDUX4 trial.

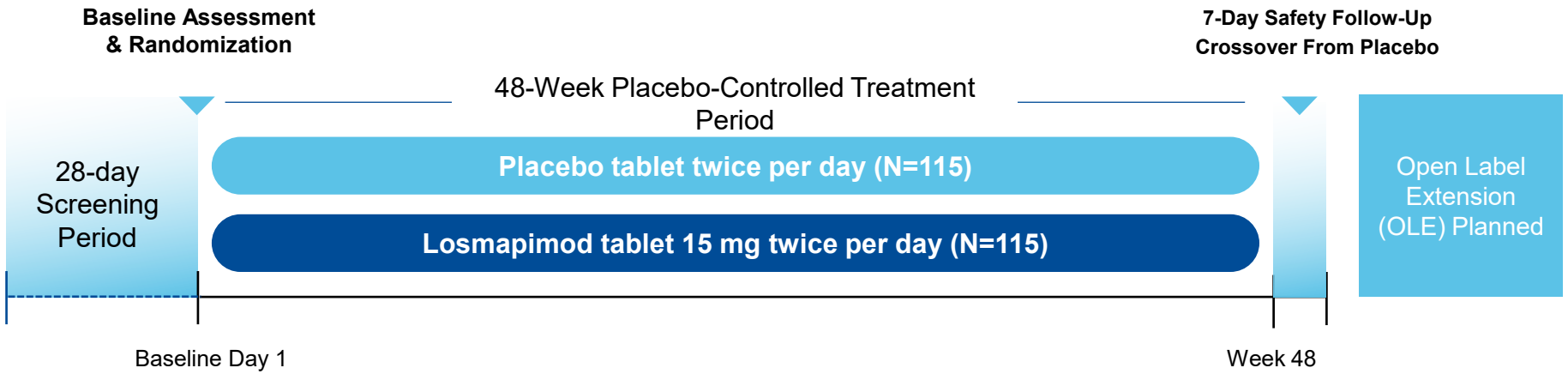
REACH: Global Phase 3 Trial of Losmapimod in FSHD

Study Population

Enrollment completed:
260 patients*, 18-65 years old



Study Design



Study Endpoints

Primary

Average RWS quantification of total relative surface area with 500g wrist weight in dominant arm and non-dominant arms

Secondary

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

Exploratory

- Healthcare utilization questionnaire
- EQ-5D questionnaire

RWS: Reachable Workspace; MFI: Muscle Fat Infiltration; PGIC: Patients' Global Impression of Change
*Trial was oversubscribed

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-in-class 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 participants 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

Pociredir

for Sickle Cell Disease

Fast Track Designation

Orphan Drug Designation

Fulcrum Therapeutics

Sickle Cell Disease: Debilitating Disease with High Unmet Need

The Disease

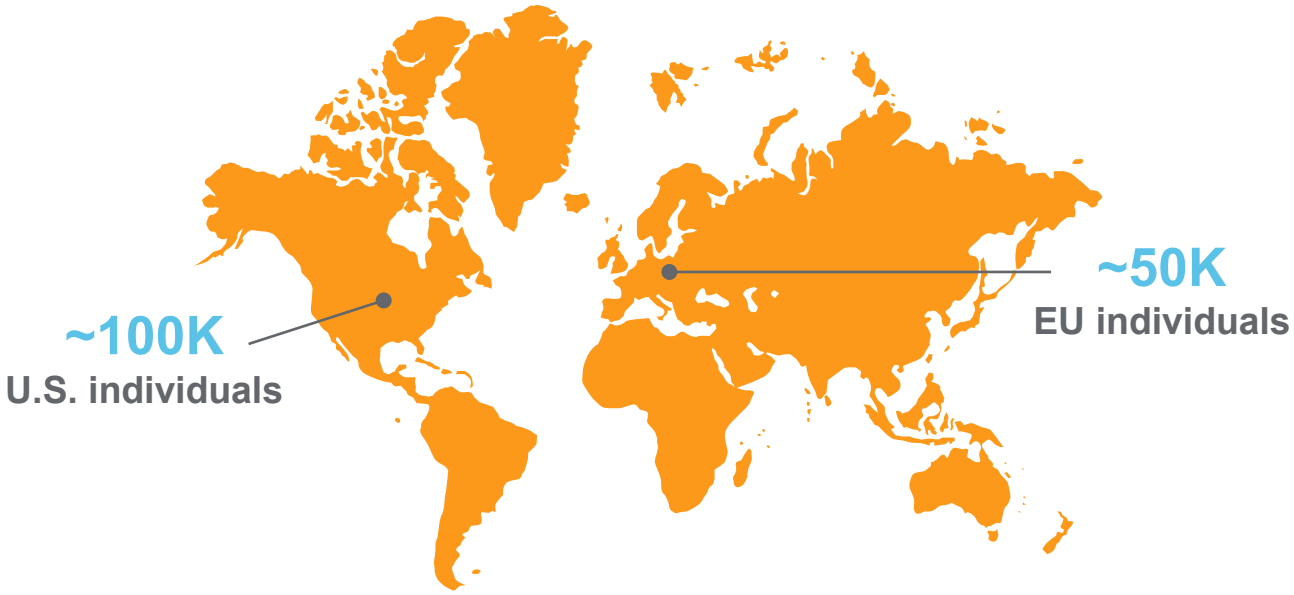
Genetic disorder caused by mutation in Hemoglobin-Beta (*HBB*) gene

