UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of report (Date of earliest event reported): October 4, 2019

Fulcrum Therapeutics, Inc.
(Exact Name of Registrant as Specified in Charter)

Delaware	001-38978	47-4839948
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(IRS Employer Identification No.)

26 Landsdowne Street Cambridge, Massachusetts	02139
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code: (617) 651-8851

Not applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common stock, par value $0.001 per share	**FULC**	**Nasdaq Global Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On October 4, 2019, Fulcrum Therapeutics, Inc. (the "Company") issued a press release announcing data from its Phase 1 clinical trial of losmapimod in facioscapulohumeral muscular dystrophy patients and healthy volunteers. The Phase 1 data were presented on October 4, 2019 in an oral presentation at the 24th International Annual Congress of the World Muscle Society in Denmark, Copenhagen. A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K, and a copy of the materials to be presented during the oral presentation is furnished as Exhibit 99.2 to this Current Report on Form 8-K.

The information in Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.1 and 99.2, is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

The following exhibits are furnished herewith:

99.1	Press Release issued by the Company on October 4, 2019
99.2	Presentation by the Company on October 4, 2019

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

FULCRUM THERAPEUTICS, INC.

Date: October 4, 2019

By: /s/ Robert J. Gould
Name: Robert J. Gould
Title: President and Chief Executive Officer

Exhibit 99.1

Fulcrum Therapeutics Announced Results of Phase 1 Clinical Trial of Losmapimod in FSHD

Data presented in an oral presentation at World Muscle Society meeting highlighted safety, tolerability, pharmacokinetics and target engagement of losmapimod in patients with facioscapulohumeral dystrophy.

CAMBRIDGE, Mass., October 4, 2019 – **Fulcrum Therapeutics, Inc.** (Nasdaq: FULC), a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined rare diseases, today announced preliminary results of a Phase 1 clinical trial of losmapimod to treat the root cause of facioscapulohumeral dystrophy (FSHD). Losmapimod is a selective p38α/b mitogen activated protein kinase (MAPK) inhibitor. Fulcrum exclusively in-licensed losmapimod following Fulcrum's discovery that the inhibition of p38α/b reduced expression of the DUX4 gene in muscle cells derived from patients with FSHD, a disease which is caused by the mis-expression of DUX4 in skeletal muscle. Results were presented today by Michelle Mellion, MD, medical director at Fulcrum Therapeutics, in an oral presentation during the 24th International Annual Congress of the World Muscle Society in Copenhagen, Denmark.

"Losmapimod has previously been shown to have adequate safety and tolerability in over 3,500 patients and healthy volunteers across multiple indications, with no safety signals attributed to the drug in those trials. Until now, losmapimod had not been tested in patients with FSHD, nor was it known if it was muscle-penetrant in humans." said Dr. Mellion. "The preliminary results from our Phase 1 clinical trial of losmapimod in patients with FSHD indicate that losmapimod was generally well-tolerated and achieved dose-dependent concentrations in plasma and muscle believed to be adequate for efficacy based on preclinical pharmacology studies."

The primary objective of the trial was to investigate the safety and tolerability of losmapimod in healthy volunteers and in FSHD patients. The secondary objective was to evaluate repeated dose pharmacokinetics (PK) and target engagement (TE) in FSHD patients. In the first cohort, 10 healthy volunteers were randomized to a single oral dose of losmapimod (n=8) 7.5 mg followed by a single oral dose of 15 mg after a wash out period or to single oral dose placebo (n=2) in both dosing periods. In the second cohort, 15 FSHD patients were randomized and treated with placebo (n=3) or losmapimod 7.5 mg (n=6) or 15 mg (n=6) taken orally twice daily for 14 days.

