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Whole Body MRI Quantitative muscle analysis to evaluate Efficacy of Losmapimod in a Phase 2 Placebo-Controlled Study in Subjects with FSHD (ReDUX4): ReDUX4 (NCT04003974)

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Disclosure Statement

Dr. Christopher Morabito is a full-time employee of Fulcrum Therapeutics.

FSHD is a Relentlessly Progressive Disease Leading to Significant Disability that Impacts Quality of Life

Symptoms and Progression





Facial weakness

Scapular winging



Impaired ability to raise arms caused by scapular elevation



Wheelchair dependence

- 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

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

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Wasting of muscles in chest, shoulders, and

upper arms; Protuberant abdomen

Sources: Mul et al., 2016; Wagner, 2019; FSHD Voice of the Patient Report; November 5, 2020.

Losmapimod



- Highly selective p38α/β MAPK inhibitor
- Generally well-tolerated, with clinical experience in >3,600 people across 11 indications
- Reduced DUX4 expression in preclinical studies
 - Aberrant expression DUX4 gene is known root cause of FSHD



- Assess the efficacy of losmapimod with whole-body MRI using quantitative muscle and composite analyses.
- Quantitative muscle analyses include muscle fat fraction (MFF), lean muscle volume (LMV), and muscle fat infiltration (MFI).

ReDUX4 Trial Design*



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*<u>All analyses were pre-specified in the statistical analysis plan, with the exception of dynamometry, which is now presented as percent change from baseline.</u> †Protocol amended due to COVID-19 to allow collection of data to inform study endpoints. 16 subjects had completed the Wk24 visit and had already rolled over to the OLE at the time of amendment approval. *PK measurements will not be assessed in OLE study. COAs=clinical outcome assessments; FSHD-HI=facioscapulohumeral muscular dystrophy health index; MFF=muscle fat fraction; MFI=muscle fat infiltration; MFM=motor function measure; MRI=magnetic resonance imaging; LMV=lean muscle volume; PGIC=patients' global impression of change; PK=pharmacokinetics; PROs=patient reported outcomes; RWS=reachable workspace; TUG=timed up and go.

Patient Demographics

		Placebo BID (N=40)	Losmapimod 15 mg BID (N=40)
Age (years)	Ν	40	40
	Mean (SD)	45.7 (+/- 12.69)	45.7 (+/- 12.44)
Race n (%)	White	39 (97.5)	31 (77.5)
Body Mass Index (BMI) (kg/m²)	N	39	40
	Mean (SD)	26.19 (+/- 4.914)	25.71 (+/- 5.434)
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	6 (15.0)	7 (17.5)
	4-9 Repeats	34 (85.0)	33 (83.50)
Ricci Score n (%)	2	0	0
	2.5	7 (17.5)	5 (12.5)
	3	18 (45.0)	19 (47.5)
	3.5	7 (17.5)	11 (27.5)
	4	8 (20.0)	5 (12.5)

New Paradigm of Image analysis in NMD









Imaging a slice(s) of select muscles in lower limbs Imaging of whole muscle, proximal to distal, in the whole body

Personalized set of muscles to follow over time

Skeletal Muscle MRI Muscles Studied- 18 muscles bilaterally; 36



Neck

- Supraspinatus
- Infraspinatus
- Subscapularis
- Teres Minor

Legs

- Quadriceps
- Hamstrings
- Adductors
- Tibialis Anterior
- Gastrocnemius Medialis

Torso

- Pectoralis Major
- Rhomboideus
- Latissimus Dorsi & Teres Major
- Trapezius
- Serratus Anterior
- Paraspinal (C3-Sacrum)

Arm

- Deltoid
- Biceps Brachii
- Triceps Brachii

Evaluating Skeletal Muscle Health by Whole Body Musculoskeletal MRI*



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*Please see poster: "Quantitative Muscle Analysis in FSHD Using Whole-Body MRI: Composite Muscle Measurements for Cross-Sectional Analysis".