Results in abnormal sickle-shaped red blood cells that 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



4.4 million worldwide

SOC: Standard of Care; VOC: Vaso-occlusive crisis; CDC; WHO; UpToDate.

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

Ex Vivo Genetic Therapies

BCL11A Editing & Beta-globin Gene Delivery

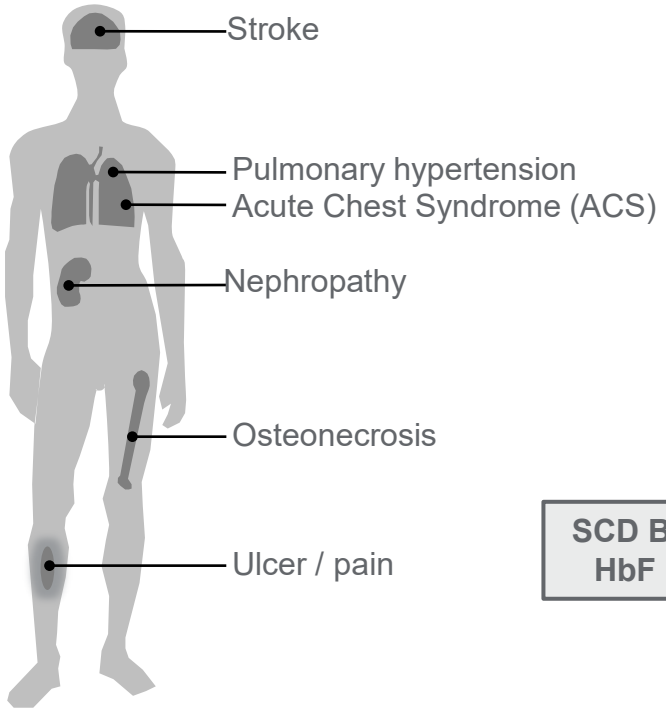
- \+ Potential for a cure
- − Highly invasive
- − Unknown durability
- − Barriers to access

SCD: Sickle cell disease; VOC: Vaso-occlusive crisis

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

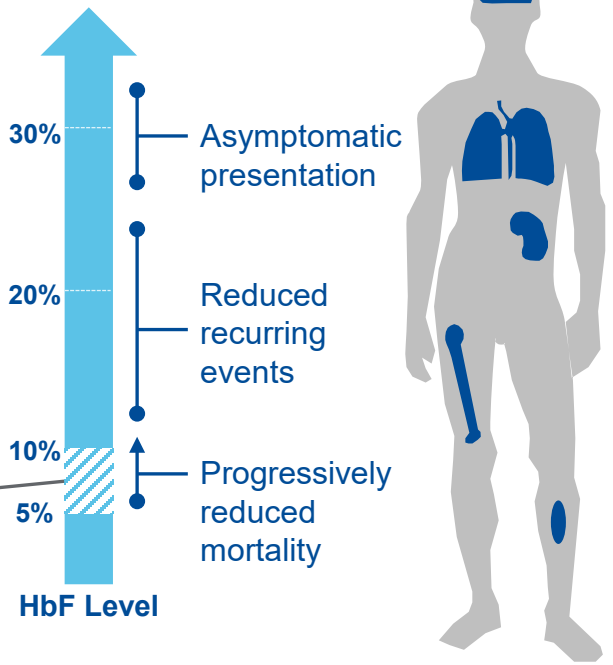
Even incremental increases in HbF can lead to meaningful improvement in disease severity

