Fulcrum Therapeutics

ReDUX4

Assessing losmapimod in FSHD

Emerging Therapeutic Approaches in Facioscapulohumeral Muscular Dystrophy

July 14, 2021 10AM EST

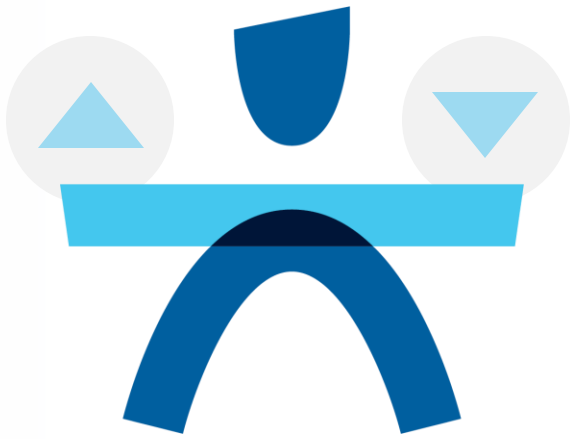
Today's Agenda and Objective

Agenda Topic	Lead	Time (ET)
Welcome, Objective, and Overview of Meeting	Jennifer McNary	10:00-10:05am
Background on FSHD	Chris Morabito, MD	10:05-10:15am
Overview of Pre-Clinical Data	Chris Moxham, PhD	10:15-10:20am
ReDUX4 Study Results	Michelle Mellion, MD	10:20-10:40am
Putting it all together	Chris Morabito, MD	10:40-10:50am
Q&A / Discussion	All	10:50-11:00am

Objective: Provide the opportunity to connect with people living with FSHD and caregivers about the newly released data results.

Fulcrum Overview

Clinical stage biopharmaceutical company using systematic approach to identify small molecules able to rebalance gene expression



FulcrumSeek Platform identifies targets that have the potential to rebalance gene expression

- ~7,000 genetically defined diseases today
- We are building on decades of research highlighting gene expression role in disease
- High-throughput product engine designed to rapidly identify and validate drug targets that can modulate gene expression and treat disease at its root cause
- Focus on small molecules as therapeutic modality

Our vision is to treat genetically defined diseases by addressing their root cause

Fulcrum Therapeutics

Background on FSHD – *Chris Morabito, MD*

Currently, There Are No Treatment Options for People Living With FSHD That Address Disease Progression

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD) is 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

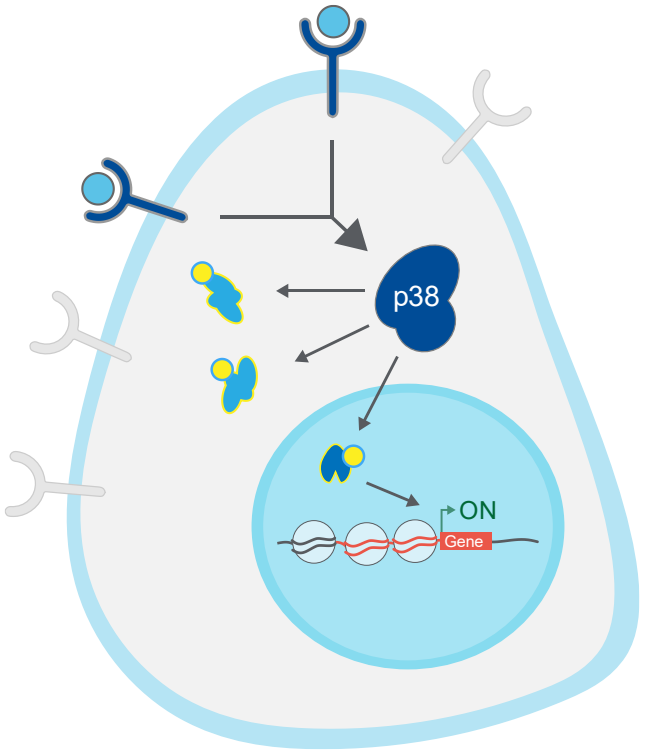
PROGRESSIVE MUSCLE LOSS AND FATTY REPLACEMENT can cause a slowly progressive descending weakness and loss of function in those affected

MUSCLE PATHOLOGY leads to accumulation of disability

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

Losmapimod is a Selective p38 α/β MAP kinase inhibitor

- Four different p38 MAP Kinase proteins have been identified: alpha, beta, delta, and gamma (α, β, δ, γ)
- Losmapimod inhibits the activity of p38 MAP Kinase α and β and reduces phosphorylation of substrates, including HSP27 and other proteins that result in the regulation of DUX4 expression
- Losmapimod has favorable safety and tolerability, as demonstrated across:
  - > 3500 study participants
  - > 25 clinical trials
  - > 30 countries, and
  - > 11 different target indications in adults[1]



1. Cadavid D, Mellion M, Wallace O, et al. Safety and tolerability of losmapimod, a selective p38α/β MAPK inhibitor, for treatment of FSHD at its root cause. Poster presented at the 26th Annual FSHD International Research Congress; June 19-20, 2019; Marseille, France.

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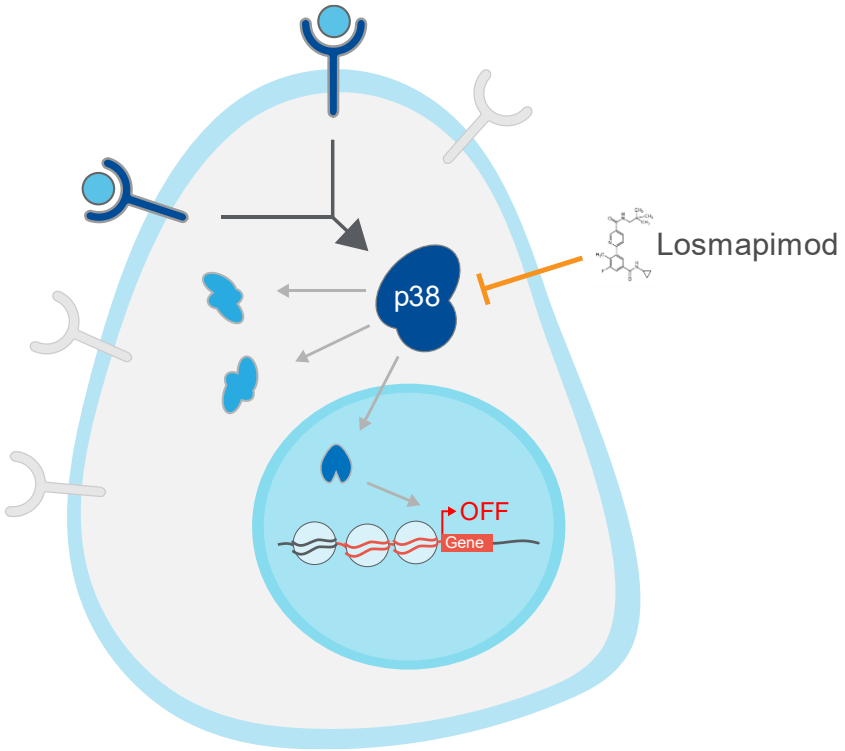

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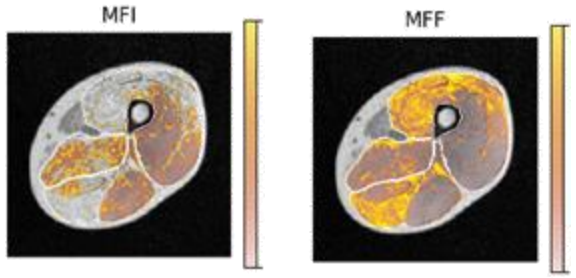
ReDUX4 Hypothesis: Losmapimod Modifies the Course of FSHD

Hypothesis: Losmapimod will reduce FSHD-related muscle degeneration through reduction of myotoxic DUX4, leading to decreased muscle fat replacement and, ultimately, slowing of functional loss

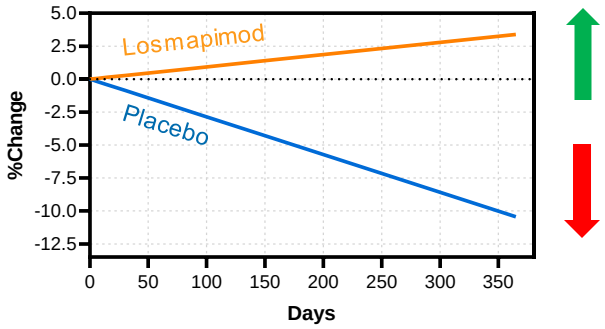
Muscle Health

Decrease of fat replacement in muscle



Function

Preserve and/or improve muscle function



Quality of Life

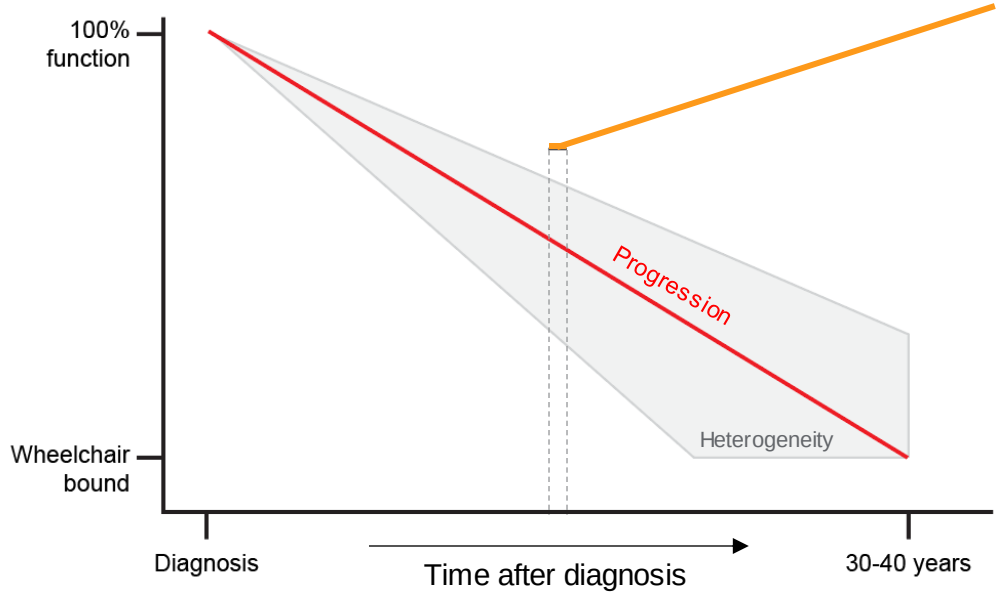
Significant patient-reported improvements

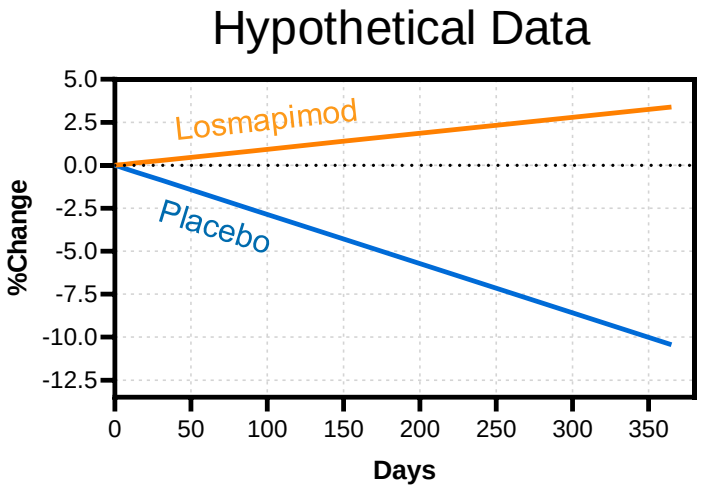
Scores	PGIC
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Worse
6	Much worse
7	Very much worse

FSHD is a Progressive, Lifelong Disease

How can losmapimod slow or halt progressive change in a 48-week study?

- Can an **80 participant, 48-week trial show patient benefit safely?**
  - Can trends across multiple analyses converging on benefit provide support for efficacy?
  - Is losmapimod well tolerated and does it appear safe?