Losmapimod was well tolerated with no serious adverse events (SAEs) reported. Similar tolerability, safety and PK were observed in healthy volunteers and patients with FSHD. Treatment with losmapimod demonstrated dose-dependent PK and TE in blood. This was consistent with previously reported data from more than 3,500 patients treated with losmapimod across multiple other indications. FSHD patients treated with losmapimod also achieved dose-dependent concentrations in skeletal muscle, with a muscle to plasma exposure ratio of approximately 1:1. The losmapimod 15 mg dose taken orally twice daily demonstrated sustained drug concentrations that in preclinical models with human FSHD myotubes resulted in a robust reduction of DUX4-driven gene expression. Analysis of target engagement in muscle is ongoing. These data support the selection of the 15 mg dose of losmapimod taken orally twice daily in the Company's ongoing Phase 2b placebo-controlled 24-week clinical trial, referred to as ReDUX4, as well as its ongoing Phase 2 open label-study of losmapimod for the treatment of patients with FSHD.

“There are currently no approved treatment options available for patients with FSHD. They face a lifetime of accumulating disability that can severely impact their day-to-day function and quality of life,” said Diego Cadavid, MD, senior vice president of clinical development at Fulcrum Therapeutics. “We are very encouraged by these results and are working rapidly to advance our development program for losmapimod.”

About FSHD

FSHD is characterized by progressive skeletal muscle loss that initially causes weakness in muscles in the face, shoulders, arms and trunk, and progresses to weakness throughout the lower body. Skeletal muscle weakness results in significant physical limitations, including an inability to smile and difficulty using arms for activities, with many patients ultimately becoming dependent upon the use of a wheelchair for daily mobility.

FSHD is caused by mis-expression of DUX4 in skeletal muscle, resulting in the presence of DUX4 proteins that are toxic to muscle tissue. Normally, DUX4-driven gene expression is limited to early embryonic development, after which time the DUX4 gene is silenced. In people with FSHD, the DUX4 gene is turned “on” as a result of a genetic mutation. The result is death of muscle and its replacement by fat, leading to skeletal muscle weakness and progressive disability. There are no approved therapies for FSHD, one of the most common forms of muscular dystrophy, with an estimated patient population of 16,000 to 38,000 in the United States alone.

About Losmapimod

Losmapimod is a selective p38α/b mitogen activated protein kinase (MAPK) inhibitor that was exclusively in-licensed by Fulcrum Therapeutics following Fulcrum’s discovery of the role of p38α/b inhibitors in the reduction of DUX4 expression and an extensive review of known compounds. Utilizing its internal product engine, Fulcrum discovered that inhibition of p38α/b reduced expression of the DUX4 gene in muscle cells derived from patients with FSHD. Although losmapimod has never previously been explored in muscular dystrophies, it has been evaluated in more than 3,500 subjects in clinical trials across multiple other indications, including in several Phase 2 trials and a Phase 3 trial. No safety signals were attributed to losmapimod in any of these trials. Fulcrum is currently conducting Phase 2 trials investigating the safety, tolerability, and efficacy of losmapimod to treat the root cause of FSHD.

About Fulcrum Therapeutics

Fulcrum Therapeutics is a clinical-stage biopharmaceutical company focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need, with an initial focus on rare diseases. Fulcrum’s proprietary product engine identifies drug targets which can modulate gene expression to treat the known root cause of gene mis-expression. Please visit **www.fulcrumtx.com**.

Forward-Looking Statements

This press release 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 and the timing of 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; replicate in later clinical trials positive results found in preclinical studies and early-stage clinical trials of losmapimod and its other product candidates; advance the development of its product candidates under the timelines it anticipates in current and future clinical trials; obtain, maintain or protect intellectual property rights related to its product candidates; manage expenses; and raise the substantial additional capital needed to achieve its business objectives. For a discussion of other risks and uncertainties, and other important factors, any of which could cause the Company’s actual results to differ from those contained in the forward-looking statements, see the “Risk Factors” section, as well as discussions of potential risks, uncertainties and other important factors, in the Company’s most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this 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.

