Muscle Ultrasound in an Open-Label Study of Losmapimod in Subjects with FSHD1

Joost Kools[1], Nicol Voermans[1], Karlien Mul[1], John Jiang[2], Markus Karlsson[3]

[1]Radboud University Medical Centre (Radboudumc), Nijmegen, NL, [2]Fulcrum Therapeutics, Cambridge, MA, USA [3]AMRA Medical AB, Linköping, Sweden

Introduction

- FSHD is a serious, rare, progressive and heterogeneous disease, caused by the aberrant expression of DUX4 in skeletal muscle leading to progressive muscle loss and accumulation of disability.
- **Losmapimod** is an investigational small molecule inhibitor of p38α/β Mitogen Activated Protein Kinase (MAPK), being developed for the treatment of FSHD
- Structural changes in the muscle, such as fatty infiltration, fibrosis, or edema, produce an increase in echogenicity, observable via **muscle ultrasound**.

Rationale

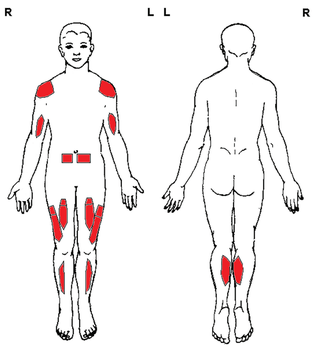
Natural history studies have identified muscle ultrasound (US) as a viable imaging biomarker for FSHD muscle progression, complementary to MRI

Objective

- Evaluate muscle ultrasound in an open-label clinical trial with losmapimod in FSHD type 1 patients.

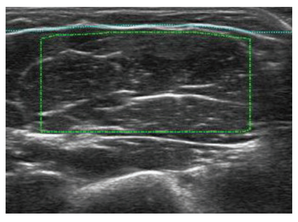
Methods

- Muscle Ultrasound was performed in 7 muscles bilaterally using a standardized protocol
- A region of interest was drawn to calculate the average grey-value (echogenicity) using local software
- The raw grey-value is expressed as a z-score relative to matched healthy controls. Z-scores < -2 and >2 are considered abnormal

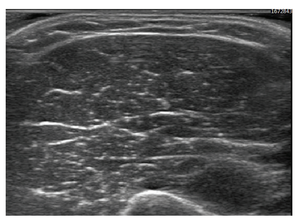


Muscle	Localization ultrasound transducers
Deltoid	At 1/4 of the distance between the acromion and the elbow crease.
Biceps Brachii	At 2/3 of the distance between the acromion and elbow crease.
Rectus Abdominis	Approximately 2 cm above the umbilicus, lateral from the linea alba.
Rectus Femoris	At 1/2 of the distance between the anterior superior iliac spine and the upper edge of the patella.
Vastus Lateralis	At 2/3 of the distance between the anterior superior iliac spine and the upper edge of the patella.
Gastrocnemius Medialis	At 1/3 of the distance between the head of the fibula and the lateral malleolus.
Tibialis Anterior	At 1/3 of the distance between the head of the fibula and the lateral malleolus.

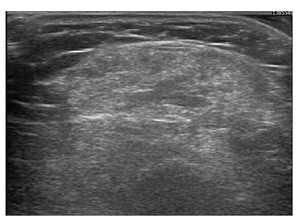
Region of interest



Normal Biceps Brachii



Abnormal Biceps Brachii

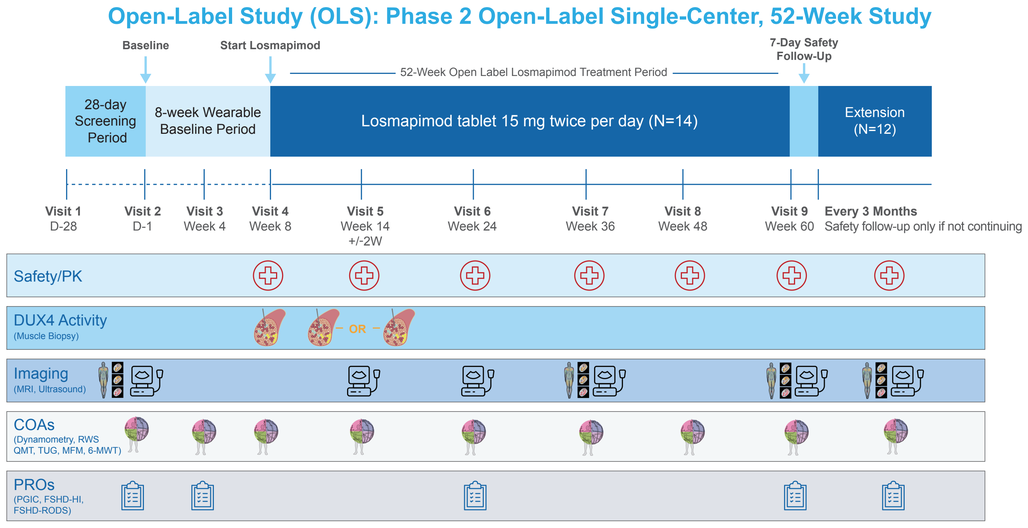


Study Design

- Single center open label study (OLS) at Radboud University, Netherlands
- Study Population: Enrolled 14 participants with genetically confirmed FSHD1