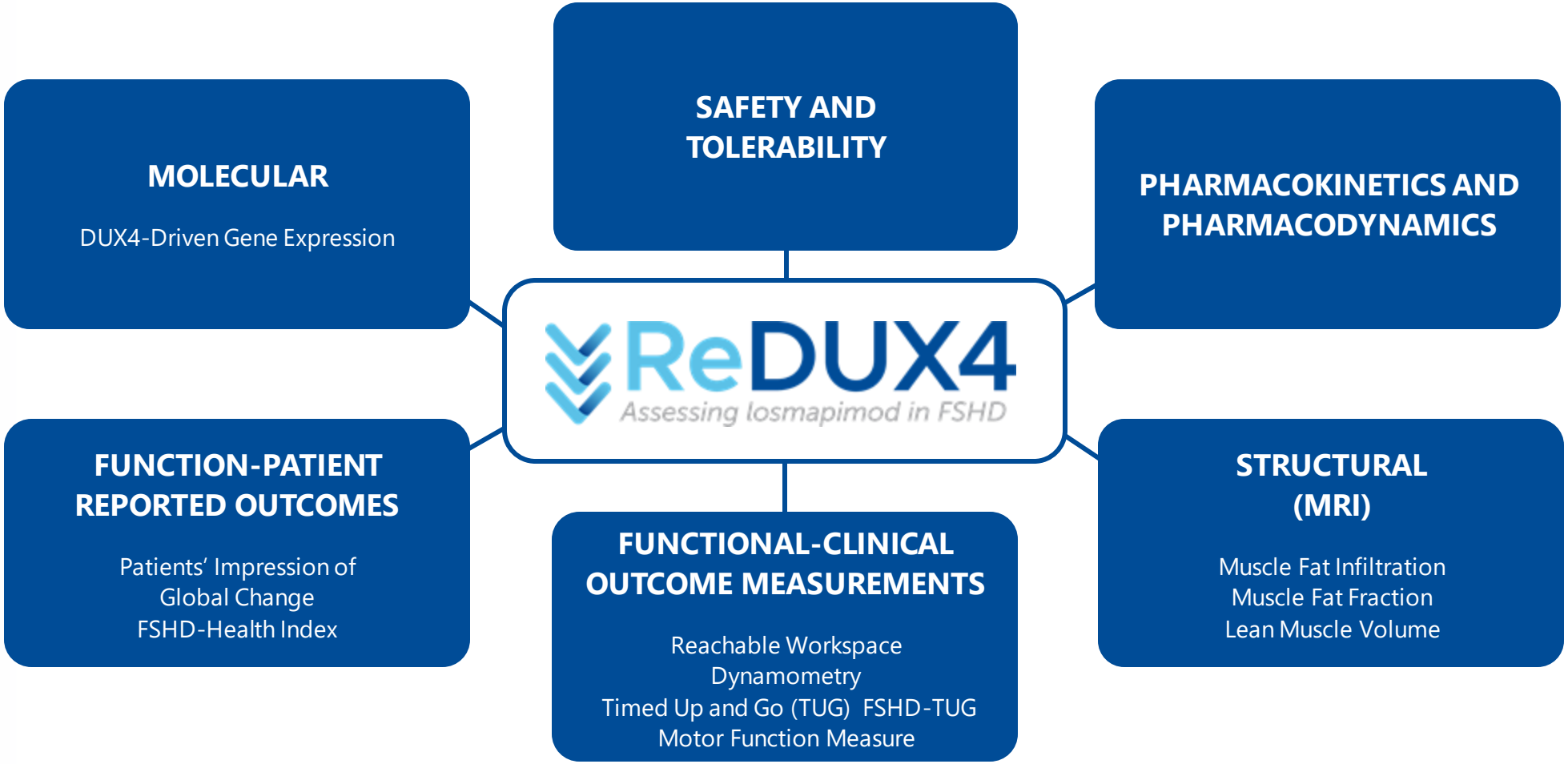
*Illustrative model of FSHD progression

Losmapimod Clinical Development Program

Complete	Fulcrum Preparatory Studies	▪ Refined clinical endpoints: DUX4, MRI, Muscle Function, PROs
	Phase 1	▪ Safe and tolerable in FSHD subjects ▪ Target engagement demonstrated ▪ Losmapimod penetrates FSHD muscle
Ongoing Studies	Phase 2 Open Label Study > 52 weeks dosing	▪ Molecular endpoint in muscle biopsy ▪ MRI assessment of skeletal muscle ▪ Clinical assessments of mobility ▪ Patient reported outcomes
	Phase 2b ReDUX4 *24 or 48 weeks dosing then* Long Term Open Label Extension	▪ Phase 2b trial results to be presented

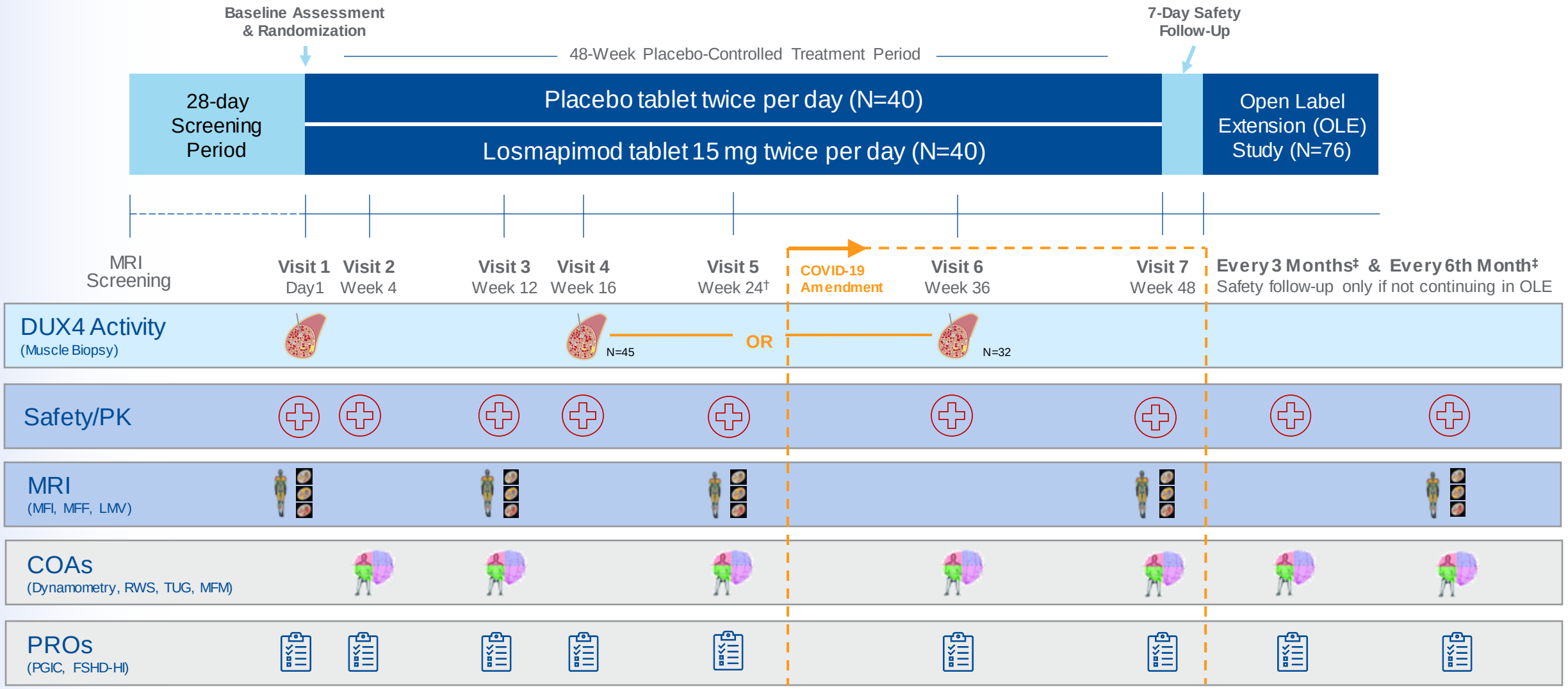
ReDUX4 Trial Was Designed To Capture a Wide Range of FSHD Disease Progression

Phase 2b, randomized, double-blind, placebo-controlled, multi-site international study*



*This study (N=80) was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint). Protocol amendment to accommodate COVID-19 impact (extend trial to 48 weeks and allow 2nd biopsy to occur at either 16 or 36 weeks). (77 participants completed, treatment group=39, placebo group=38). 98.7% of eligible participants rolled over to open-label portion.

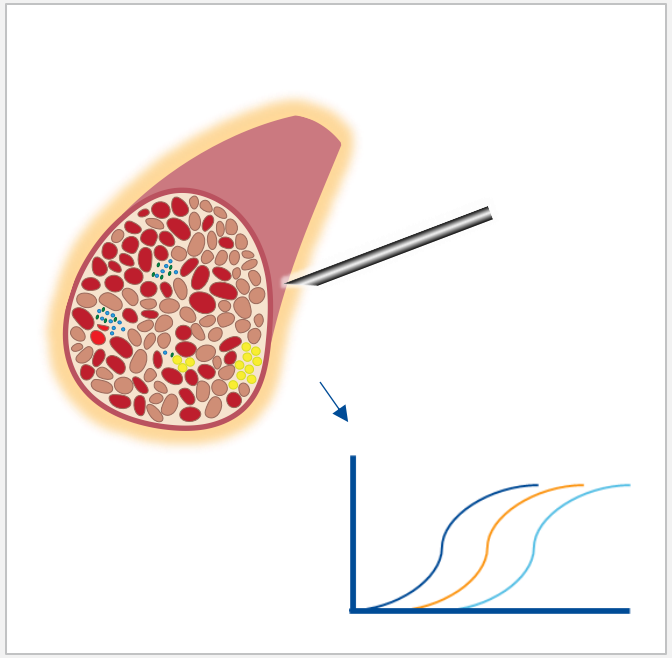
ReDUX4 Trial Design*



*All analyses were pre-specified in the statistical analysis plan, with the exception of dynamometry, which is now presented as percent change from baseline. †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.

Evaluating Biomarkers in ReDUX4

DUX4-Driven Gene Expression in Muscle Biopsies by RT-qPCR



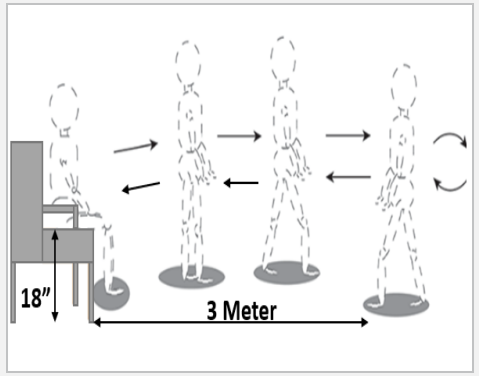
*Analyses at 16 or 36 weeks.

Whole-Body Musculoskeletal MRI

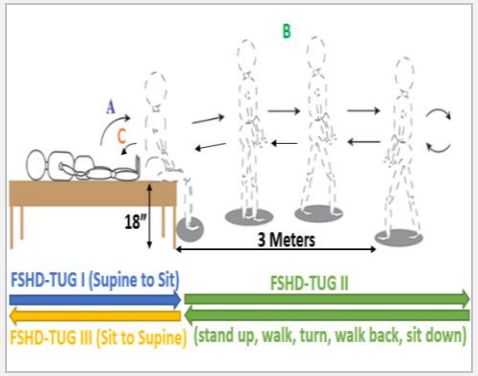
*Analyses at 48 weeks.

Evaluating Clinical Outcome Assessments (COAs)*

Timed Up and Go (TUG)



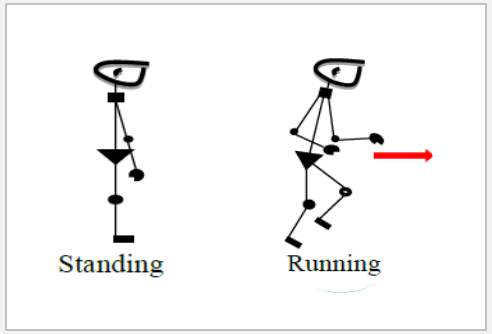
FSHD-TUG



Dynamometry

Reachable Workspace (RWS)

Motor Function Measurement Domain 1



*Analyses at 48 weeks.

