P6.05

Safety and Tolerability Data with Losmapimod in FSHD

Mihaela Levitchi Benea, MD; Marie-Helene Jouvin, MD; Vivekananda Ramana, MD; John Jiang, PhD

Fulcrum Therapeutics, Cambridge, MA, USA

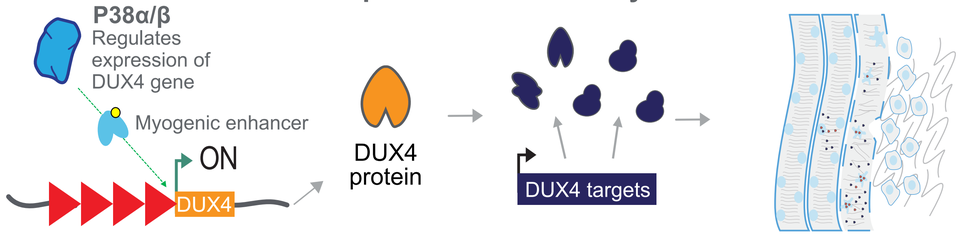
Introduction

- Facioscapulohumeral muscular dystrophy (FSHD) is the second most common muscular dystrophy in adults with a prevalence estimated at 12/100,000.[1]
- FSHD is caused by the toxic gain of function of the embryogenic transcription factor double homeobox 4 (DUX4) in skeletal muscle.[2]
- FSHD is a rare, serious, and disabling disease characterized by progressive muscle weakness and loss of muscle mass resulting ultimately in significant impairment of upper extremity function and mobility and in many patients being unable to work or live independently.
- In typical forms, FSHD initially affects facial and scapular muscles, eventually progressing to the arms, trunk, and lower extremities.
- **Currently, there is no treatment for people living with FSHD that prevents and/or slows muscle wasting and weakness.**

Rationale

A treatment that reduces or prevents aberrant DUX4 activity in skeletal muscles may stop or prevent functional impairment and accumulation of disability and decrease/arrest loss of muscle mass.

DUX4 Expression and Activity in FSHD[3]



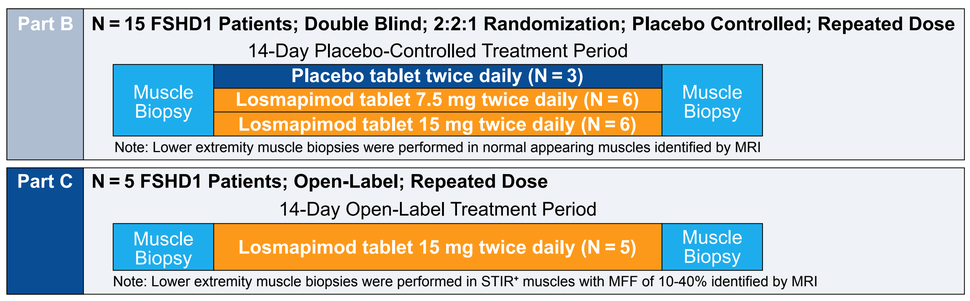
In FSHD, loss of repression in D4Z4 repeats allows for aberrant DUX4 expression in muscle

In FSHD, **DUX4 aberrant expression** in muscle causes muscle cell death, immune infiltration, and ultimately, fat infiltration

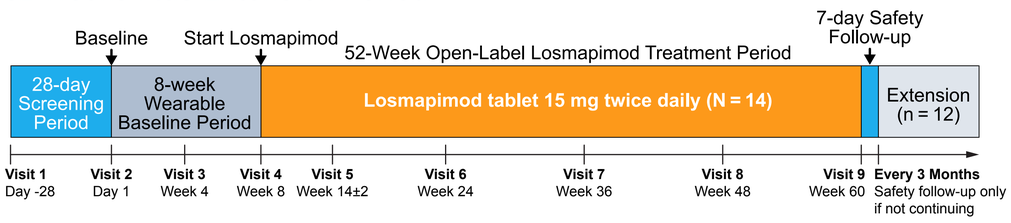
- Fulcrum is developing **losmapimod**, an investigational small molecule inhibitor of p38α/β Mitogen Activated Protein Kinase (MAPK), for the treatment of FSHD.
- Losmapimod has been generally well-tolerated in more than 3,600 subjects across multiple clinical studies performed in non-rare, non-muscular indications, including > 100 subjects with FSHD.
- Fulcrum has assessed losmapimod in FSHD in one completed Phase 1 study (FIS 001-2018) and two ongoing Phase 2 studies in the open label extension period (FIS 001-2019 Open Label Study [OLS] and FIS 002-2019 [ReDUX4]).[4,5] A Phase 3 study (1821-FSH-301 [REACH]) is ongoing.
- The Phase 2 efficacy assessments demonstrated losmapimod was associated with potential improvements in structural, functional, and patient-reported outcomes.