Typical SCD Subject



SCD Baseline HbF 5-10%

SCD Subject with High HbF Levels



- Reduced hemolysis
- Reduced anemia
- Reduced VOCs
- Fewer recurring events

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

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

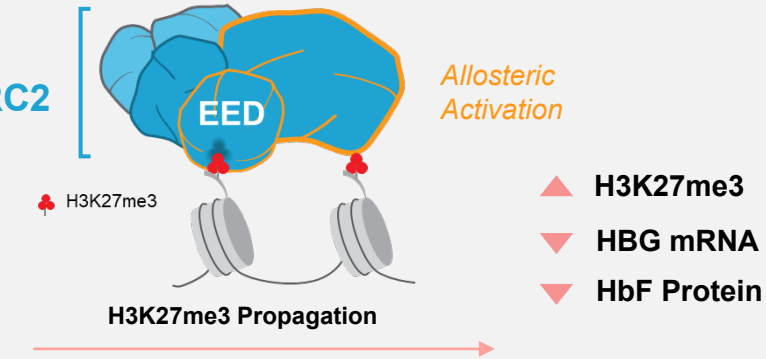
Targeting EED Results in HbF Increases

CRISPR + Compound Screening Engine
Experimentally screened candidate targets

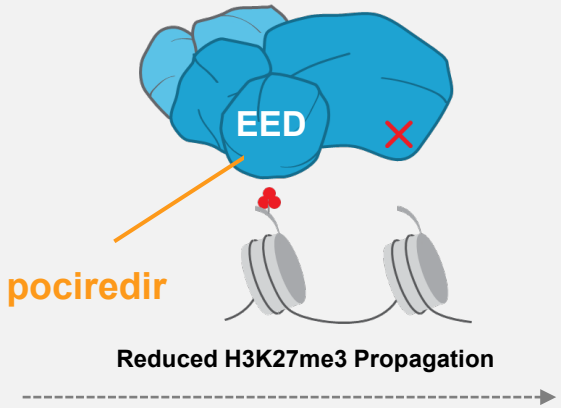
Computational Data Mining
Computationally mined candidate targets

Identified Targets that Regulate HbF

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



Pociredir is a Potent and Selective EED Binder



- H3K27me3 ▼
- HBG mRNA ▲
- HbF Protein ▲

pociredir

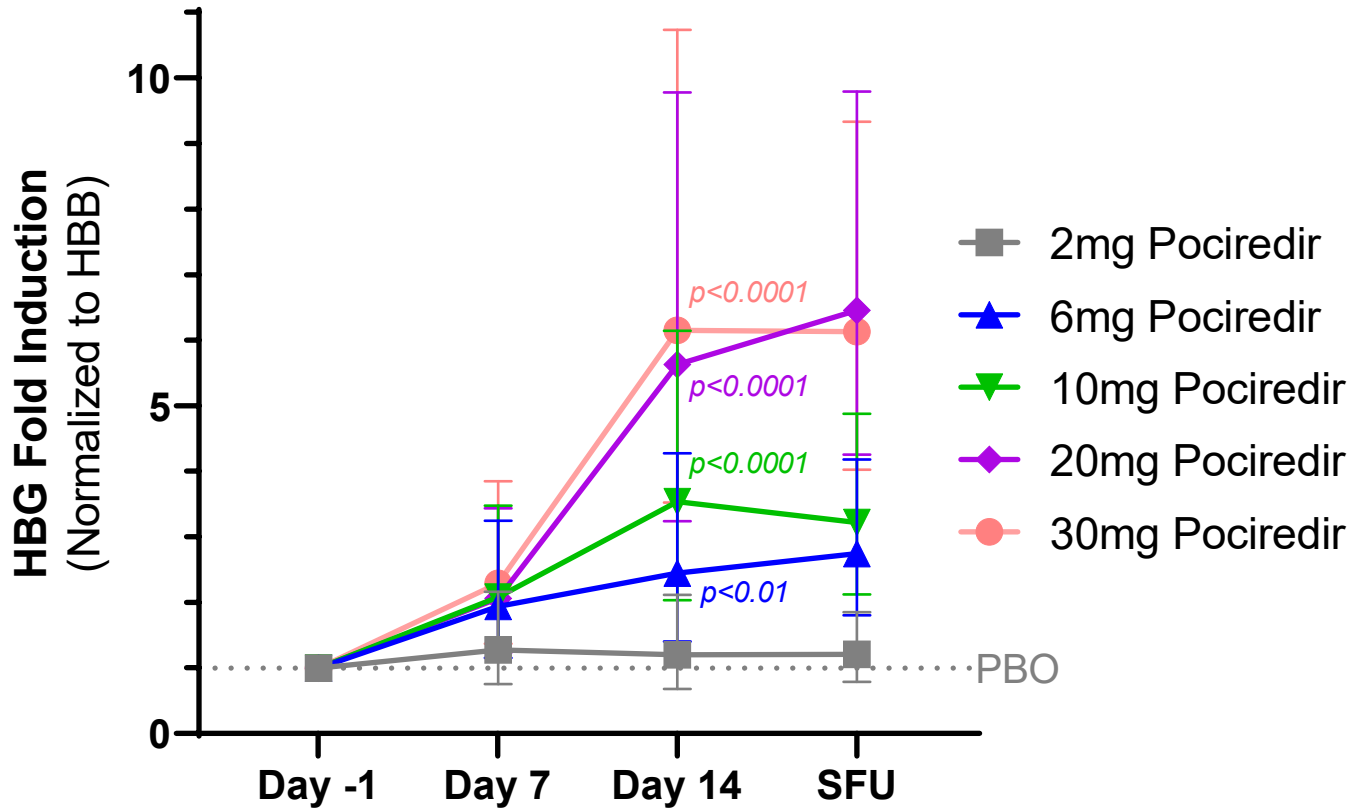
- **Highly Selective**
- **Clean Off-target Profile**
- **Composition of Matter Patent Expires 2040**

