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Fulcrum Therapeutics

An Open-Label Study of Losmapimod to Evaluate the Safety, Tolerability, and Biomarker and Clinical Outcome Assessment Changes in Subjects with FSHD1

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Introduction

- FSHD is a serious, rare, progressive and disabling disease, caused by the aberrant expression of DUX4 in skeletal muscle
- Stochastic DUX4 expression contributes to disease heterogeneity, asymmetry, and variability in disease phenotype
- Pathological activity and maladaptive remodeling lead to muscle fiber death and immune and fat infiltration
- Progressive muscle loss and fatty replacement causes heterogeneous, progressive descending weakness and loss of function
- Muscle pathology leads to accumulation of disability

Currently, there are with no approved disease modifying therapies 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.

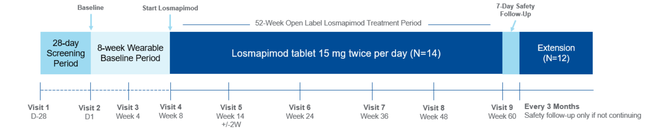
- Losmapimod is an investigational small molecule inhibitor of p38α/β Mitogen Activated Protein Kinase (MAPK).
- Pre-clinical studies demonstrated treatment with losmapimod and other p38 inhibitors resulted in dose-dependent reduction of DUX4 protein, DUX4 transcriptional program and skeletal muscle cell death in FSHD myotubes across all genotypes tested.
- Clinical studies in over 3,600 subjects across a diversity of diseases evidenced acceptable safety and tolerability for up to one year of treatment at relevant doses.

Objective

- Evaluate the long-term safety and tolerability of losmapimod in participants with FSHD
- Evaluate on-treatment change from baseline in selected clinical outcome assessments and imaging modalities

Open-Label Study Design

- This is an open-label, single-site study of losmapimod to evaluate the safety, tolerability, and changes in biomarker and clinical outcome assessments in subjects with facioscapulohumeral muscular dystrophy 1 (FSHD1)



Muscle biopsies were to be preformed at baseline, pre-treatment (Visit 4, Week 8), and on-treatment 4 or 8 weeks later (Visit 5, Week 14 ± 2 weeks)
Due to COVID-19, visit windows were extended

Main Inclusion Criteria:	Main 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

Study Endpoints

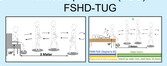
1. Safety and Tolerability
2. Pharmacodynamics in muscle and blood and Pharmacokinetics in plasma and muscle
3. Exploratory Endpoints – see right

Exploratory Endpoints

Reachable Workspace

Timed Up and Go (TUG) FSHD-TUG

Quantitative Myometry



Handheld Dynamometry

Other:
- Spirometry
- 6-Minute Walk Test
- MFM Domain 1

PROs:
- FSHD-HI
- FSHD-RODS
- PGIC

NCT04004000

*outpatient wearables to be presented at a later time

Results

Baseline and Demographic Information

		Losmapimod 15 mg BID (N=14)
Age (years)	Mean (SD)	45.7 (11.12)
Race, White	n (%)	13 (92.9)
Body Mass Index (BMI) (kg/m²)	Mean (SD)	24.0 (2.94)
D4Z4 Repeat Category, n (%)	1-3 Repeats	3 (21.4)
	4-9 Repeats	11 (78.6)
Ricci Score, n (%)	2	0
	2.5	1 (7.1)
	3	5 (35.7)
	3.5	2 (14.3)
	4	6 (42.9)
Enrolled	n (%)	14
Completed the study	n (%)	14 (100)
Discontinued from study	n (%)	0
Entered extension	n (%)	12 (85.7)

- All subjects completed the study
- 2 subjects declined participation in the extension study for reasons unrelated to study drug/adverse events