Study Designs

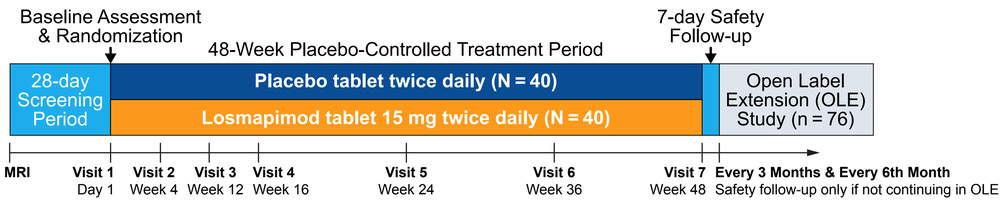
Phase 1 Study (FIS-001-2018)



Open-Label Study (OLS): Phase 2 Open-Label Single-Center Study, 52 Weeks Plus Extension Period



ReDUX4: Phase 2 Randomized Placebo-Controlled, Multi-Site Study, 48 Weeks Plus Extension Period



Main Inclusion / Exclusion Criteria Across FSHD Studies

Inclusion Criteria	Exclusion Criteria
■ Age 18-65 years ■ Genetically confirmed diagnosis of FSHD1 ■ Ricci score 2–4* ■ STIR+ muscle, as determined by a central reader, safely accessible by needle biopsy	■ Medical conditions that can confound results of the study ■ Contraindication to MRI ■ Contraindication to muscle biopsy

*Phase 1 study included Ricci score 1–4.5

Study Demographics and Baseline Characteristics

		Phase 1 Study			OLS	ReDUX4	
		Part B Losmapimod 7.5 mg BID (N=6)	Part B Losmapimod 15 mg BID (N=6)	Part C Losmapimod 15 mg BID (N=5)	Losmapimod 15 mg BID (N=14)	Placebo BID (N=40)	Losmapimod 15 mg BID (N=40)
Age (years)	Mean (SD)	47.3 (10.3)	35.2 (10.1)	48.6 (8.6)	45.7 (11.1)	45.7 (12.7)	45.7 (12.4)
Race, n (%)	White	6 (100.0)	5 (83.3)	5 (100.0)	13 (92.9)	39 (97.5)	31 (77.5)
	Asian	0	0	0	0	0	5 (12.5)
	Other	0	1 (16.7)	0	1 (7.1)	0	1 (2.5)
	N/A	0	0	0	0	1 (2.5)	3 (7.5)
BMI (kg/m²)	Mean (SD)	26.43 (3.4)	24.17 (2.1)	24.36 (3.7)	24.04 (2.9)	26.19 (4.9)*	25.71 (5.4)
D4Z4 Repeat Unit, n (%)	1-3	—	—	—	—	6 (15.0)	7 (17.5)
	4-6	—	—	—	—	26 (65.0)	29 (72.5)
	7-9	—	—	—	—	8 (20.0)	4 (10.0)
D4Z4 Repeat Category, n (%)	1-3 Repeats	—	—	—	3 (21.4)	6 (15.0)	7 (17.5)
	4-9 Repeats	—	—	—	11 (78.6)	34 (85.0)	33 (82.5)
Ricci Score, n (%)	1.5	1 (16.7)	2 (33.3)	0	—	—	—
	2	0	1 (16.7)	0	0	0	0
	2.5	1 (16.7)	1 (16.7)	1 (20.0)	1 (7.1)	7 (17.5)	5 (12.5)
	3	3 (50.0)	1 (16.7)	3 (60.0)	5 (35.7)	18 (45.0)	19 (47.5)
	3.5	0	1 (16.7)	0	2 (14.3)	7 (17.5)	11 (27.5)
	4	1 (16.7)	0	1 (20.0)	6 (42.9)	8 (20.0)	5 (12.5)

*n = 39

Results

A Total of 108 Participants with FSHD1 Have Been Exposed to Losmapimod in Phase 1 and Phase 2 Studies