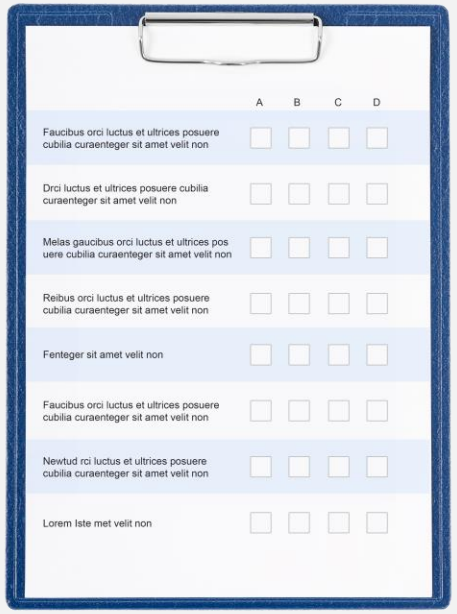
Evaluating Patient Reported Outcomes (PROs)*

Patients' Global Impression of Change (PGIC)

"Since the start of the study, my overall status is":

Scores	PGIC
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Worse
6	Much worse
7	Very much worse

FSHD-Health Index (FSHD-HI)



*Analyses at 48 weeks.

Fulcrum Therapeutics

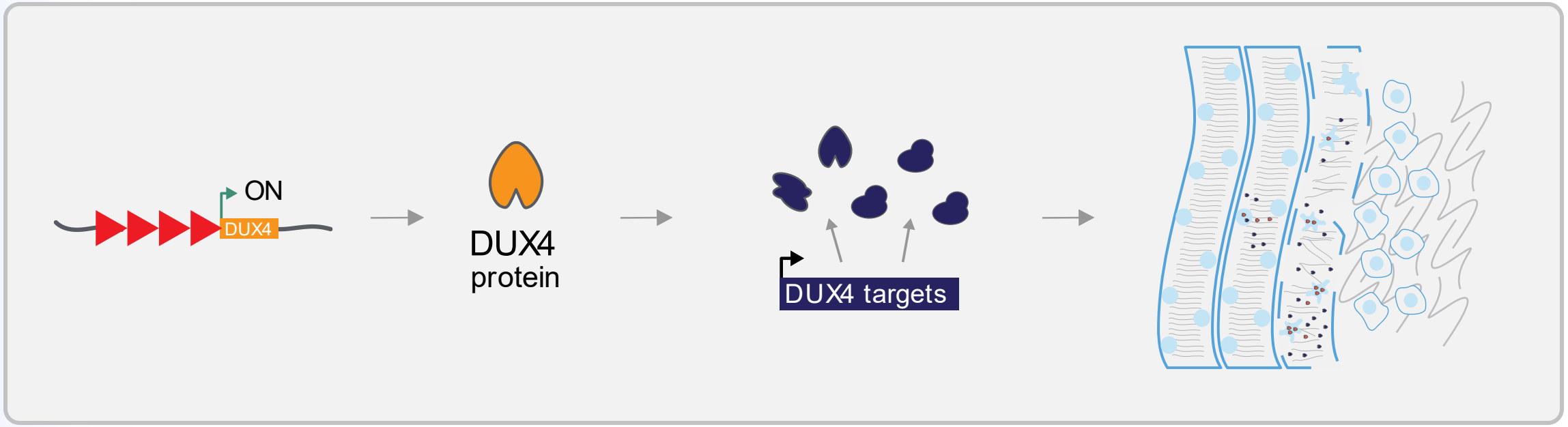
ReDUX4
Assessing losmapimod in FSHD

Overview of Pre-Clinical Data –
Chris Moxham, PhD

Measuring DUX4-Driven Gene Expression

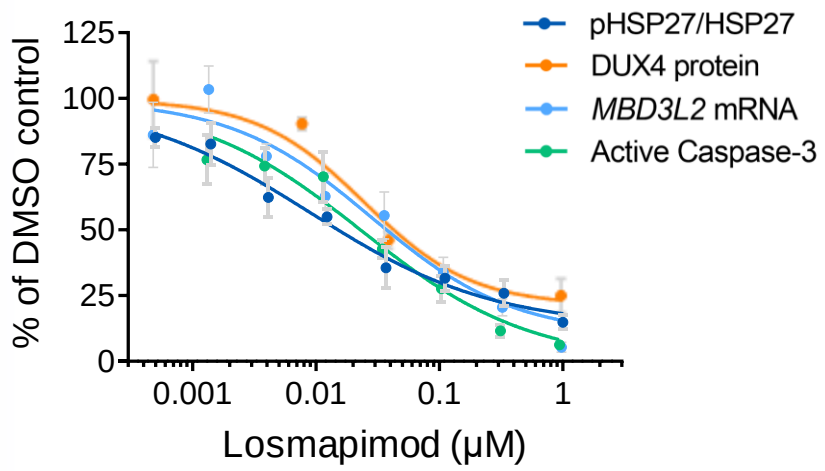
DUX4 is the root cause of FSHD

- Present in very low amounts in the FSHD muscle
- Activates expression of DUX4 targets genes during embryogenesis
- DUX4 target genes should not be expressed in skeletal muscle
- Measuring DUX4 target gene expression can tell us about the amount of DUX4 in the muscle



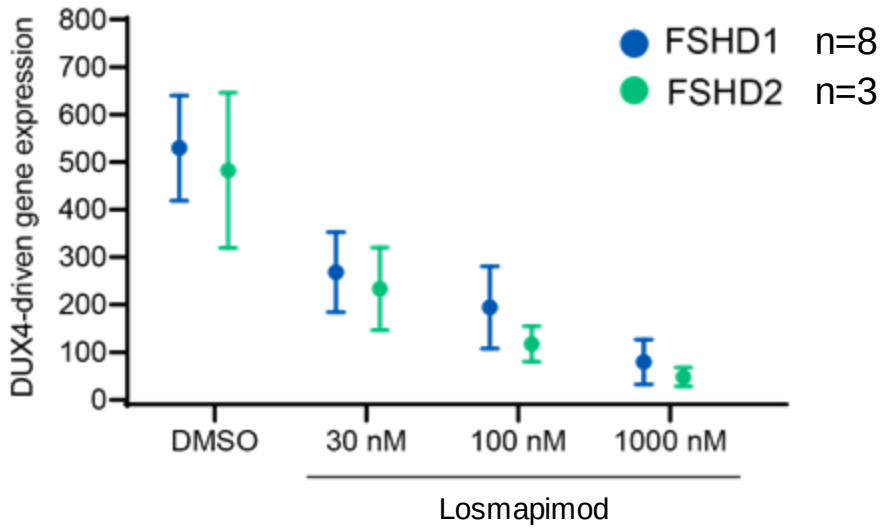
Losmapimod Reduced DUX4 Expression in Preclinical FSHD Studies

Losmapimod reduced p38 activity, DUX4 expression, DUX4 activity, and cell death in patient-derived FSHD myotubes



- **HSP27** is a substrate of p38 MAP kinase pathway
- ***MBD3L2*** is a DUX4-target gene
- **Caspase-3** is an indicator of cell death

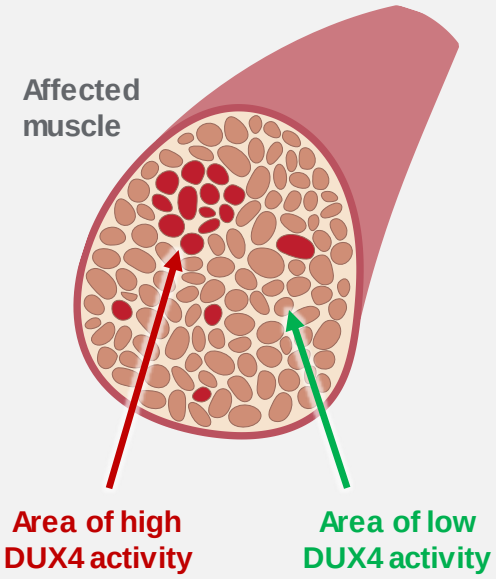
Preclinical study demonstrated a reduction of DUX4 activity across multiple patient-derived FSHD1/2 myotubes



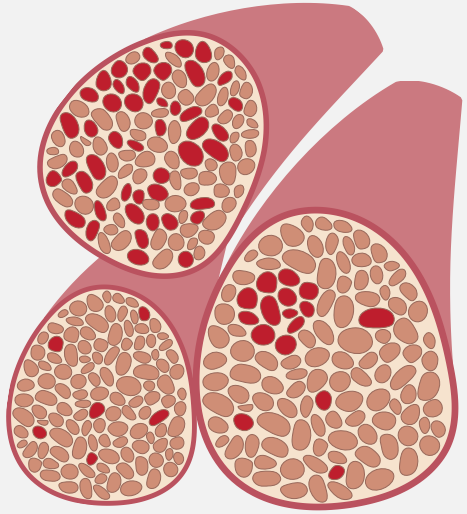
Heterogeneity of muscle composition in FSHD

Stochastic DUX4 expression and FSHD pathology in the FSHD muscle

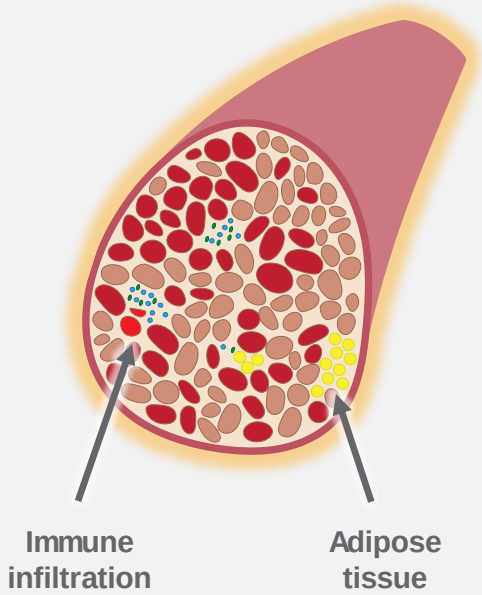
DUX4 expression happens in a subset of myonuclei and myofibers in the FSHD muscle



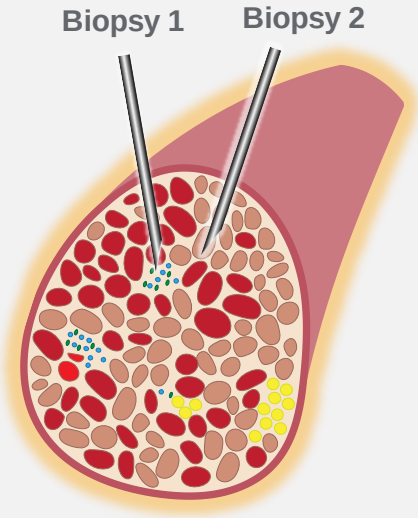
Different muscles in an individual with FSHD have different DUX4 expression levels and patterns



STIR signal in MRI helps to identify muscles most likely to express DUX4



Biopsy procedure was designed to sample proximal regions in repeated biopsies



Imprecision in sampling and heterogeneity in muscle result in high variability between measurements

Fulcrum Therapeutics

ReDUX4
Assessing losmapimod in FSHD

ReDUX4 Study Results – *Michelle Mellion, MD*

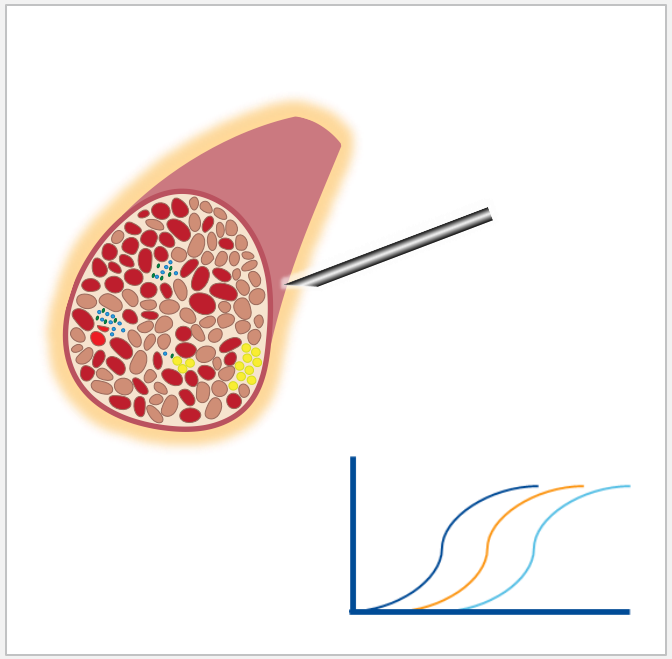
ReDUX4 Study Participant Randomization Was Well Balanced

		Placebo BID (N=40)	Losmapimod 15 mg BID (N=40)
Completed		38 (95%)	39 (97.5%)
Discontinued*		2 (5.0%)	1 (2.5%)
DEMOGRAPHICS			
Age (years)	N	40	40
	Mean (SD)	45.7 (+/- 12.69)	45.7 (+/- 12.44)
Race n (%)	White	39 (97.5)	31 (77.5)
	Asian	0	5 (12.5)
	Other	0	1 (2.5)
	Not Applicable	1 (2.5)	3 (7.5)
Ethnicity n (%)	Hispanic or Latino	3 (7.5)	0
	Not Hispanic or Latino	36 (90.0)	37 (92.5)
	Not Applicable	1 (2.5)	3 (7.5)
Body Mass Index (BMI) (kg/m^2)	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)

*Discontinuations were not related to study drug.