Muscles Were Classified as Normal-Appearing "A", Intermediate "B", or End-Stage "C"¹⁻³

The intermediate "B" class of muscles are at high risk of progression



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Composites Measurement to Evaluate Treatment Efficacy and correlations with FSHD Relevant COAs



Muscles Included in Functional Correlations and Associated COAs



Test	Muscles				
	Upper Extremity	<u>Trunk</u>	Lower Extremity		
FHSD TUG	Supraspinatus Infraspinatus Subscapularis Teres Minor Deltoid Biceps Brachii Triceps Brachii	Pectoralis Major Rhomboideus Latissimus Dorsi & Teres Major Trapezius Serratus Anterior Paraspinal (C3-Sacrum)	Quadriceps Hamstrings Adductors Tibialis Anterior Gastrocnemius Medialis		
Classic TUG	N/A	N/A	Quadriceps Hamstrings Adductors Tibialis Anterior Gastrocnemius Medialis		
RWS	N/A	Pectoralis Major Rhomboideus Latissimus Dorsi & Teres Major Trapezius Serratus Anterior	N/A		

Similar Number of Muscles were Included in Each Group

	Losmapimod N=40	Placebo N=40	Total N=80				
Baseline							
Total Number of Evaluable Muscles	1325	1358	2,683				
Week 48							
Average Number of 'A' Muscle per subject	15 17		N/A				
Average Number of 'B' Muscles per subject	6	7	N/A				
Subjects with non-missing values	28	30	58				
Muscles with non-missing Values	899	1002	1901				
Category A n (%)	423 (47.1)	515 (51.4)	938 (49.3)				
Category B n (%)	173 (19.2)	208 (20.8)	381 (20.0)				
Category C n (%)	303 (33.7)	279 (27.8)	582 (30.6)				

Muscle Categorization Captures Disease Heterogeneity and Enables identification of a unique population of muscles at high risk of progression



Losmapimod Treated Participants Showed Significantly Less Muscle Fat Infiltration (MFI) vs Placebo in Intermediate Muscles



Normal-Appearing Muscles Appear Preserved With Losmapimod vs Placebo



Moderate and Strong Cross-Sectional Correlations of Regional Composites with COA at week 48 Regardless of Treatment Arm

	MFI		MFF		LMV	
	LOS	РВО	LOS	РВО	LOS	PBO
Dominant Total RSA with weight p-value N	-0.63 (0.0018) 22	-0.11 (0.5659) 28	-0.66 (0.0008) 22	-0.36 (0.0603) 28	0.74 (0.0001) 22	0.67 (0.0001) 28
Non-Dominant Total RSA with weight p-value N	-0.70 (0.0003) 22	-0.33 (0.0851) 28	-0.77 (<.0001) 22	-0.55 (0.0023) 28	0.62 (0.0023) 22	0.61 (0.0006) 28
TUG p-value N	0.38 (0.0800) 22	0.69 (0.0001) 28	0.48 (0.0229) 22	0.68 (0.0001) 28	-0.42 (0.0492) 22	-0.60 (0.0007) 28
FSHD TUG p-value N	0.60 (0.0054) 20	0.51 (0.0049) 29	0.70 (0.0007) 20	0.70 (<.0001) 29	-0.51 (0.0218) 20	-0.62 (0.0004) 29

Conclusions

- The efficacy of losmapimod to treat FSHD is supported by this WB-MSK MRI quantitative muscle assessment demonstrating a decrease or arrest of fat accumulation in muscles at high risk of progression and normal appearing muscles.
- After 48 weeks, reduction in the progression of MFI and MFF in A and B muscles suggests losmapimod has an impact on fat accumulation in muscles that have not yet reached end-stage which has been previously reported to have little remaining functional capacity.
- WB-MSK-MRI captured the heterogeneity of the disease and provided important information about disease severity as it correlates with FSHD-relevant clinical endpoints
 - MRI efficacy composites demonstrated sensitivity to disease progression.
 - The clinical relevance of these MRI assessments supported by the strong crosssectional correlations with FSHD relevant COAs





People Living With FSHD Participating in This Study

Study Sites

Physical Therapists

Study Coordinators

Clinical and Scientific Advisors

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- Jeffrey Statland, MD. KUMC
- Lee Sweeney, PhD. UFL
- Leslie Leinwand, PhD. UC Boulder
- Peter Jones, PhD. UNR
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Other Collaborators

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Thank you!