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

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



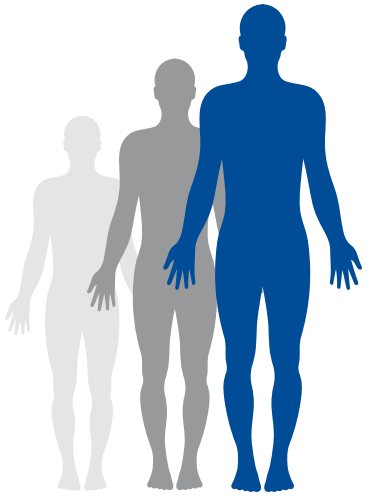
Safety follow-up (SFU) samples were collected 7 – 10 days post 14-day treatment period; PBO: placebo; Data presented as geometric LS mean ratio (to placebo) with 95% confidence interval; mixed-effects model for repeated measures (MMRM) analysis performed for Day 7 and Day 14; analysis of covariance (ANCOVA)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

Pioneer Phase 1b Clinical Trial in SCD Subjects

Study Population

Males and females with SCD, between age 18 – 65

Approximately 10 subjects per cohort



Study Design

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 lifted the clinical hold for pociredir on August 18, 2023. *Reinitiated trial at the 12mg dose, to be followed by the 20mg dose

Pociredir Was Generally Well-tolerated with No Serious Treatment-related Adverse Events (Pioneer Ph1b – Open Label)

Number of Patients with:	Pociredir (n=16) n (%)
Any TEAE	10 (62.5)
Any treatment-related TEAE	5 (31.3)
Any serious adverse event (SAE)*	4 (25.0)
Any TEAE leading to treatment discontinuation	0
Any lab-related TEAE	0
Patients with TEAE (by Maximum Severity)	
Mild	4 (25.0)
Moderate	5 (31.3)
Severe	1 (6.3)
Most Common TEAEs	
Pain crisis	4 (25.0)
Headache	3 (18.8)

* In 3 (of 4) patients, SAE began prior to first dose of study drug

- 23 Treatment Emergent Adverse Events (TEAEs) in 10/16 (62.5%) patients
  - 8/23 treatment-related TEAEs in 5/16 (31.3%) patients: (headache [x2], lip numbness, diarrhea, fatigue, somnolence, nausea, tinnitus)
    - All mild in severity, non-serious and resolved while patient remained on study drug
- 4/23 TEAEs (in 4 patients) characterized as VOC (pain crisis) per protocol definition
  - None reported as related to study drug
  - Two VOCs occurred in patients documented non-adherent to study drug
- Single SAE in patient on study drug*
  - VOC with chest syndrome, reported as not related to study drug

TEAE: Treatment-emergent Adverse Event; SAE: Serious adverse event; VOC: Vaso-occlusive crisis;