Evaluating Biomarkers in ReDUX4

DUX4-Driven Gene Expression in Muscle Biopsies by RT-qPCR



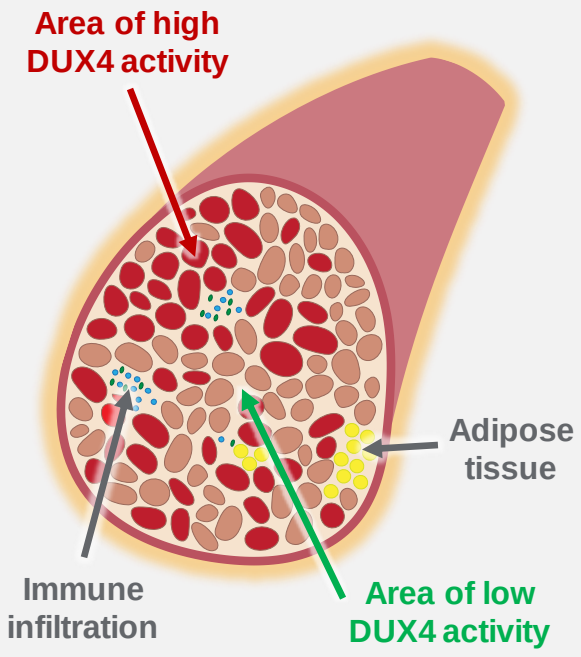
*Analyses at 16 or 36 weeks.

Whole-Body Musculoskeletal MRI

*Analyses at 48 weeks.

A Novel Biomarker, DUX4-Driven Gene Expression, Was Selected as the Primary Endpoint

STIR signal in MRI helps to identify muscles more likely to express DUX4



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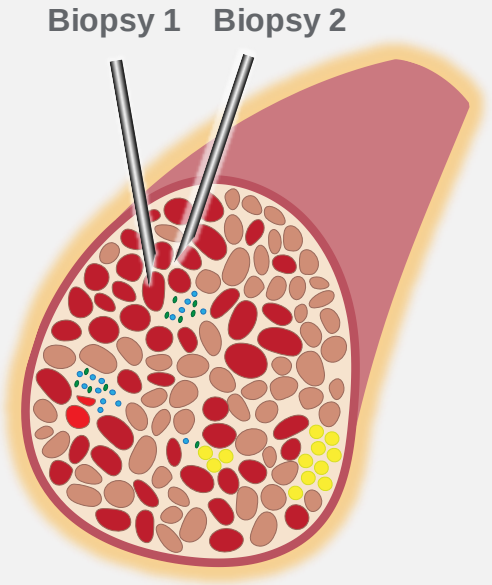


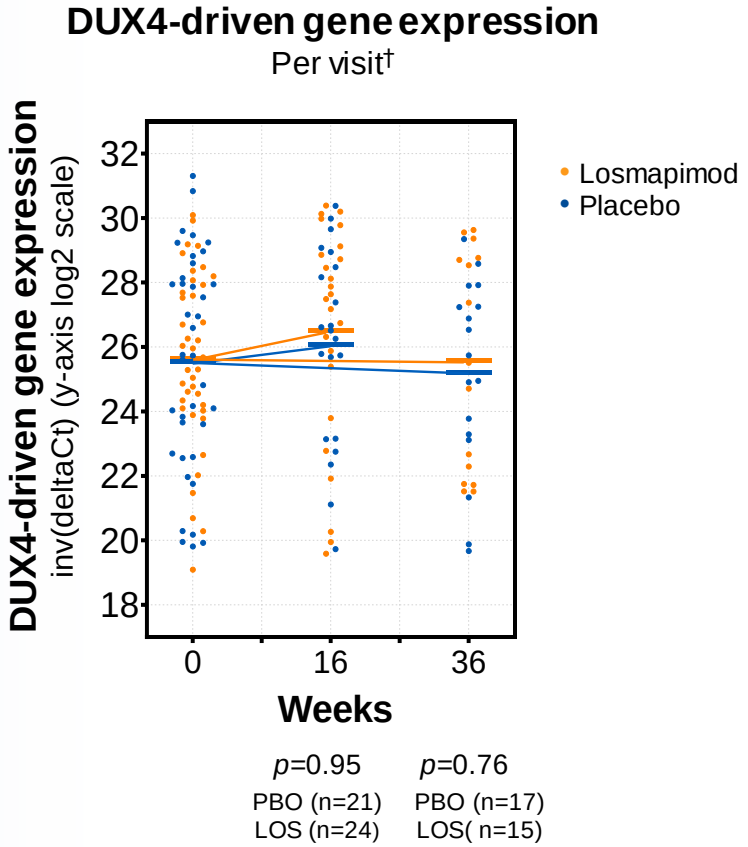
- DUX4-driven gene expression levels represent DUX4 activity
- RT-qPCR assay validated to quantify DUX4 target gene expression*
- Assessed by the mean signal of 6 DUX4 target genes
- Primary analysis performed at 16 or 36 weeks of treatment

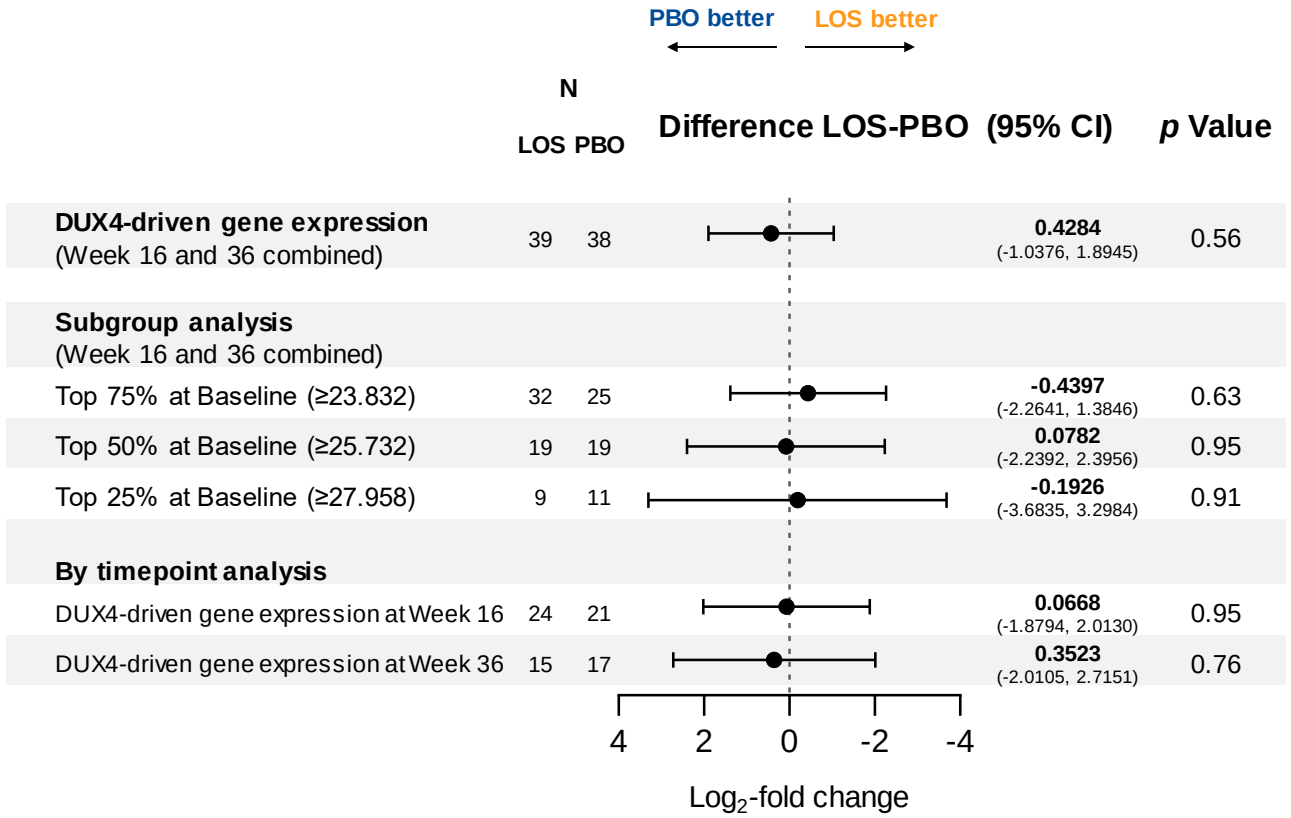
*Fulcrum validated a Fluidigm RT-qPCR assay to measure expression of these 6 transcripts (*CCNA1, KHDC1L, MBD3L2, PRAMEF6, SLC34A2, ZSCAN4)* in addition to 3 reference genes (TBP, HMBS, CDKN1B).
STIR= Short-TI Inversion Recovery.

Primary Endpoint: Reduction of DUX4-Driven Gene Expression in Muscle Biopsies

Changes in either group were not observed in the treatment period*, and the primary endpoint was not met

- Subgroup analysis by quartile of DUX4-driven gene expression showed no differences
- DUX4-driven gene expression was highly variable in both groups





*Primary analysis at 16 or 36 weeks. †Y-axis in log2 scale. Lines represent mean.

Challenges of DUX4 Experimental Biomarker

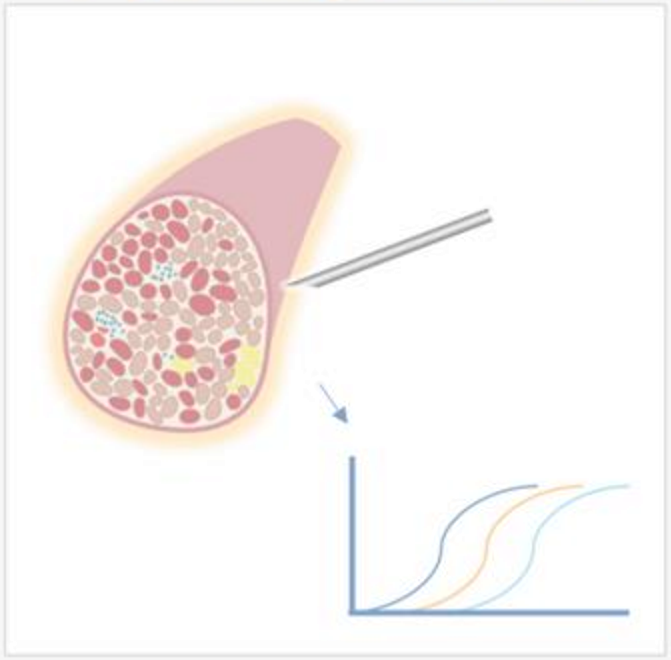
- Losmapimod reduced DUX4-driven gene expression preclinically in vitro and in vivo

- Translation to clinic was limited despite having validated qPCR assay
  - Stochastic expression - dynamic range varies by ~1000-fold
  - Scarce expression - ~1/1000 myonuclei shown to express DUX4
  - Needle biopsy samples a relatively small muscle segment from heterogeneous cell environment
  - Sampling a dynamic, scarce signal in a heterogenous cell population with needle biopsy was not sufficiently robust to detect treatment-related changes over time
  - Inter- and intra-patient heterogeneity introduces additional variability
  - Relative imprecision in the needle biopsy procedure across multiple clinical trial sites

