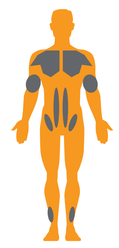
Safety and Tolerability Data with Losmapimod in FSHD

Marie-Helene Jouvin, MD; Vivekananda Ramana, MD; John Jiang, PhD
Fulcrum Therapeutics, 26 Landsdowne St. Cambridge, MA. 02139

Introduction

- FSHD is a relentless, variably progressive disease leading to accumulation of disability over decades
- FSHD initially affects facial and scapular muscles, eventually progressing to the arms, trunk and legs
- Muscle pathology leads to accumulation of disability
- Progression ultimately leads to significant impairment of upper extremity function and mobility, and many patients are unable to work or live independently

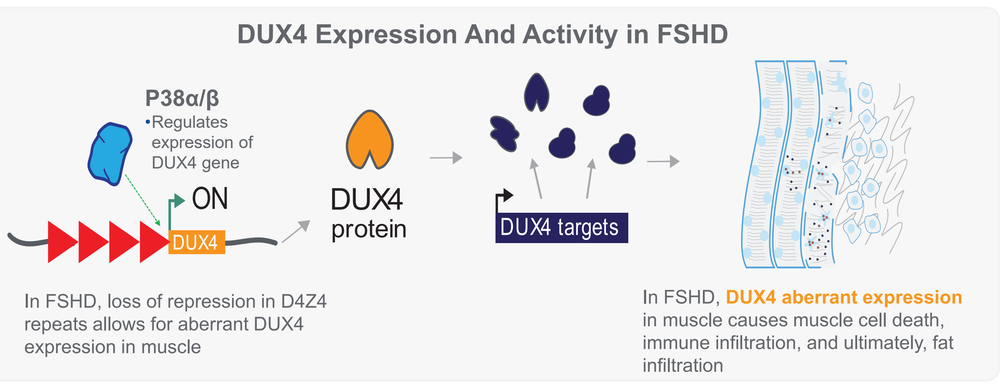


Fat infiltrates muscle

Currently, there are no treatment options for people living with FSHD that prevent and/or slow muscle wasting and weakness

Rationale

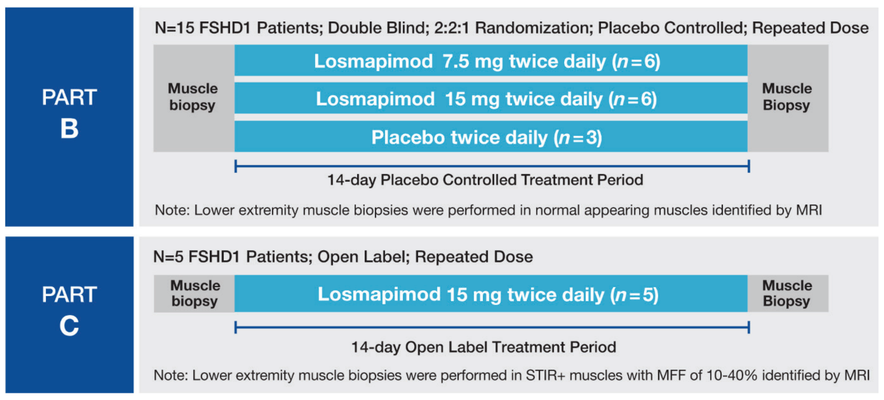
A treatment that reduces or prevents aberrant DUX4 activity in skeletal muscles may stop or prevent functional impairment and accumulation of disability and decrease/arrest replacement of muscle by fat.



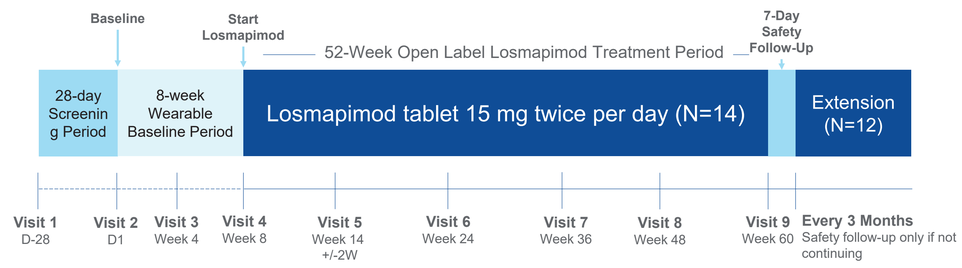
- Fulcrum is developing **losmapimod**, an investigational small molecule inhibitor of p38α/β Mitogen Activated Protein Kinase (MAPK), for the treatment of FSHD
- Losmapimod has been generally well-tolerated in more than 3,600 subjects across multiple clinical studies, including >100 subjects with FSHD.
- 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 and FIS 002-2019). A Phase 3 study (1821-FSH-301 [REACH]) is ongoing.
- Nonclinical studies have shown that losmapimod (a small molecule p38 α/β MAPK inhibitor) reduces the aberrant expression of DUX4, the underlying cause of FSHD.