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Phase 1 clinical trial of losmapimod in FSHD: safety, tolerability and target engagement

EudraCT number: 2018-004754-19

Michelle L. Mellion[1], Lucienne Ronco[1], Drew Thompson[1], Michelle Hage[1], Sander Brooks[2], Emilie van Brummelen[2], Lisa Pagan[2], Umesh Badrising[3], William Tracewell[1], Shane Raines[1], Baziel van Engelen[4], Geert Jan Groeneveld[2], Diego Cadavid[1]

[1]Fulcrum Therapeutics, Cambridge, MA, USA

[2]Centre for Human Drug Research (CHDR), Leiden, NL

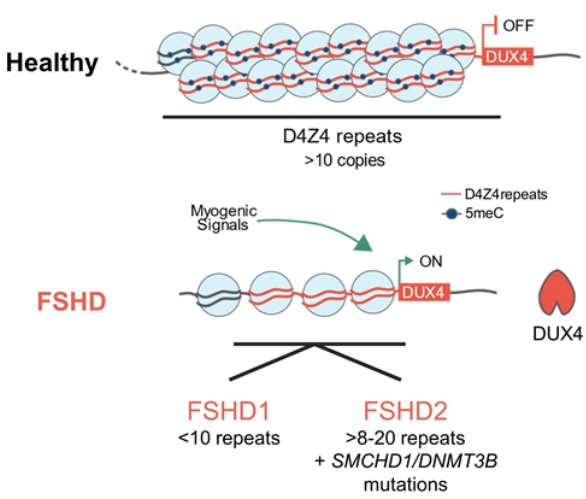
[3]Leiden University Medical Centre, Leiden, NL

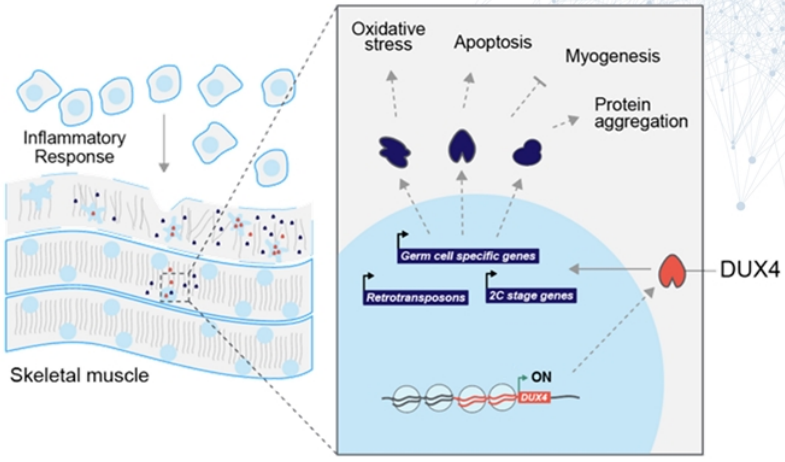
[4]Radboud University Medical Centre, Nijmegen, NL

Disclosures

- Stock/Stock Options in Biogen, Vertex Pharmaceuticals, and Fulcrum
- Full-time employee as Medical Director at Fulcrum Therapeutics

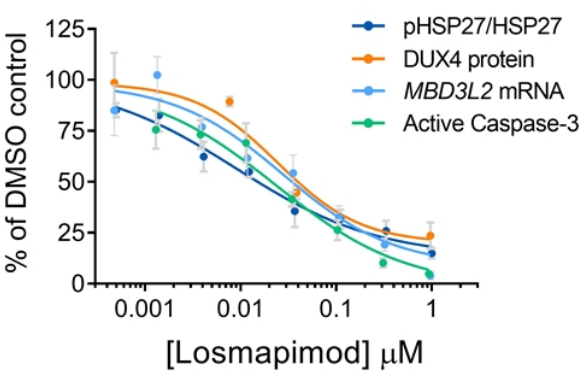
Aberrant expression of DUX4 causes FSHD

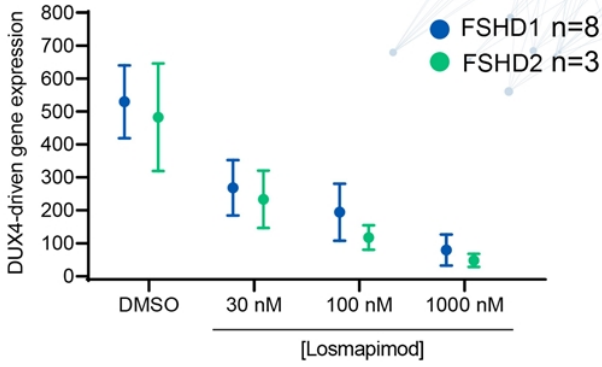




DUX4 is a homeodomain transcription factor

Losmapimod, a selective p38α/β MAPK inhibitor, reduced DUX4 expression in FSHD myotubes