ReDUX4 Showed Downstream Benefits of DUX4 Reduction

Evaluating Biomarkers in ReDUX4

DUX4-Driven Gene Expression in Muscle Biopsies by RT-qPCR



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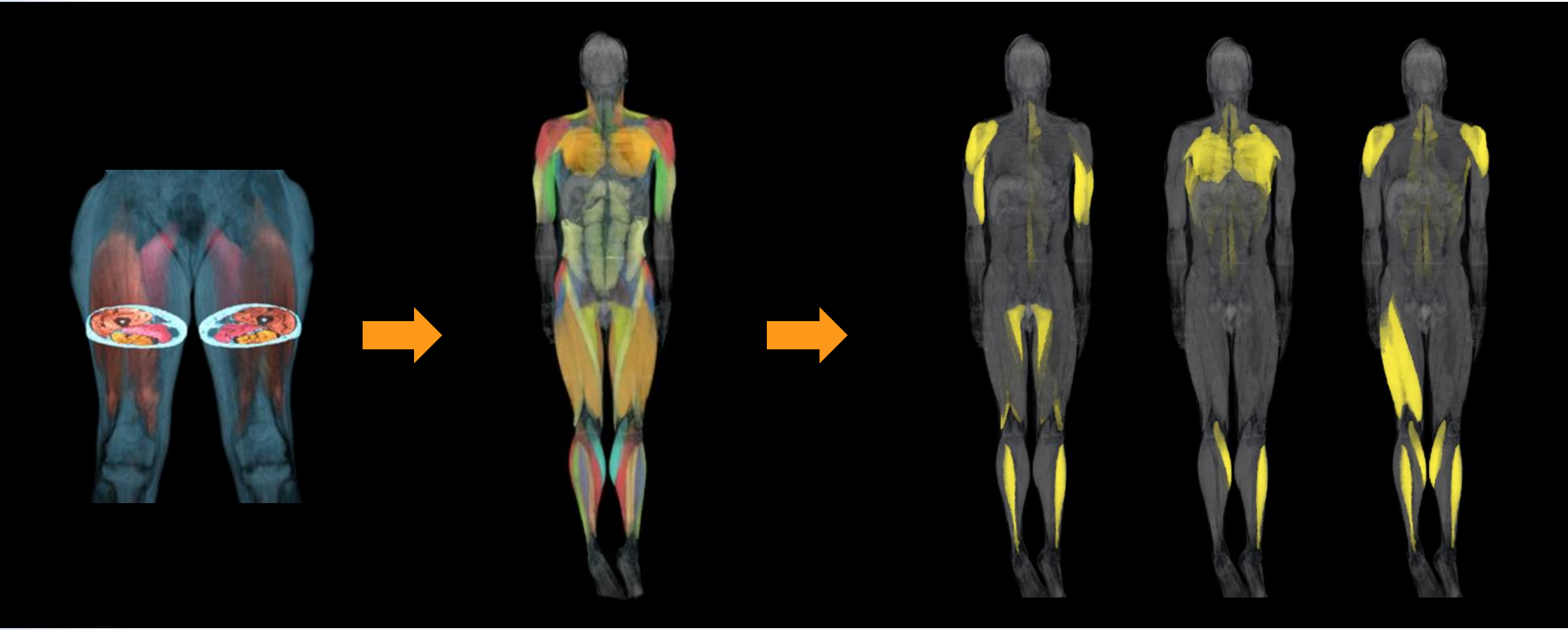
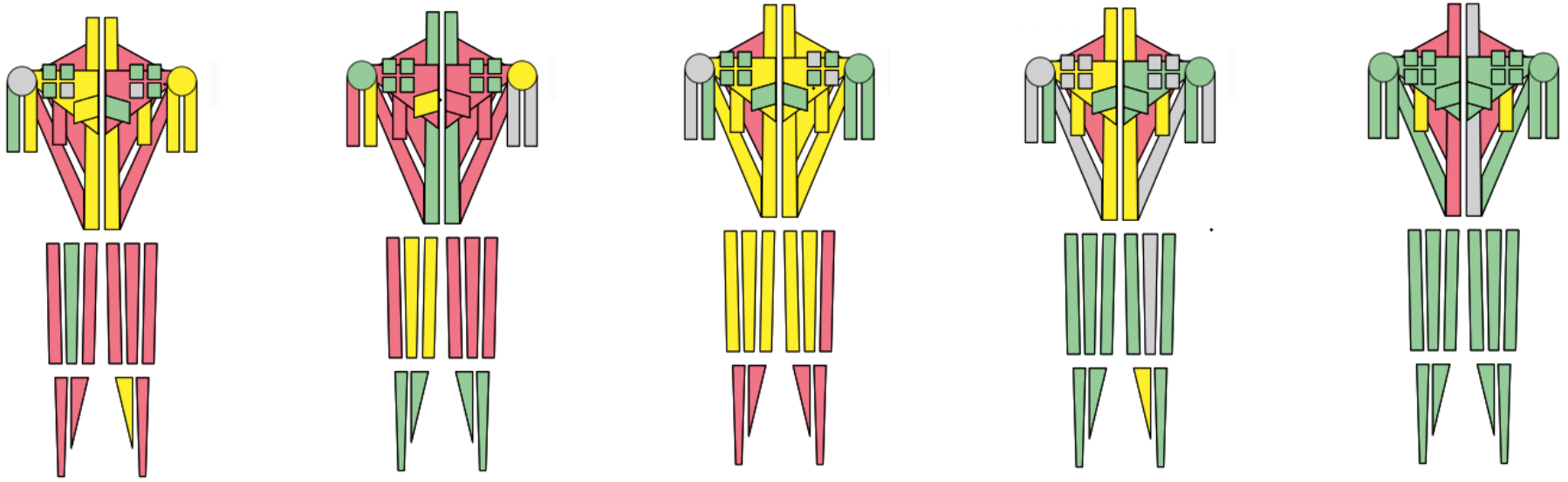
Whole-Body Musculoskeletal MRI

*Analyses at 48 weeks.

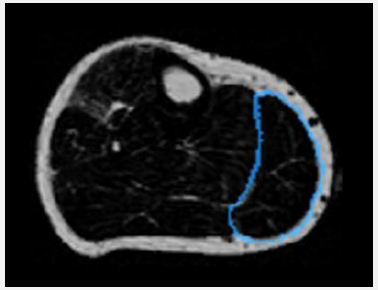
New Paradigm of Image Analysis in NMD



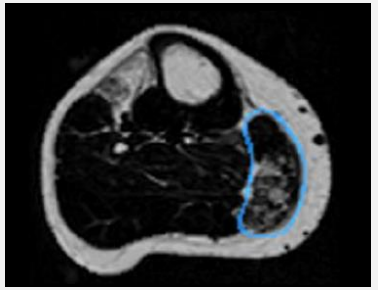
Muscle Categorization Captures FSHD Disease Heterogeneity



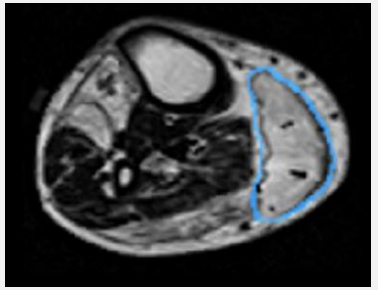
Normal-Appearing "A"



Intermediate "B"

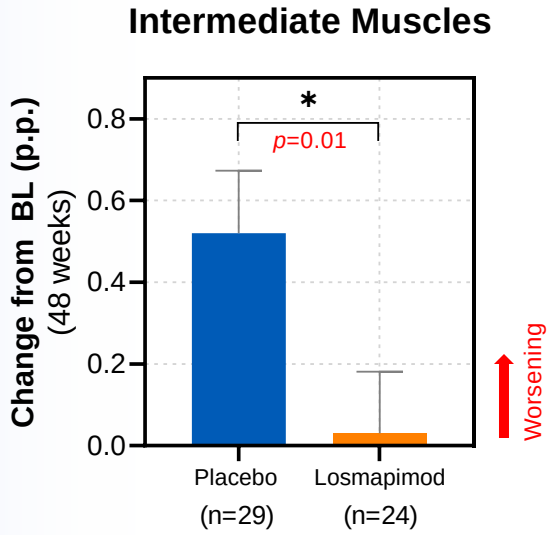


End-Stage "C"



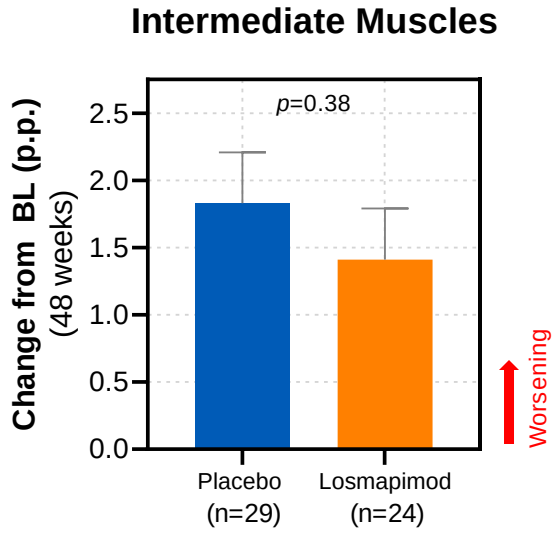
Losmapimod Treated Participants Showed Significantly Less Muscle Fat Infiltration (MFI) vs Placebo in Intermediate Muscles*

Muscle Fat Infiltration (MFI)



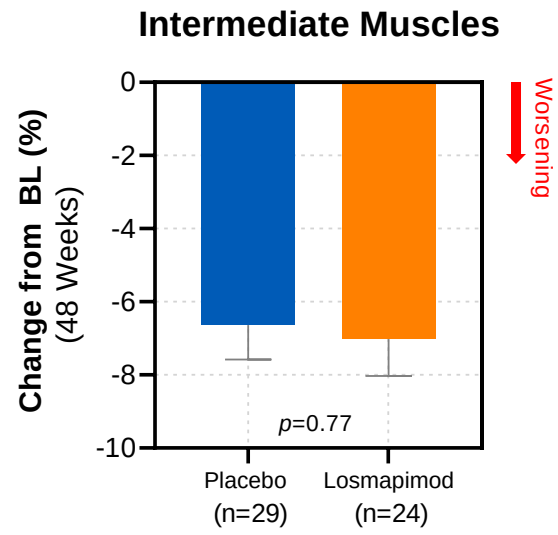
LS means + SE

Muscle Fat Fraction (MFF)



LS means + SE

Lean Muscle Volume (LMV)



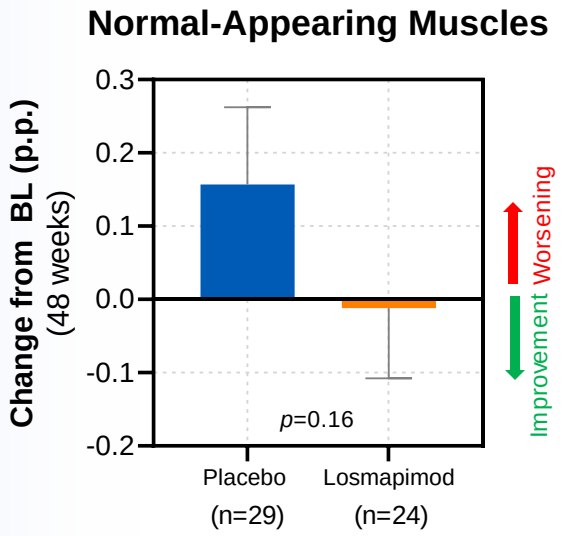
LS means + SE

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

*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint). Mixed-Effects Model for Repeated Measures (MMRM) analysis. Intermediate muscles included in the longitudinal composite score because they are most likely to progress; MFI ≥ 10%, MFF < 50%. LMV by MRI was pre-specified for hypothesis testing.