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

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



Study Week 60 = 52 weeks of losmapimod treatment

Demographics Characteristics

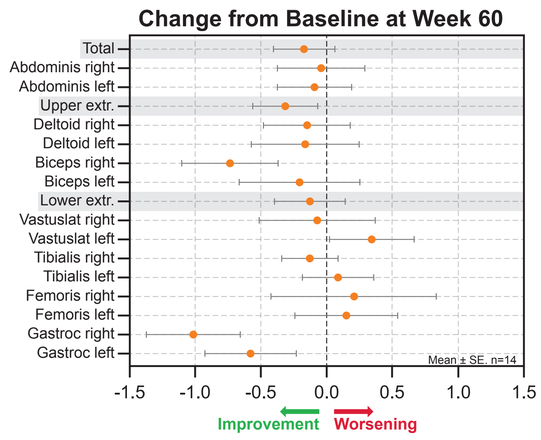
		Losmapimod 15 mg BID (N=14)
Age (years)	Mean (SD)	45.7 (11.12)
Race, White	n (%)	13 (92.9)
Body Mass Index (BMI) (kg/m²)	Mean (SD)	24.0 (2.94)
D4Z4 Repeat Category, n (%)	1-3 Repeats	3 (21.4)
	4-9 Repeats	11 (78.6)
Ricci Score, n (%)	2	0
	2.5	1 (7.1)
	3	5 (35.7)
	3.5	2 (14.3)
	4	6 (42.9)
Enrolled	n (%)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

- All subjects completed the study
- Due to COVID-19, 2 subjects had a start of treatment delay of ~12 weeks. These subjects are included in the Week 60 analysis.
- 2 subjects declined participation in the extension study for reasons unrelated to study drug/adverse events

Results

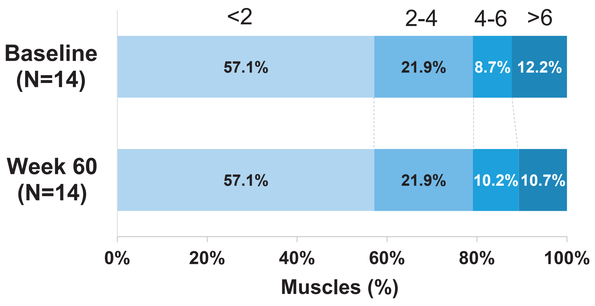
Muscle Ultrasound Echogenicity

Change from Baseline at Week 60



- Most muscles demonstrated stability or improvement over 52 weeks of treatment
- Natural history studies previously demonstrated increases or worsening in echogenicity over 1 year (Goselink et al 2020)

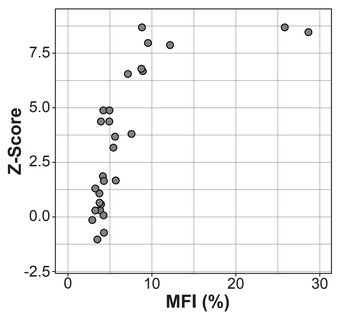
Distribution of Muscles Z-score



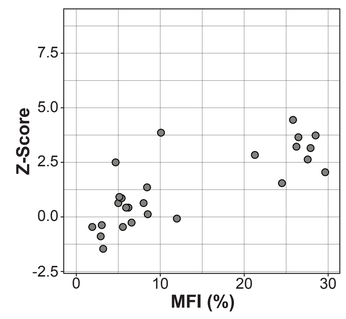
- The distribution of the z-scores of muscles at baseline vs the last visit stayed the same or decreased, consistent with stability