- HSP27 is a substrate of p38 MAP kinase pathway
- *MBD3L2* is a DUX4-target gene

Objectives

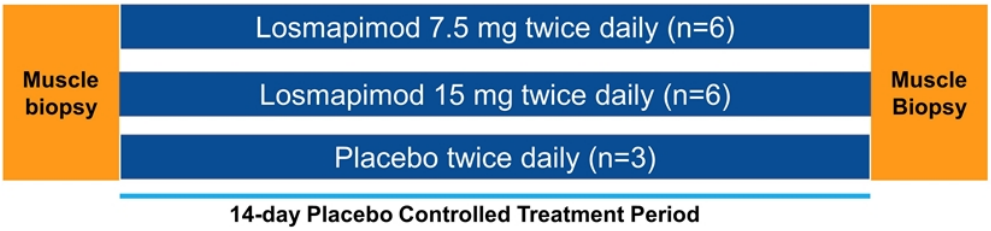
- **Primary Objective:** Initial Safety and Tolerability in FSHD
  - Note: Safety and tolerability previously demonstrated in 25 studies in over 3,500 healthy adult volunteers and patients across other multiple indications
    (see poster P.44, Cadavid D et al).

- **Secondary Objective:** PK and Target Engagement in blood and muscle
  - Note: Muscle biopsies performed at baseline and on treatment at approx. Cmax in FSHD patients

Study design

Part A: N=10 Healthy Volunteers; Single Ascending Dose; 4:1 randomization

Part B: N=15 FSHD1 Patients; Double Blind; 2:2:1 Randomization; Placebo Controlled; Repeated Dose



Note: Lower extremity muscle biopsies were performed in normal appearing muscles identified by MRI

Demographics

	Part A Healthy Volunteers	Part B FSHD1
Gender (M:F)	6M:4F	6M:9F
Age **Mean** SD Min/Max	 **31.4** 17.2 22/64	 **41.6** 11.6 26/64
BMI **Mean** SD Min/Max	 **22.7** 2.4 19.6/27.2	 **24.8** 3.0 20.7/31.4
Ricci (FSHD Disability Score) **Mean** SD Min/Max	 **N/A**	 **2.6** 0.7 1.5/4

Safety and tolerability

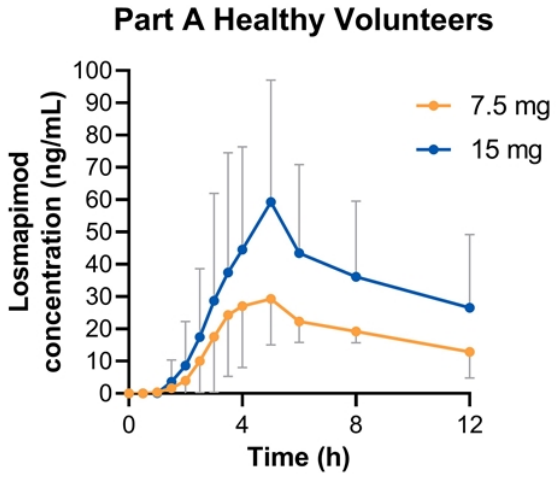
- No Serious Adverse Events (SAE)