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

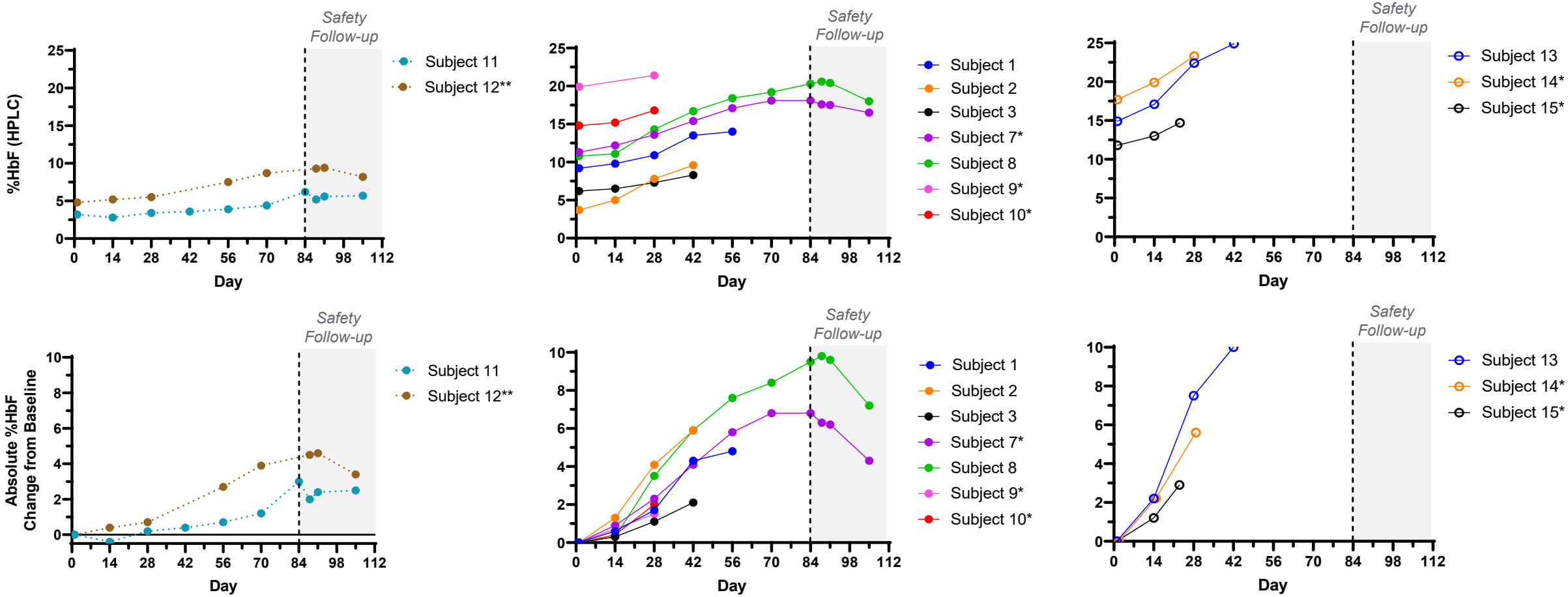
Subject	Dose	Confirmed treatment duration (days)	On-treatment analysis eligible**
1	6 mg	56	✓
2	6 mg	42	✓
3	6 mg	42	✓
4	6 mg	0	
5	6 mg	0	
6	6 mg	0	
7*	6 mg	84	✓
8	6 mg	84	✓
9*	6 mg	28	✓
10*	6 mg	28	✓
11	2 mg	84	✓
12	2 mg	84	✓
13	12 mg	51	✓
14*	12 mg	25	✓
15*	12 mg	22	✓
16	12 mg	4	

U.S. FDA issued a full clinical hold for pociredir 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

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

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

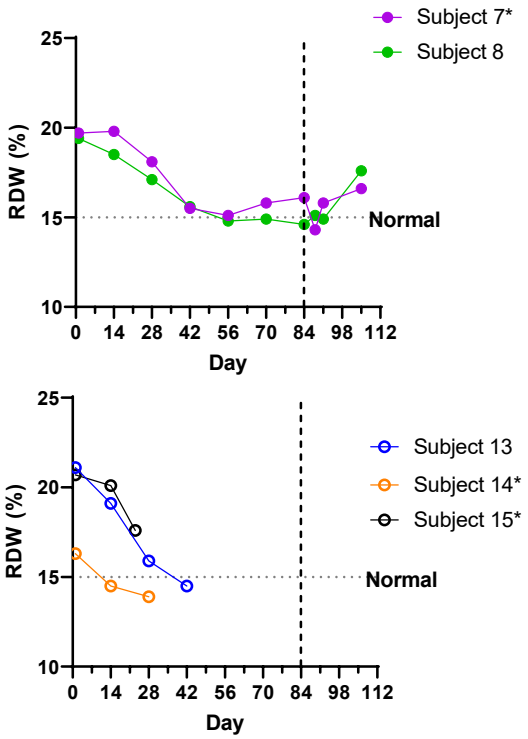


U.S. FDA issued a full clinical hold for pociredir on February 23, 2023. Safety data collection continued with data cutoff of March 3, 2023.

*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

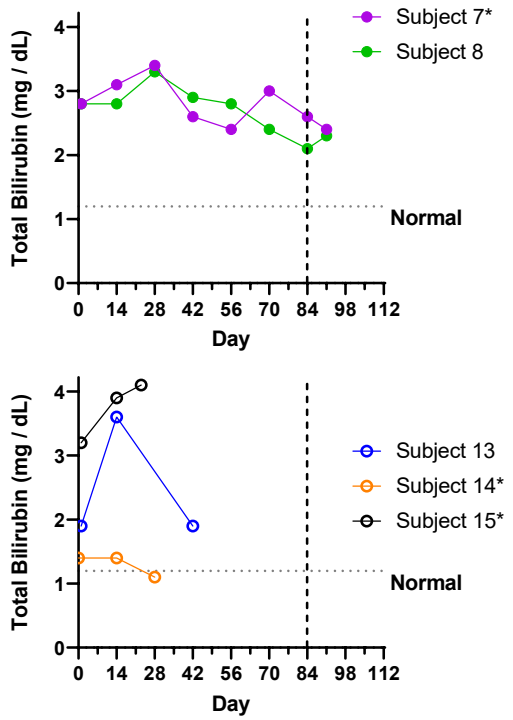
Initial Data from 6 mg and 12 mg Pociredir Demonstrates Improvements in Biomarkers of Hemolysis

Red Cell Distribution Width (RDW)