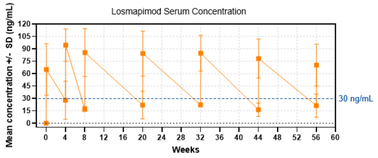
Safety and Tolerability

	Overall (N=14) n (%)
Any TEAE	14 (100)
Any treatment-related TEAE	14 (100)
Any serious adverse event (SAE)	0
Any TEAE leading to treatment discontinuation	0
Any TEAE leading to death	0
AE by Maximum Severity	
Mild	4 (28.6)
Moderate	5 (35.7)
Severe	5 (35.7)
Most Common AEs (>25%)	
Alanine aminotransferase (ALT) increased*	5 (35.7)
Dry skin	4 (28.6)
Myalgia	4 (28.6)

- *ALT increases were mild and transient – All cases resolved with continued dosing, and none led to treatment discontinuation
- No significant changes in vital signs, laboratory studies or EKG were observed
- Nine subjects (64.3%) reported events in the SOC of Skin and Subcutaneous tissue disorders

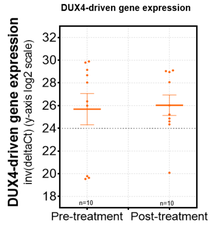
Pharmacodynamics and Pharmacokinetics

- Blood and muscle concentrations were within the expected range based on pre-clinical data
- Target engagement in blood was within the expected range (~40% to 55% change from baseline at Cmax)



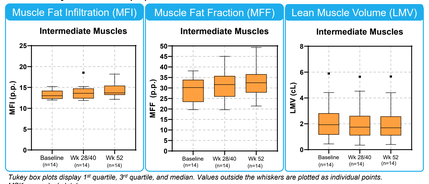
DUX4 Activity

- Changes from baseline were not observed
- DUX4-driven gene expression was highly variable



Whole Body MSK MRI

- Essentially no change was observed in this population. This result is likely related to the small sample size of this study and broad range of disease severity with more severe disease (Ricci 4) in nearly half of the population.



Tukey box plots display: 1st quartile, 3rd quartile, and median. Values outside the whiskers are plotted as individual points.
MSK: musculoskeletal

Cross-sectional Composite Correlations

- Moderate and strong correlations between MRI and TUG and FSHD-TUG at Week 52 (n=14)
- Moderate correlations to Total RWS for LMV and MFF at Week 52 (n=14)

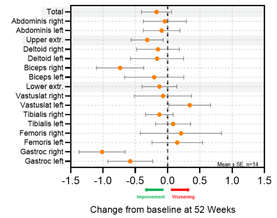
MRI Composite	Statistic	TUG Cross-sectional	FSHD-TUG Cross-sectional
LMV (cL)	r (p-value)	-0.89 (<0.0001)	-0.83 (0.0002)
MFF (%)	r (p-value)	0.86 (<0.0001)	0.77 (0.0003)
MFI (%)	r (p-value)	0.77 (0.0014)	0.77 (0.0014)

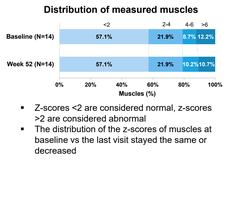
MRI Composite	Statistic	Dom Total RSA Weighted	Non-Dom Total RSA weighted
LMV (cL)	r (p-value)	0.55 (0.0666)	0.43 (0.1591)
MFF (%)	r (p-value)	-0.66 (0.0199)	-0.52 (0.0800)
MFI (%)	r (p-value)	-0.24 (0.4568)	-0.09 (0.7787)

For full details see poster Widholm P, et al. Quantitative muscle analysis in FSHD using Whole-Body MRI: Composite Muscle Measurements for Cross-Sectional Analysis

Muscle Ultrasound Echogenicity

- Various structural changes in the muscle, such as fatty infiltration, fibrosis, or edema, produce an increase in echogenicity
  - Echogenicity is expressed as z-score compared to reference healthy control populations
- Most muscles demonstrated stability or improvement over 52 weeks