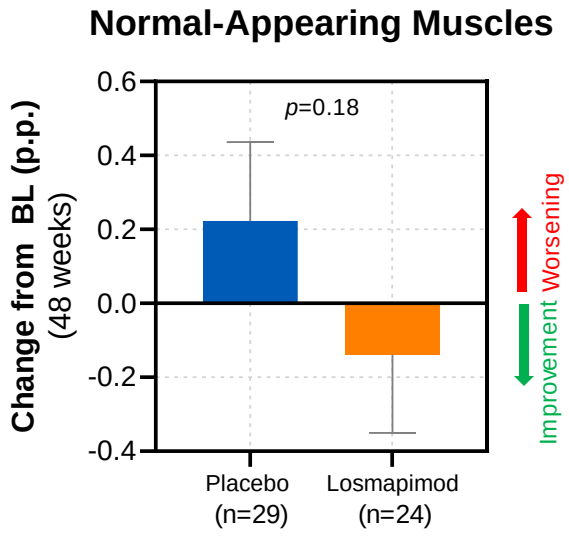
Normal-Appearing Muscles Appear Preserved With Losmapimod vs Placebo*

Muscle Fat Infiltration (MFI)



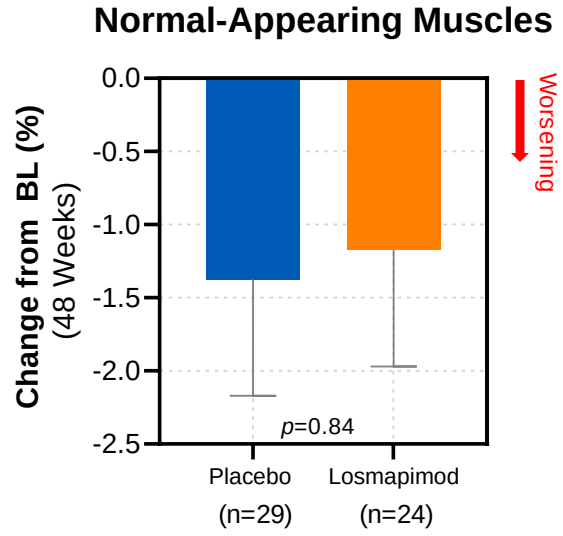
LS means + SE

Muscle Fat Fraction (MFF)



LS means + SE

Lean Muscle Volume (LMV)

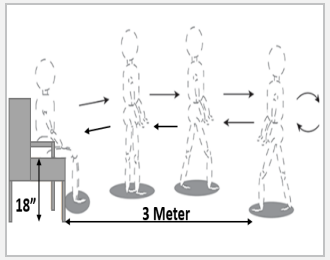


LS means + SE

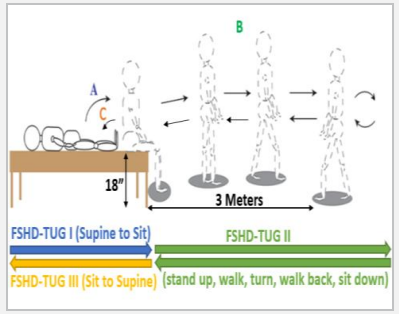
*Post-hoc analysis. Results are not statistically significant. Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint). Normal muscles do not appear to be affected by disease; MFI < 10%.; MFF<50%

Evaluating Clinical Outcome Assessments (COAs) and Patient Reported Outcomes (PROs)*

Timed Up and Go (TUG)



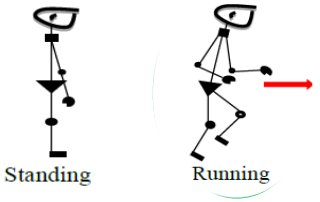
FSHD-TUG



Dynamometry

Reachable Workspace (RWS)

Motor Function Measurement Domain 1



Patients' Global Impression of Change (PGIC)

"Since the start of the study, my overall status is":

Scores	PGIC
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Worse
6	Much worse
7	Very much worse

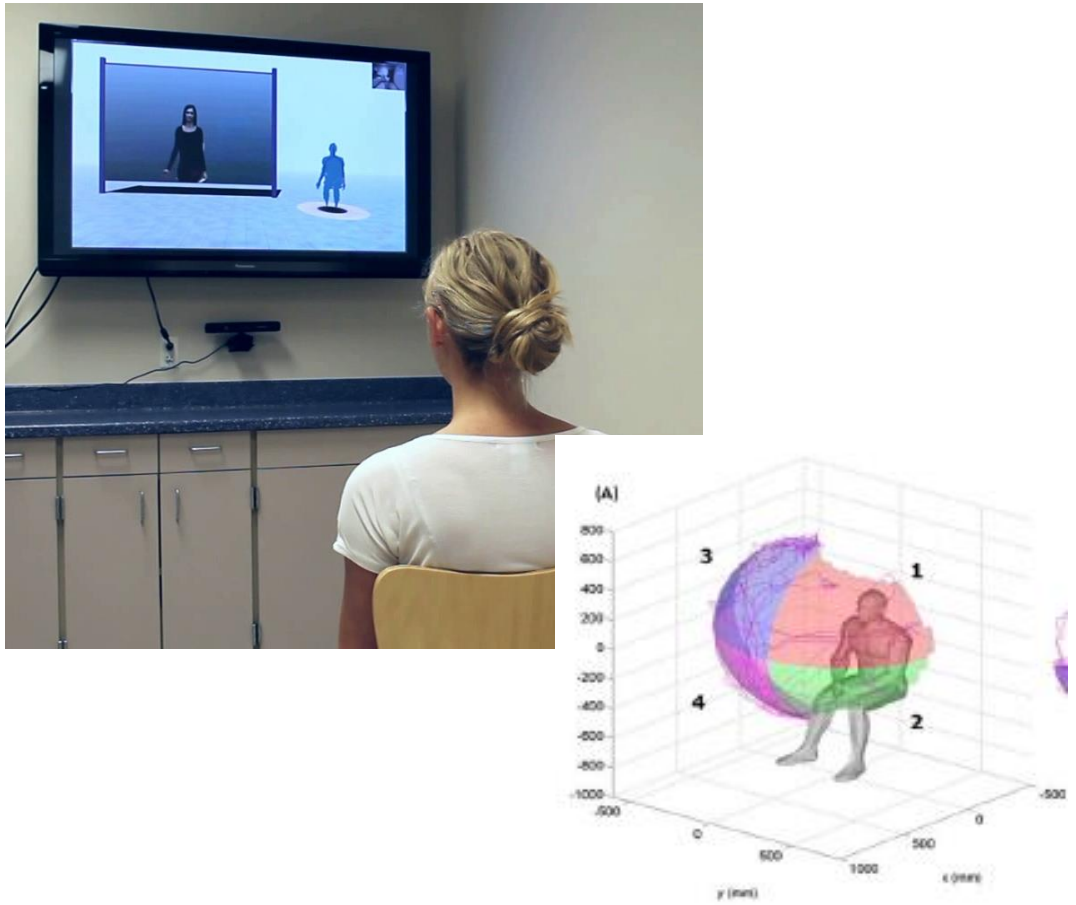
FSHD-Health Index (FSHD-HI)

*Analyses at 48 weeks.

Reachable Work Space (RWS)

Evaluating Upper Arm and Shoulder Function in FSHD subjects

- ***Centrally read*** evaluation of individual global upper extremity function, including shoulder and proximal arm
  - Tracks 3D upper limb trajectory
    - Divided into 5 regions; shoulder as origin
    - Calculation of total RWS surface envelope area (m^2) and areas for each quadrant
- Subjects sit in front of Microsoft Kinect sensor and undergo standardized upper extremity movement protocol
  - Evaluation performed with and without weights
  - Scaling of data by each subject's arm length allows normalization and comparison between subjects
- Reliable and sensitive to change
- **Annualized change; % change/year will be presented**

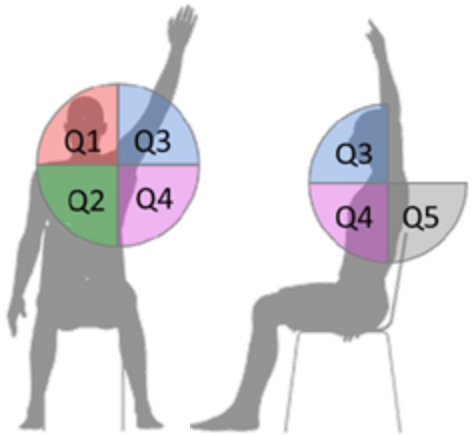


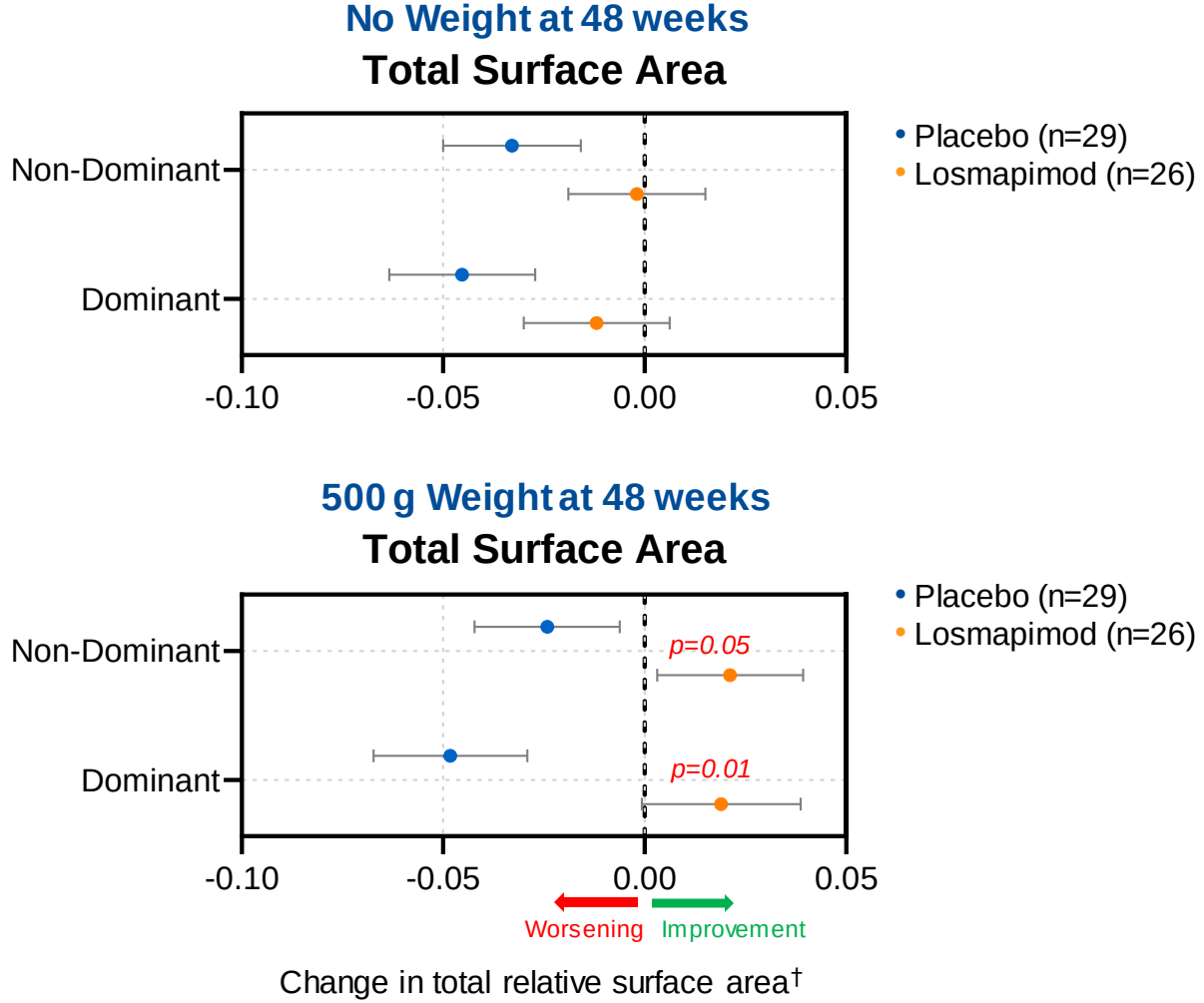
Validated for UE function (FSHD evaluation scale for UE function) and Strength (MVICT)[1]

[1]*Han et al., 2015 "Reachable workspace reflects dynamometer-measured upper extremity strength in facioscapulohumeral muscular dystrophy"*

Losmapimod Showed Significant Improvement in Total Surface Area by Reachable Workspace*

- Placebo group lost about 2% to 4% of Total Surface Area (with and without weight)
- Losmapimod group showed trends of slower disease progression as well as improvements of up to 1.5% in surface area with weight





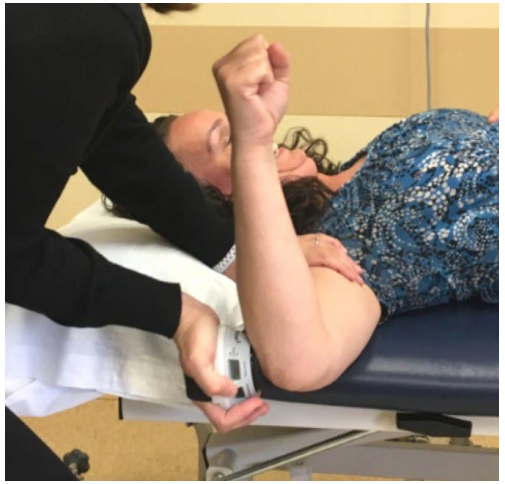
*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).
†Total relative area for the 5 quadrants used to calculate the approximate percentages of total area that participants experienced change on was 1.25. LS means ± SE.