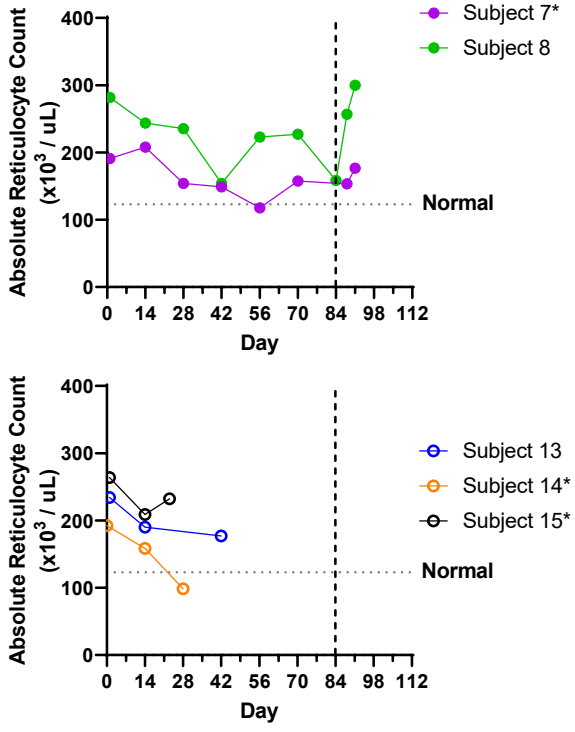
Reductions in RDW indicate RBCs are becoming more uniform in shape