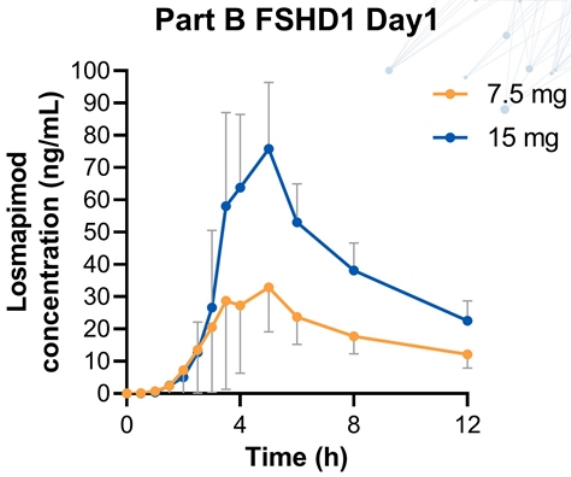
	Adverse Effects (AE) (n)
Part A	Somnolence (5) Headache (4) Dizziness (2)
Part B	Headache (4) Backpain (3) Fatigue (3) Constipation (1) Dizziness (1) Pain (1)

- No clinically significant changes in vital signs, laboratory analyses, ECG or urinalysis
- Muscle needle biopsies were well tolerated

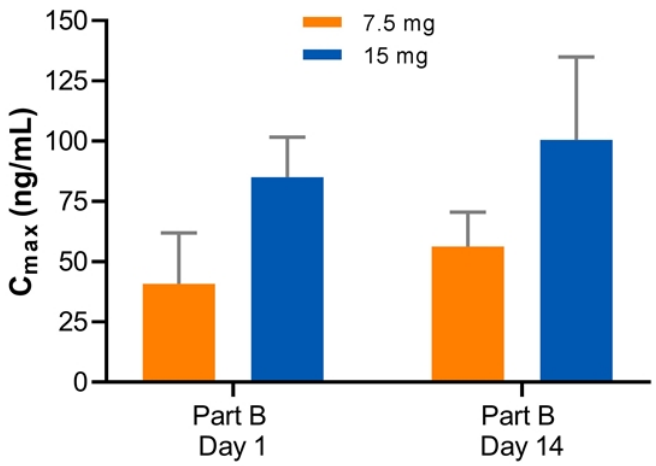
Assessment of Pharmacokinetics (PK)

Similar PK profile in HV and FSHD1 subjects





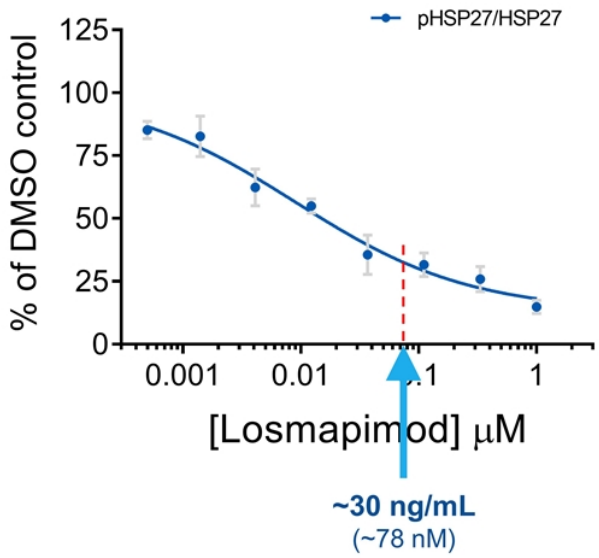
Accumulation observed with repeated dosing



	C_{max} (ng/ml)		AUC_{0-12} (ng*hr/ml)		T_{max} (hr)
	mean (SD)	CV %	**mean** (SD)	CV %	**median**
Part B (Day 1)					
7.5 mg	**40.8** (21.1)	51.7	**201.5** (74.6)	37.0	4.5
15 mg	**85.0** (16.7)	19.7	**410.2** (50.3)	12.0	4.6
Part B (Day 14)					
7.5 mg	**56.3** (14.2)	25.3	**394.6** (92.8)	23.5	4.5
15 mg	**100.5** (34.4)	34.3	**632.7** (175.4)	27.7	5.0