		Phase 1 Study			OLS	ReDUX4	
		Part B Losmapimod 7.5 mg BID (N=6)	Part B Losmapimod 15 mg BID (N=6)	Part C Losmapimod 15 mg BID (N=5)	Losmapimod 15 mg BID (N=14)	Placebo BID (N=40)	Losmapimod 15 mg BID (N=40)
Main Study							
Study Disposition, n (%)	Completed	6 (100)	6 (100)	6 (100)	14 (100)	38 (95)	39 (97.5)
	Discontinued	0	0	0	0	2 (5.0)	1 (2.5)
Exposure Duration	Mean (SD)	14 (0.0) days	14 (0.0) days	14 (0.0) days	360.8 (30.0) days	42.6 (11.3) weeks	42.4 (10.2) weeks
	Min, Max	14, 14	14, 14	14, 14	292, 397	11.9, 53.7	21.6, 52.3
Open-Label Extension					Losmapimod 15 mg BID (N=12)	Placebo BID (N=37) [n=7]*/[n=30]**	Losmapimod 15 mg BID (N=39) [n=9]*/[n=30]**
Study Disposition	Entered OLE	—	—	—	12	37	39
	Discontinued from OLE, n (%)	—	—	—	0	6 (16.2)	5 (12.8)
	Ongoing, n (%)	—	—	—	12 (100)	31 (83.8)	34 (87.2)
Exposure Duration	Mean Weeks (SD)	—	—	—	139.9 (5.2)	164.4 (54.6)* 157.8 (13.6)**	206.0 (36.2)* 203.0 (26.5)**
	Min, Max	—	—	—	132, 149	60, 204* 99, 170**	114, 228* 96, 228**

*Participants that started OLE after Week 24; **Participants that started OLE after Week 48. Final analysis data from FIS-001-2018 Parts B,C (12May2020); Updated analysis data from OLS (09Jan2024); Updated analysis data from ReDUX4 (09Jan2024).

Safety Data With Losmapimod Across FSHD Studies

	Phase 1 Study				OLS	ReDUX4	
	Part B Placebo BID (N=3)	Part B Losmapimod 7.5 mg BID (N=6)	Part B Losmapimod 15 mg BID (N=6)	Part C Losmapimod 15 mg BID (N=5)	Losmapimod 15 mg BID (N=14)	Placebo BID (N=37) [n=7]*/[n=30]**	Losmapimod 15 mg BID (N=39) [n=9]*/[n=30]**
Any TEAE	3 (100)	4 (66.7)	4 (66.7)	2 (40.0)	14 (100)	7 (100)* 30 (100)**	9 (100)* 29 (96.7)**
TEAE leading to treatment discontinuation	0	0	0	0	0	0	0
TEAE leading to study withdrawal	0	0	0	0	0	0	0
TEAE leading to death	0	0	0	0	0	0	0
SAEs	0	0	0	0	0	1 (14.3)* 3 (10.0)**	1 (11.1)* 4 (13.3)**
Treatment-related SAEs	0	0	0	0	0	0	0

*Participants that started OLE after Week 24; **Participants that started OLE after Week 48.

- Most adverse events (AEs) observed during the studies were considered mild to moderate in severity.
- The most common AEs were eczema, dry skin, fall, ALT increase, headache, and pain.
- The majority of AEs resolved with continued dosing.
- Dosing has been paused for 14 days in 4 subjects (3 in FIS 001-2019 and 1 in FIS-002-2019) due to COVID-19 infection.
- There were no reported drug related SAEs, deaths, discontinuations due to AEs, or clinically significant changes in vital signs, clinical laboratory results, or ECG parameters.

Conclusions

- Losmapimod given as up to 15 mg twice daily in > 100 subjects with FSHD1 for up to 228 weeks has been generally well-tolerated, consistent with that previously reported in other patient populations.
- These results, combined with previously reported efficacy results, contribute to the current overall benefit-risk assessment of losmapimod, and are supportive of continued development.

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Abbreviations: AE = adverse event; ALT = alanine aminotransferase; BID = twice daily; BMI = body mass index; ECG = electrocardiogram; FSHD = facioscapulohumeral muscular dystrophy; MFF = muscle fat fraction; OLE = open label extension; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

References: 1) Giardina *Clin Genet.* 2024;1-14. **2)** Engquist *Hum Mol Genet.* 2024;33(2):182-97. **3)** Rojas *J Pharmacol Exp Ther.* 2020;374(3):489-98. **4)** Mellion *Br J Clin Pharmacol.* 2021;87(12):4658-69. **5)** Tawil R *Lancet Neurol.* 2024;23(5):477-86.