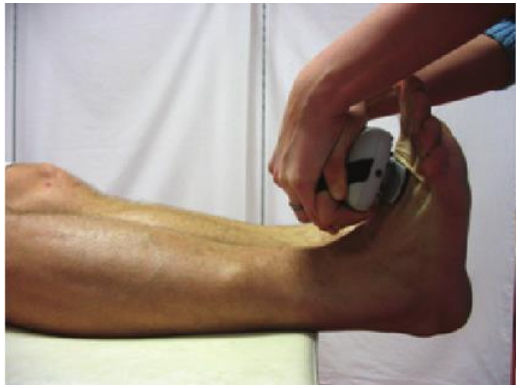
Hand-Held Dynamometry

Evaluating Upper and Lower Extremity Strength in FSHD subjects

- Quantitative isometric dynamometry used to assess muscle strength of upper and lower limbs bilaterally
- Evaluation performed by trained Physical Therapists
- Muscle groups to be assessed include
  - Shoulder abduction
  - Elbow flexion
  - Elbow extension
  - Ankle dorsiflexion
  - Hand grip (Jamar)

Shoulder Abduction

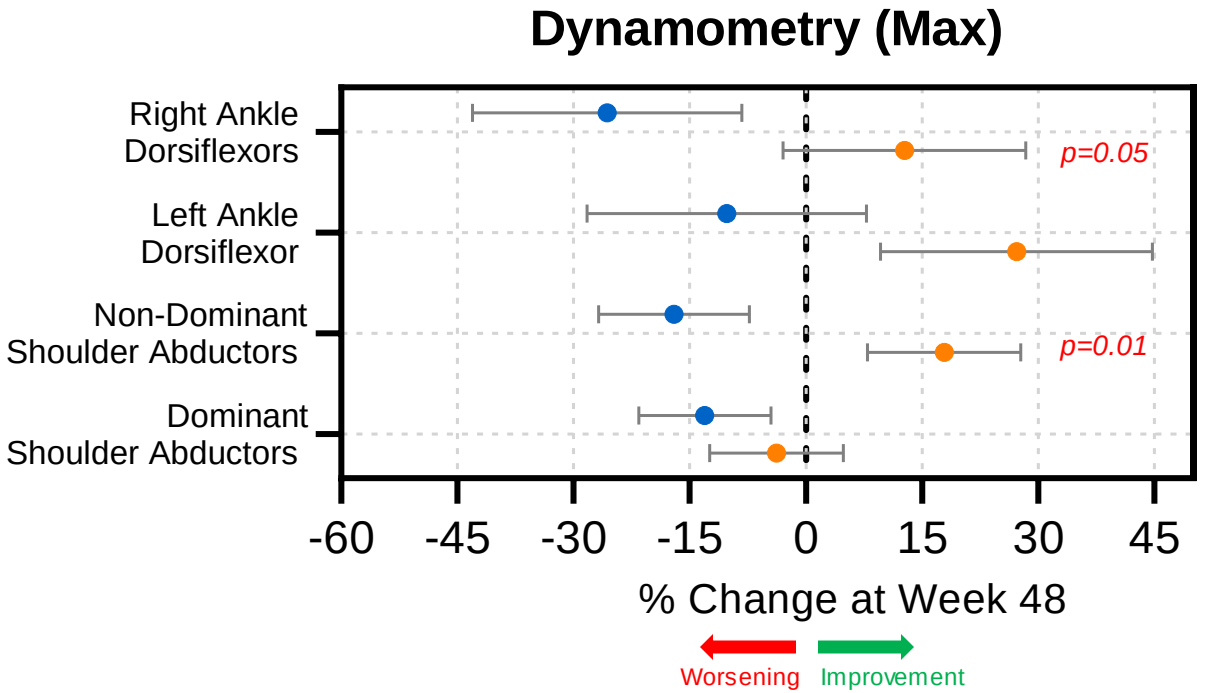




Ankle Dorsiflexion

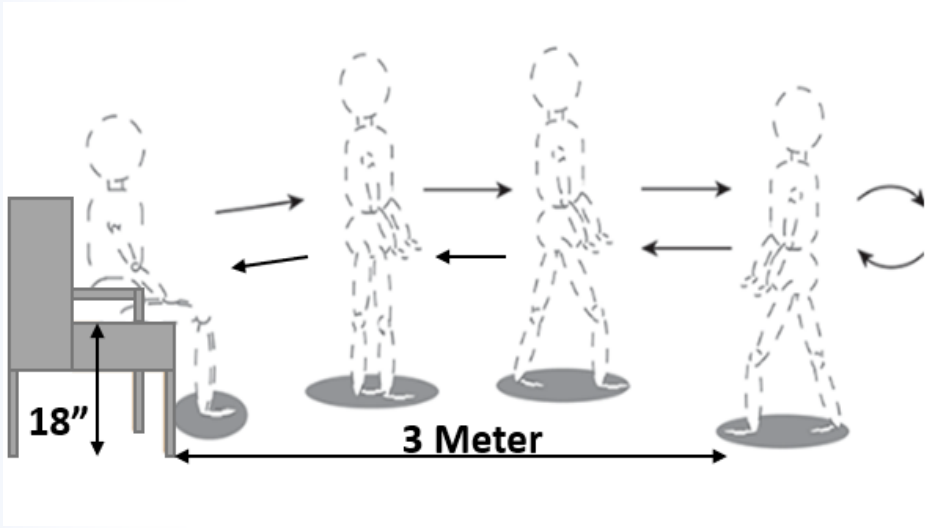
Losmapimod Showed Improved Muscle Strength vs Placebo*

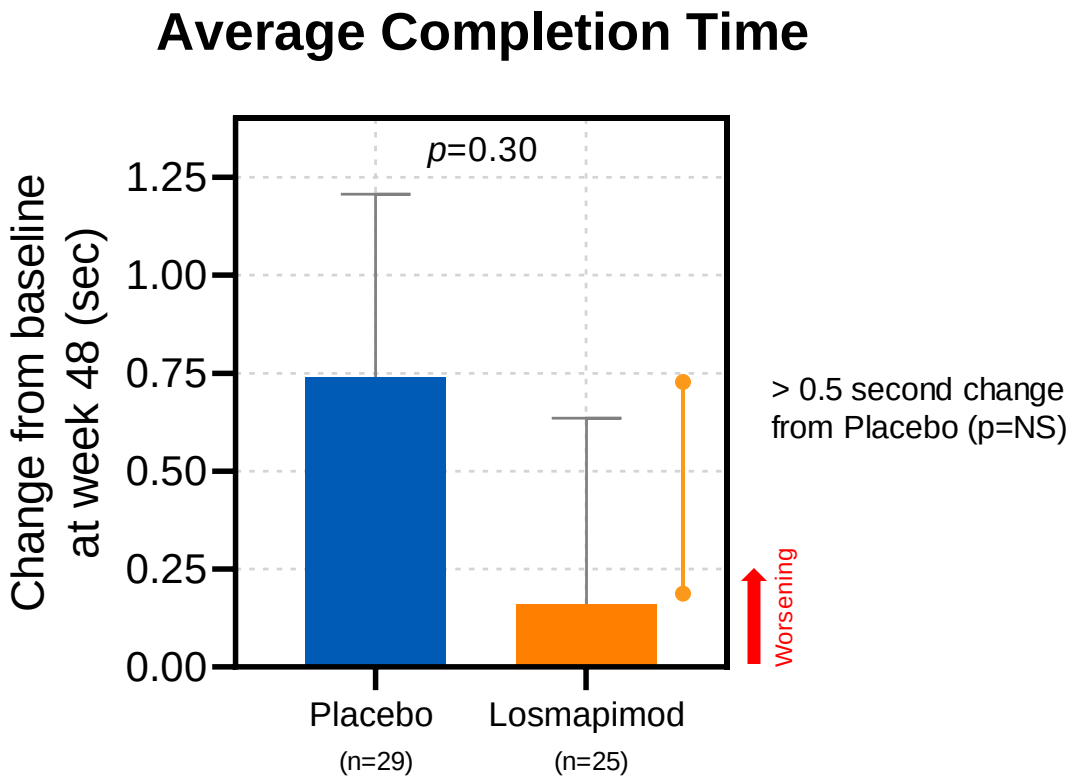
- Placebo group lost about 15% of shoulder and ankle dorsiflexors strength after 48 weeks
- Losmapimod group
  - Showed trends of slower progression (< 4% decline)
  - Improvements (12% to 27%) in the strength of non-dominant shoulder abductors and right ankle dorsiflexors compared to the placebo group



*Post hoc analysis. Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint). Data are reported as percent change from baseline, rather than the pre-specified plan to report as LS mean change from baseline in kilograms. LS mean change from baseline (kg) did not show changes.

Losmapimod-Treated Participants Showed a Trend in Decreasing Timed Up and Go (TUG) Completion Time vs Placebo*



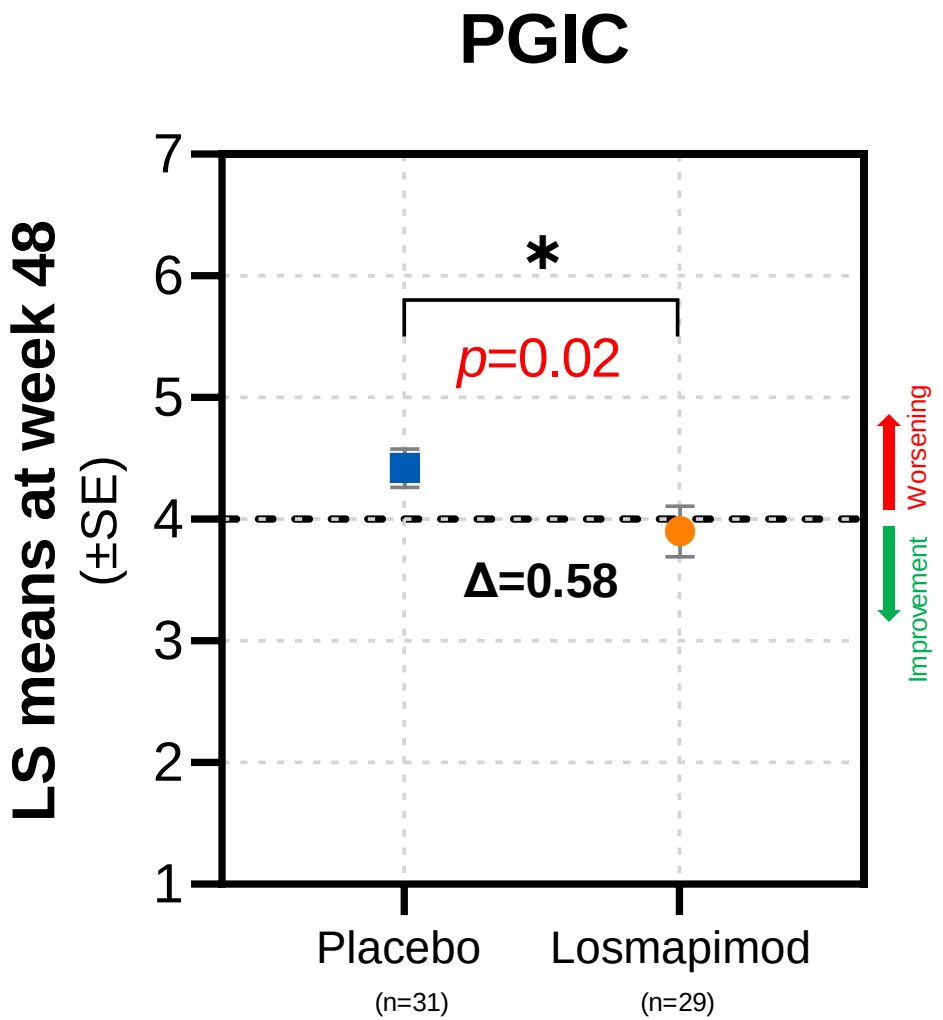


*Nominally statistically significant values (p (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint). LS means ± SE.