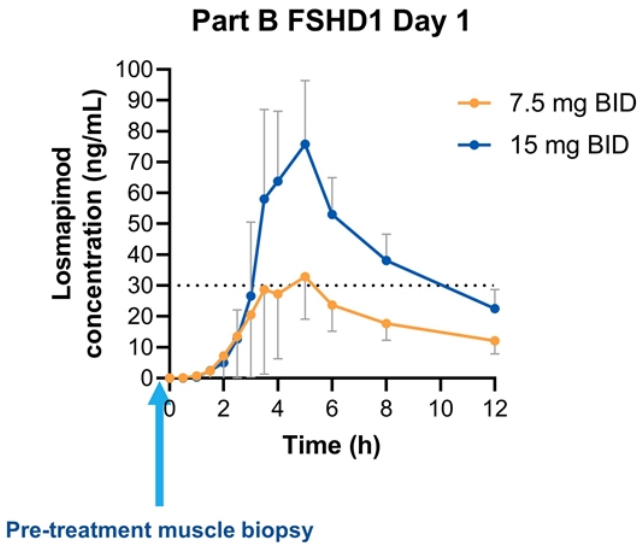
Accumulation Ratio: 7.5 mg: 2.0
15 mg: 1.5

Robust In Vitro inhibition of p38 activity at ≥30 ng/mL

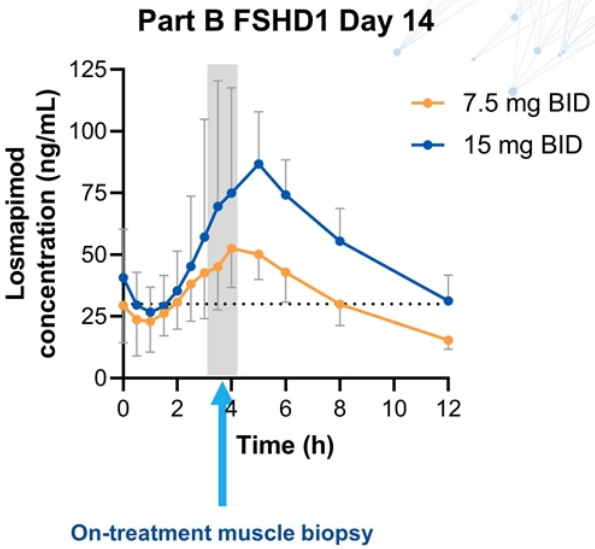


~30 ng/mL
(~78 nM)

Losmapimod 15 mg BID sustained concentrations for robust target engagement

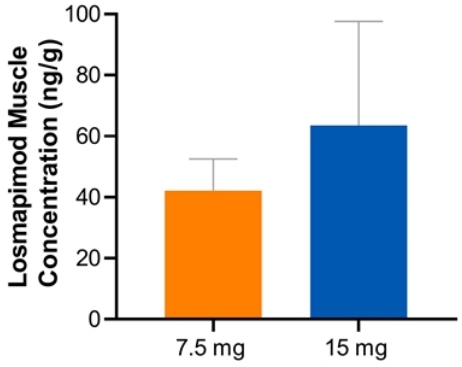


Pre-treatment muscle biopsy



On-treatment muscle biopsy

Losmapimod showed dose dependent concentrations in muscle

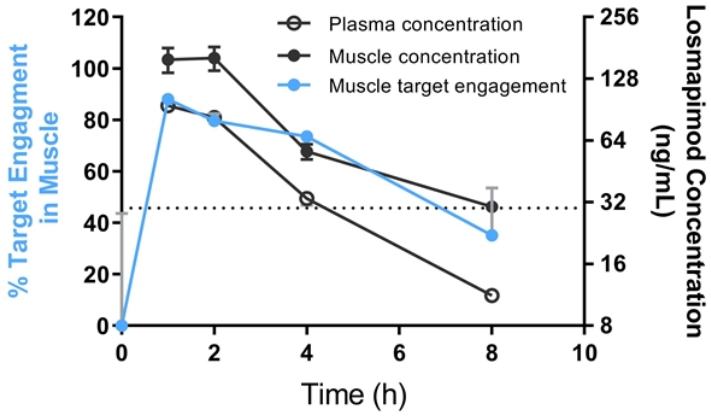


		Muscle		Plasma	
	N	**Mean** ng/g (SD)	CV(%)	**Mean** ng/ml (SD)	CV(%)
7.5 mg	6	**42.1** (10.5)	24.9	**52.6** (15.7)	30.2
15 mg	6	**63.6** (34.0)	53.5	**75.0** (42.5)	56.7