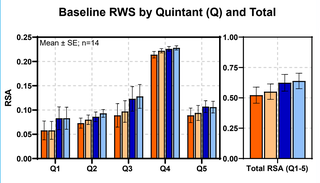


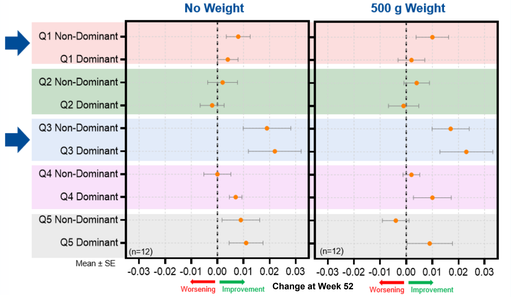


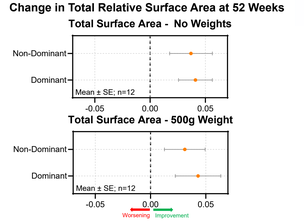
- Z-scores <2 are considered normal, z-scores >2 are considered abnormal
- The distribution of the z-scores of muscles at baseline vs the last visit stayed the same or decreased

Reachable Workspace (RWS)

- Losmapimod treated patients in OLS showed improvements in total RSA (Q1-Q5) in both weighted and non-weighted measurements in both dominant and non-dominant arms, with the largest improvements in the upper quadrants (Q1 and Q3)
- Slowing of disease progression and/or improvement was observed on multiple RWS metrics, including annualized RWS







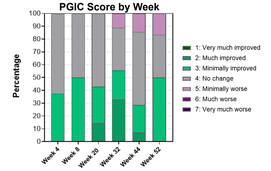
Annualized Reachable Workspace (percent change from baseline per year)

	Without Weights		With Weights	
Quintant (Q)	**Dom**	**Non-Dom**	**Dom**	**Non-Dom**
Q1	11.95	7.73	9.16	8.60
Q2	-3.39	1.36	-0.28	1.34
Q3	16.05	9.37	16.66	10.72
Q4	1.10	0.18	2.23	0.58
Q5	4.44	6.25	4.49	-2.11
Q1+Q3	14.53	8.58	13.92	9.79
Total RSA	4.90	4.28	5.68	3.28

Dom = dominant; Non-Dom = non-dominant; RSA = relative surface area

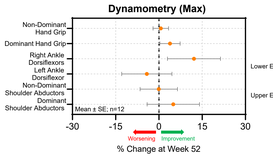
Patient Global Impression of Change (PGIC)

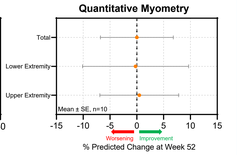
- Over 80% of subjects reported improvement or no change after 52 weeks of treatment; no patients reported feeling much worse over 52 weeks



Hand-held Dynamometry and Quantitative Myometry

- Stability or improved muscle strength from baseline in maximum hand-held dynamometry and percent predicted Quantitative Myometry was observed





TUG, FHSD-TUG, FSHD-RODS, Motor Function Measurement, FSHD-HI, 6-MWT, and Spirometry showed minimal changes over 52 weeks of treatment

Conclusion

- Losmapimod was generally well-tolerated in FSHD study participants for approximately 52 weeks of treatment in an open-label, single-site study
- Losmapimod demonstrated expected PK and PD
- Improvement or minimal changes were observed in structural (MRI and ultrasound) and FSHD-relevant functional measures (RWS, HHD, and QMT)
  - Improvements in Reachable Workspace were demonstrated across quintants, with the largest improvements in the upper quadrants (Q1 and Q3)
- Patients recognized benefit of treatment based on reported improvement on PGIC
- The results of this open-label, single site study seem to confirm and extend in an independent cohort the results of the ReDUX4 study*, supporting the benefit/risk of losmapimod as a disease-modifying therapy and continued development of losmapimod in FSHD

0.5 A phase 2, randomized, double-blind, placebo-controlled, 48-Week study of the efficacy and safety of losmapimod in subjects with FSHD: ReDUX4. R. Tawil; K. Wagner; Behalf of the ReDUX4 Study Group

Acknowledgements

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