Total Bilirubin

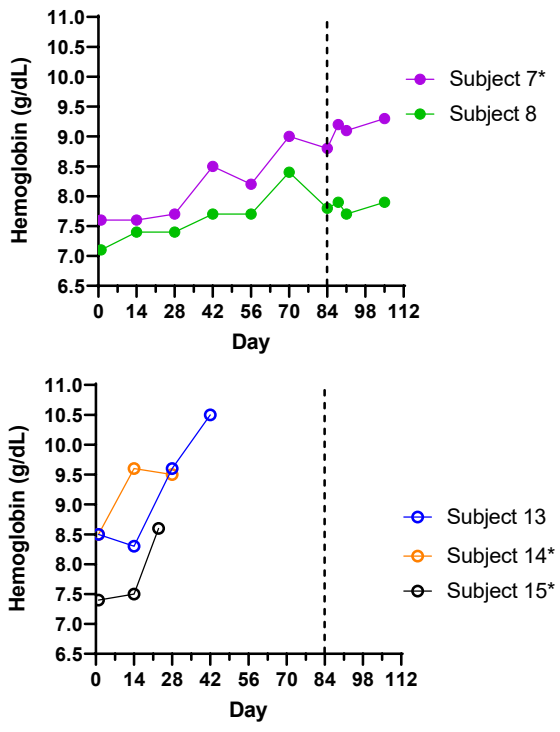


Bilirubin decreases indicate less hemolysis

Absolute Reticulocyte Count



Total Hemoglobin



6 mg

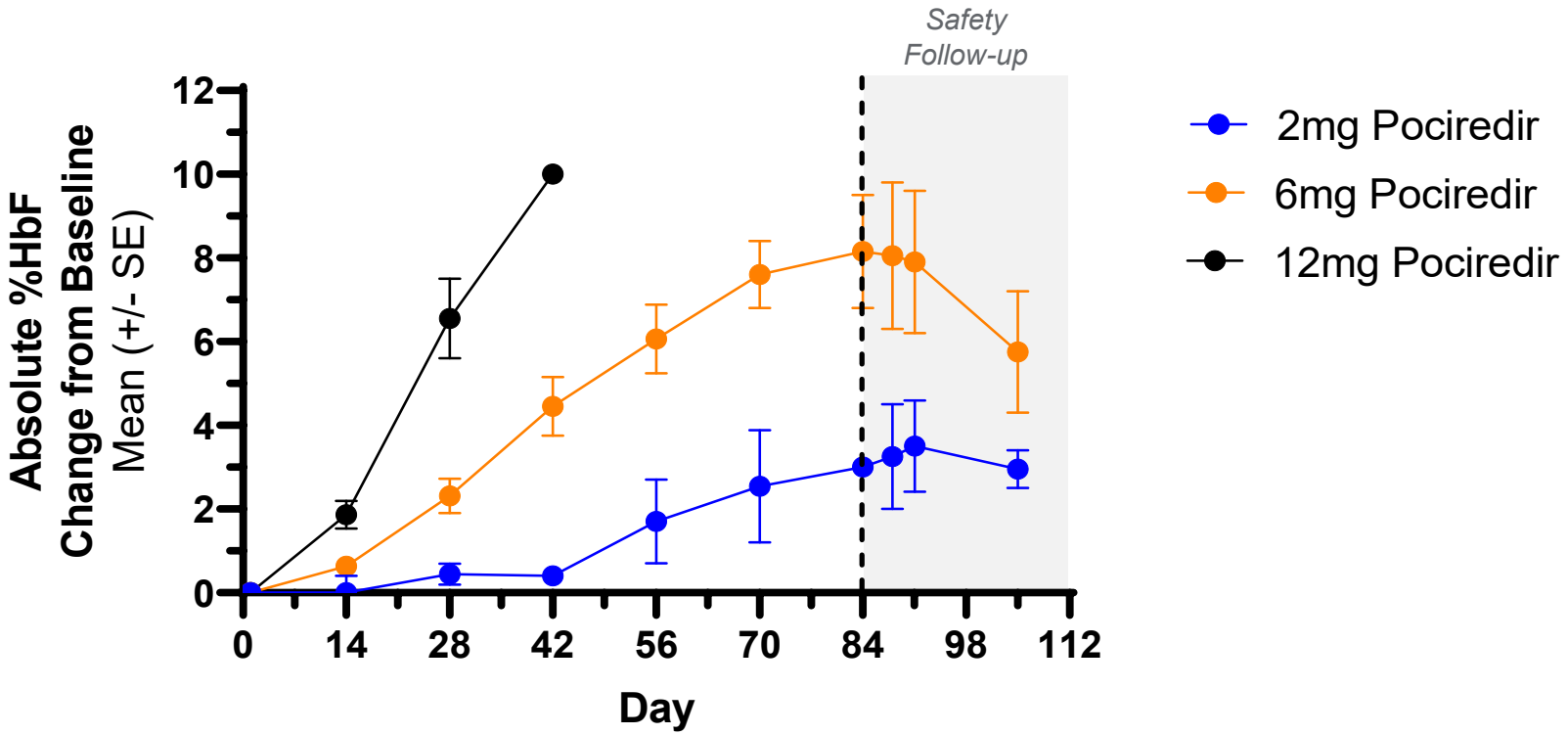
12 mg

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

Initial Pociredir Data Demonstrates Dose-dependent Increases in HbF

Absolute %HbF Change from Baseline



U.S. FDA issued a full clinical hold for pociredir 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

Overview of Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

Patient Severity

Previous experience with **hydroxyurea**

AND

Previous experience with a stable dose of **voxelotor or crizanlizumab or L-glutamine**