Ratio to Plasma approximately 1:1

Assessment of Pharmacodynamics (PD)

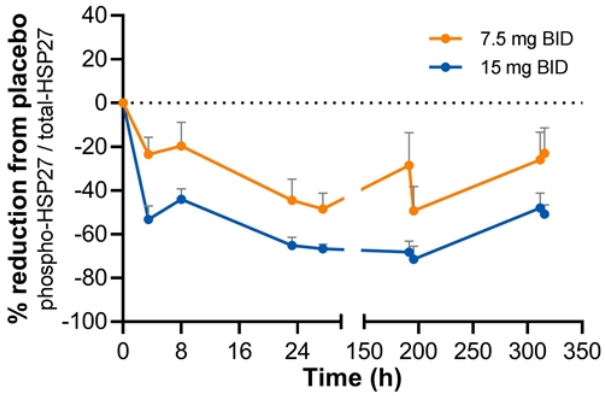
Losmapimod: in vivo PK/PD in rodents



- Muscle:plasma exposure ratio is approximately 1 in rodents
- Losmapimod inhibits p38 in muscle rapidly following acute dosing.

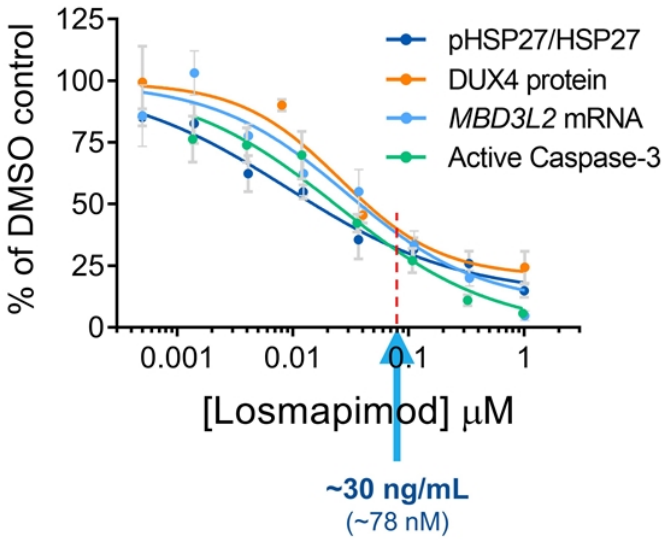
Sustained and dose dependent target engagement in blood

15 mg PO BID dose resulted in greater inhibition of p38 activity

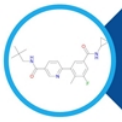


Note: measurement of TE in on-treatment muscle biopsy is ongoing

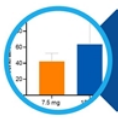
In Vitro inhibition of p38 MAPK resulted in a reduction of DUX4 activity and muscle cell death



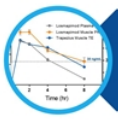
Conclusions



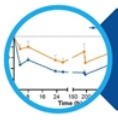
Losmapimod was safe and well tolerated in FSHD patients



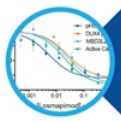
Achieved clinically relevant, dose-dependent concentrations in muscle



Similar exposures in plasma and muscle as shown in pre-clinical models



15mg PO BID dose showed sustained and robust target inhibition



Data supports the design of the ongoing Phase 2 clinical trials currently enrolling

- Placebo-controlled 24-week study ReDUX4 (NCT 04003974)
- Open label 64-week study (NCT 04004000)

Acknowledgements

- Healthy volunteers and FSHD patients who participated in the study
- Fulcrum's phase 1 study FIS 001-2018 management team
- Centre for Human Drug Research (CHDR)
- Fulcrum's FSHD Clinical Advisory Board
- Centre for Human Drug Research (CHDR)
- Leiden University Medical Center
- Radboud University Medical Center
- Vendors:
  - MRI imaging analysis vendor AMRA
  - PK vendor PPD
  - Target engagement vendor CBI