Study Designs

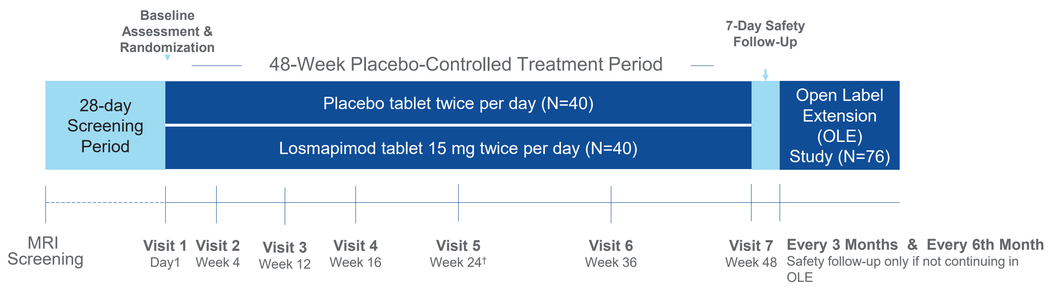
Phase 1 Study (FIS-001-2018)



Open-Label Study (OLS): Phase 2 Open-Label Single-Center, 52-Week Study



ReDUX4: Phase 2 Randomized Placebo-Controlled, 48-Week, Multi-site Study



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

*Ph1 study included CSS 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)
Demographics							
Age (years)	N	6	6	5	14	40	40
	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)
Body Mass Index (BMI) (kg/m²)	N	6	6	5	14	39	40
	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 (82.50)
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)

Results

A total of 108 subjects with FSHD1 have been exposed to losmapimod

	Phase 1 Study			OLS	ReDUX4	
Main Study	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)
Study Disposition						
Completed	6 (100%)	6 (100%)	5 (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 (0.0) days	14.0 (0.0) days	14.0 (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=14)	Placebo/ Losmapimod 15 mg BID (N=37) *Started OLE after *Week 24 (N=7) or **Week 48 (N=30)*	Losmapimod/ Losmapimod 15 mg BID (N=39) *Started OLE after *Week 24 (N=9) or **Week 48 (N=30)*
Study Disposition						
Entered OLE	-	-	-	12 (85.7%)	37 (100%)	39 (100%)
Discontinued from OLE	-	-	-	0	1	1
Ongoing	-	-	-	12 (85.7%)	36 (97.3%)	38 (97.4%)
Exposure Duration						
Mean (SD)	-	-	-	267.3 (43.4) days	72.3 (7.1) weeks* 47.0 (3.5) weeks**	101.9 (9.3) weeks* 96.0 (2.9) weeks**
Min, Max	-	-	-	194, 320	60.4, 83.7 * 36.0, 51.0 **	95.9, 119.1 * 85.4, 101.4 **

*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); Week 108 analysis data from OLS (04Feb2022); Week 96 analysis data from ReDUX4 (20Jan2022).

Safety Data With Losmapimod Across FSHD Studies

	Phase 1 Study				OLS	ReDUX4	
Safety, n (%)	Part B Placebo (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/ Losmapimod 15 mg BID (N=37) *Started OLE after *Week 24 (N=7) or **Week 48 (N=30)*	Losmapimod/ Losmapimod 15 mg BID (N=39) *Started OLE after *Week 24 (N=9) or **Week 48 (N=30)*
Any TEAE	3 (100)	4 (66.7)	4 (66.7)	2 (40.0)	14 (100)	6 (85.7) * 24 (80.0) **	9 (100) * 22 (73.3) **
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) * 0 (0.0) **	1 (11.1) * 2 (6.7) **
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, alanine aminotransferase (ALT) increase, rash, headache, and myalgia.
- The majority of AEs resolved with continued dosing.
- Dosing has been paused for 14 days in four 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.

Conclusion

- Losmapimod given as up to 15 mg twice daily in >100 subjects with FSHD1 for up to 96 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

References

- Mellion, M. L., L. Ronco, C. L. Berends, L. Pagan, S. Brooks, M. J. van Esdonk, et al. 2021. 'Phase 1 clinical trial of losmapimod in facioscapulohumeral dystrophy: Safety, tolerability pharmacokinetics, and target engagement', Br J Clin Pharmacol, 87: 4658-69.
- Rojas LA, Valentine E, Accorsi A, et al. P38α Regulates Expression of DUX4 in a Model of Facioscapulohumeral Muscular Dystrophy. 2019. doi:https://doi.org/10.1101/700195