OR

Lack of access to these advanced therapies

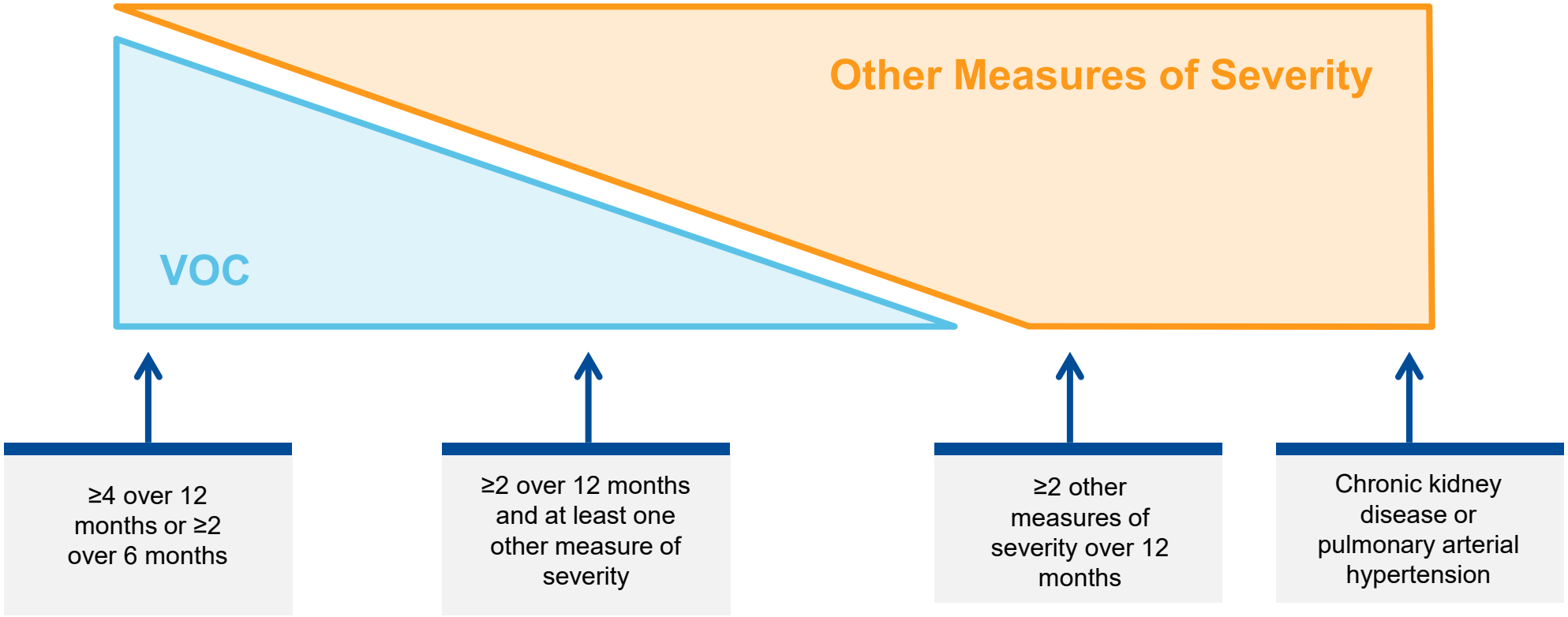
Key Exclusion Criteria

Exclude subjects currently on /having received the following therapies within 60 days prior to initiating pociredir:

hydroxyurea and voxelotor or crizanlizumab or L-glutamine

We estimate that there are approximately 7,500 to 10,000 patients in the U.S. that meet the inclusion and exclusion criteria of the amended protocol

Overview of Key Inclusion Criteria: Patient Severity



Overview of Key Inclusion Criteria: Previous Use of Hydroxyurea AND One Other Approved Therapy

Hydroxyurea

- Continued VOC or episodes of acute chest syndrome for at least 6 months at the maximum tolerated dose
- Inability to tolerate the adverse effects of the therapy
- Unmanageable drug-drug interactions
- Patient refusal

And

Voxelotor or crizanlizumab or L-glutamine

- Continued pain crises and other VOCs while on stable dose for at least 6 months
- Failure to increase Hb by 1 g/dL (for vox.) or continued VOC episodes (for criz. or L-glutamine)
- Inability to tolerate the adverse effects of the therapy
- Unmanageable drug-drug interactions
- Patient refusal

Or

Lack of access to advanced therapies

- Lack of availability
- Lack of insurance coverage

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 pociredir was generally well-tolerated

HbF: fetal hemoglobin; HU: hydroxyurea

Pociredir: 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 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*

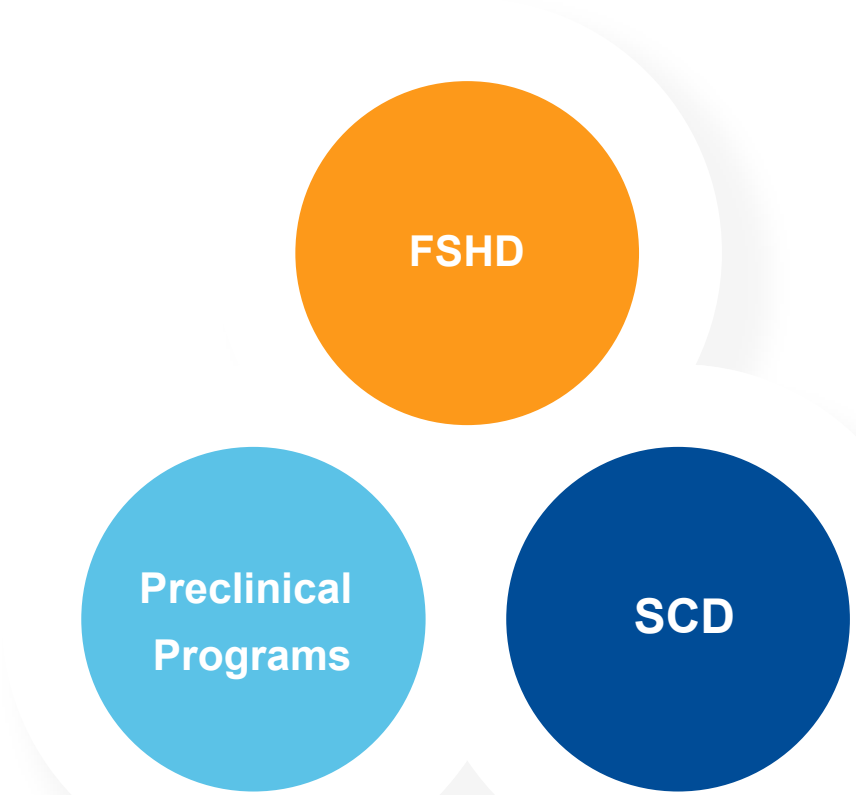
Development path forward

FDA Fast Track Designation

Composition of matter patent into 2040

Sedrak and Kondamudi, StatPearls, last update August 29, 2022; Hussain et al, Am J Prev Med, 2010

Well-Positioned for Transformational Year in 2024



Losmapimod first-to-market potential for patients with FSHD

Enrollment for REACH Phase 3 trial completed in Q3 2023; topline data expected in Q4 2024

Pociredir has best-in-class potential for SCD

Reinitiated Phase 1b trial at 12mg dose

Foundation for pipeline sustainability in target disease areas

Cash runway into 2026 – No debt or warrants

Fulcrum Therapeutics

THANK YOU