Correlation with MRI

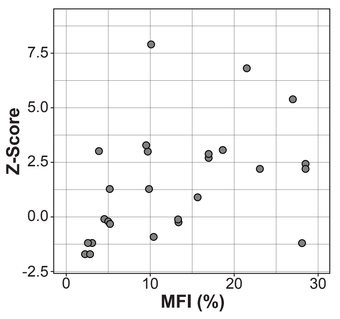
Biceps Brachii rho = 0.84, p <0.01



Tibialis Anterior rho = 0.76, p <0.01



Gastrocnemius Medialis rho = 0.50, p <0.01



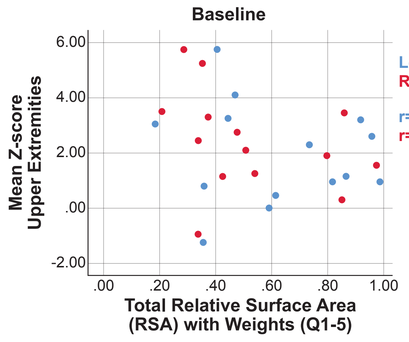
Baseline; Left and right presented

- Moderate to strong correlation of echogenicity to Muscle Fat Infiltration (MFI). Similar correlations observed to Muscle Fat Fraction
- Ceiling effect of echogenicity observed at MFI >~10% for Biceps Brachii and >~20% for Tibialis Anterior and Quadriceps (not shown above)
- Echointensity appears to falsely normalize in more severely fat replaced muscle, Gastrocnemius Medialis, at MFI >25%, due to the tissue becoming homogenous (fat)

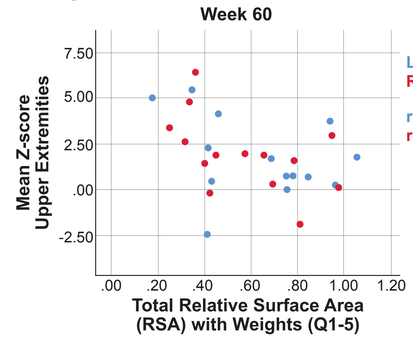
Correlation with Clinical Outcome Assessments (COAs)

Reachable Workspace

Baseline



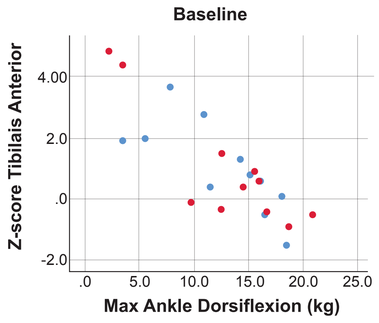
Week 60



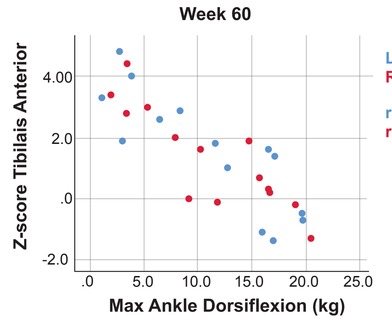
- Non-significant trend of correlation between Total Weighted RSA and upper extremity echogenicity (biceps and deltoids)

Handheld Dynamometry – Ankle Dorsiflexion

Baseline



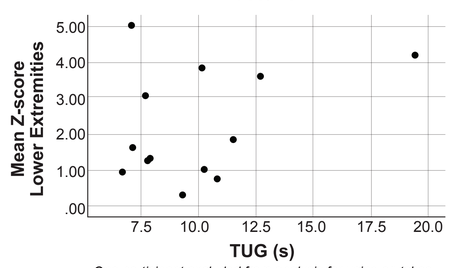
Week 60



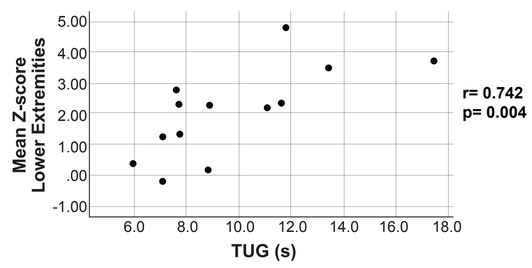
- Strong correlation of echogenicity of Tibialis Anterior to maximum ankle dorsiflexion

Timed Up-And-Go (TUG)

Baseline



Week 60



One participant excluded from analysis for using crutches

- Mean echogenicity of the lower extremities showed strong correlation to the classic TUG at Week 60. Correlation at baseline limited by outlier on TUG

Limitations

- Small sample size and heterogenous patient population
- Ceiling effect observed with muscle ultrasound compared to MRI, especially in highly fat replaced muscles
- Not all muscles involved in COAs were assessed with muscle ultrasound

Conclusion

- Stability in echogenicity of muscles demonstrated over 52 weeks of losmapimod treatment
- Moderate to strong correlations were observed between echogenicity and MRI
- Ultrasound may be a valuable imaging tool in FSHD, complementary to MRI