Trial Participants Who Received Losmapimod Reported Significant Improvement vs Placebo*

Patients' Global Impression of Change (PGIC) evaluates the impression of change in study participants by asking *"Since the start of the study, my overall status is":*

Scores	PGIC
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Worse
6	Much worse
7	Very much worse

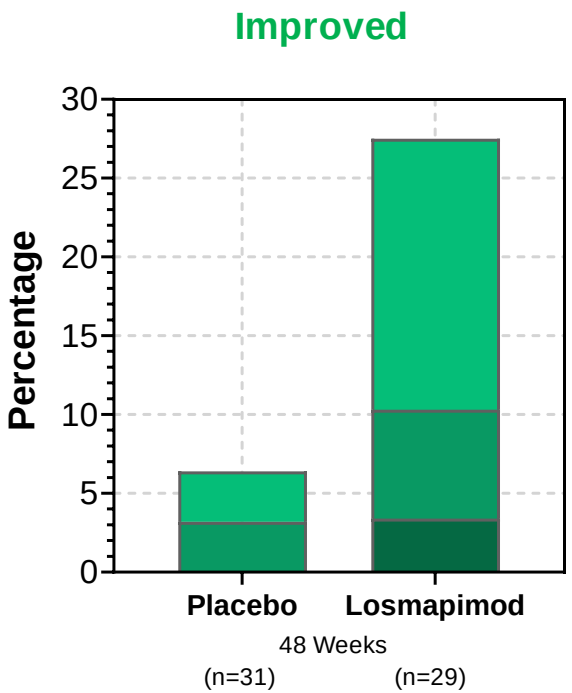


*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).

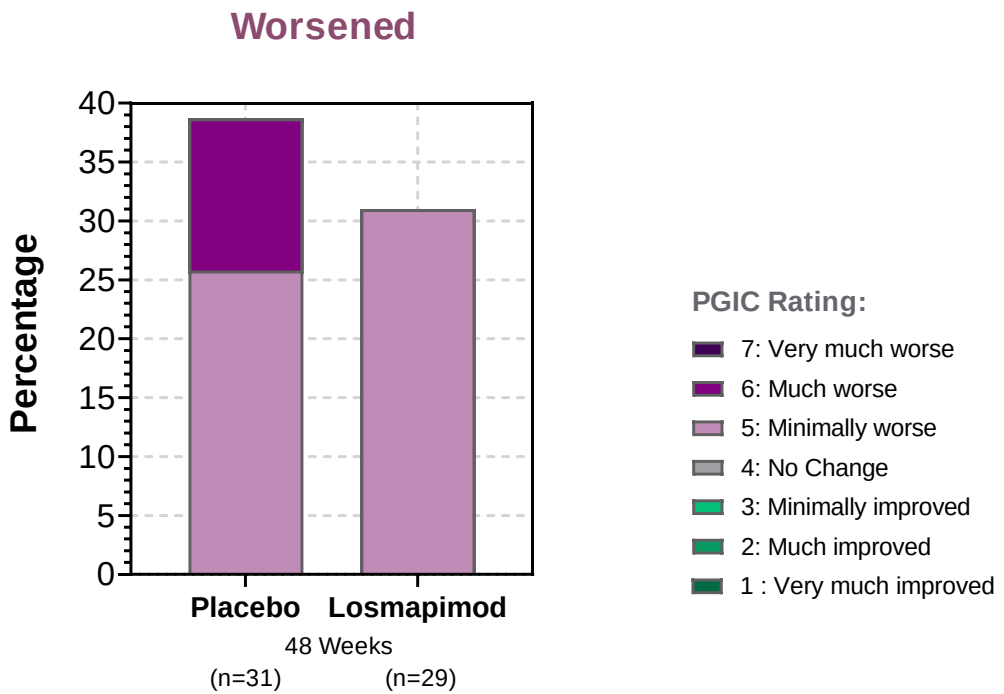
Fewer participants reported worsening on Losmapimod vs Placebo*

- Losmapimod improves the Patients' Global Impression of Change (PGIC) compared to placebo

▲ More study participants reported improvement



▼ Fewer study participants reported worsening



*Statistical testing not done here. Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 w as only pow ered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).

Losmapimod Was Generally Well Tolerated With No Severe, Drug-Related Adverse Events

- Treatment-emergent adverse events (TEAEs) occurred in 29 (72.5%) losmapimod and 23 (57.5%) placebo participants
- For both losmapimod and placebo:
  - The majority of TEAEs were assessed by the principal investigator as unlikely related or not related to study drug
  - TEAEs occurred with a frequency of 1 with the exception of dyspepsia, rash, and increased ALT, each of which occurred in 2 subjects
  - The majority of TEAEs were rated as mild or moderate
  - No TEAE led to treatment discontinuation or study withdrawal
  - No adverse events led to death and no deaths occurred during the trial
- Three serious adverse events (SAEs), post-op wound infection, alcohol poisoning, and a suicide attempt, were reported in 2 participants in the losmapimod group. All SAEs were severe and assessed as unrelated to study drug
- No significant changes in vital signs, laboratory studies, or electrocardiogram (EKG) were observed
- Losmapimod has shown favorable safety and tolerability in > 3500 subjects exposed to at least 1 dose[1]

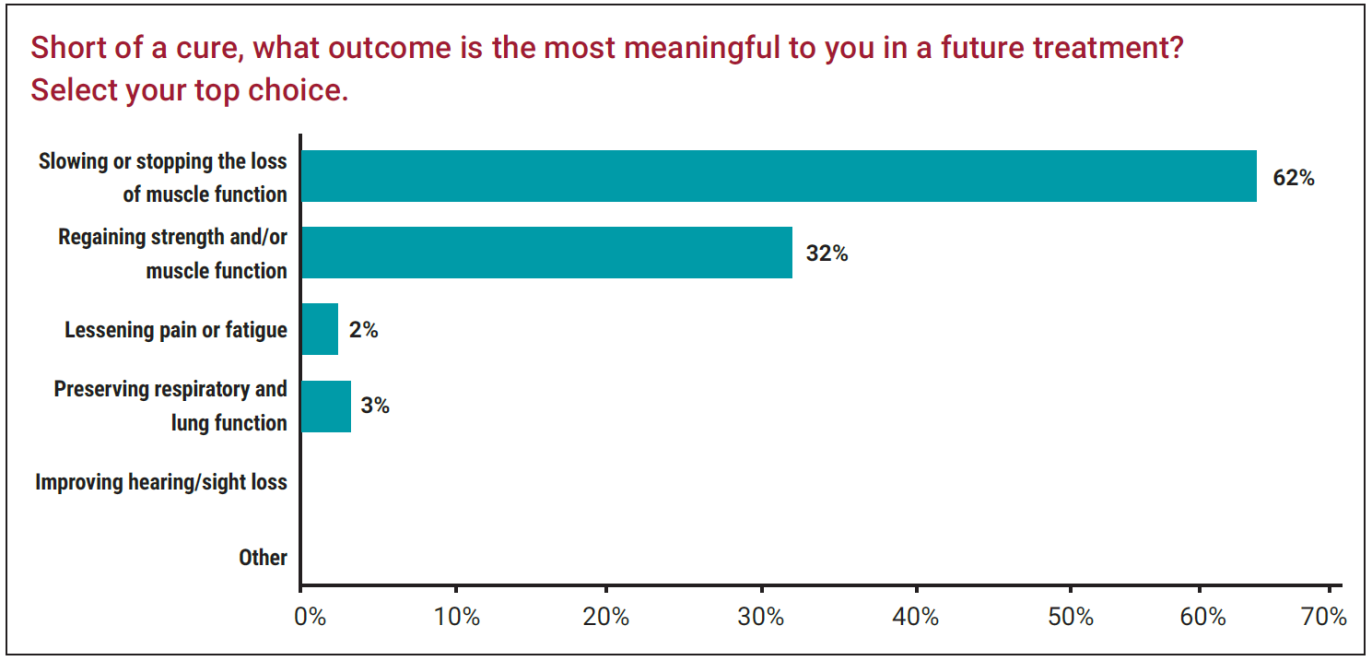
1. Cadavid D et al. Safety and tolerability of losmapimod, a selective p38α/β MAPK inhibitor, for treatment of FSHD at its root cause. Poster presented at the 26th Annual FSHD International Research Congress; June 19-20, 2019; Marseille, France.

Fulcrum Therapeutics

ReDUX4
Assessing losmapimod in FSHD

Putting it all together – *Chris Morabito, MD*

From the Voice of the Patient*…

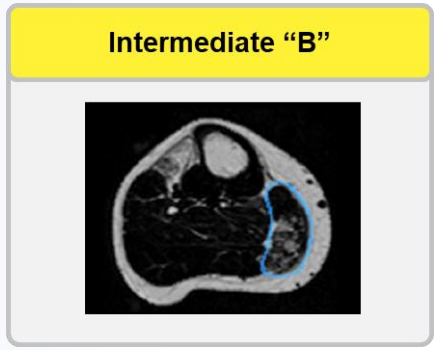


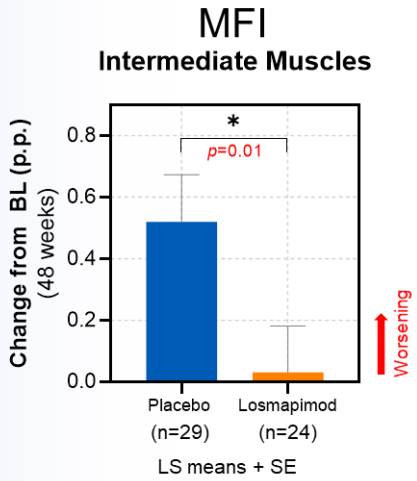
- *"Having a significant treatment for FSHD would really be life changing.* ***I would like to see something that would stop progression of the disease****. If I were to stop progression right now, I would still be able to walk in 10 years. I would still be able to smile, to get off the couch, to raise my arms, to hold my future baby and countless other things…."*
  – 26-year-old woman
- *"Our future and her's stay in limbo with so many unknowns–****that if we had a therapy that at minimum slowed the progression****… we would be able to guide and plan for what her future looks like."* – Mother of young girl with FSHD
- *"This disease is wicked and cruel in many ways, but* ***losing my independence is probably the most frightening and helpless feeling I have ever had****."* – 50-year-old man

*Landmark report in November 2020 capturing testimony given to the FDA by patients and family members about the severity of FSHD disease symptoms and the urgent need for treatment. Arjomand J, et al. Facioscapulohumeral muscular dystrophy (FSHD) voice of the patient report. Published November 5, 2020. Accessed March 1, 2021. https://www.fshdsociety.org/wp-content/uploads/2020/11/Voice-of-the-Patient-Report-FINAL.pdf.

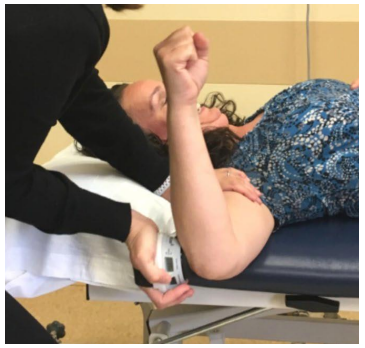
Treatment with Losmapimod Resulted in Improved Muscle Health, Strength, and Upper Body Function: Clinical Outcome of Reachable Workspace

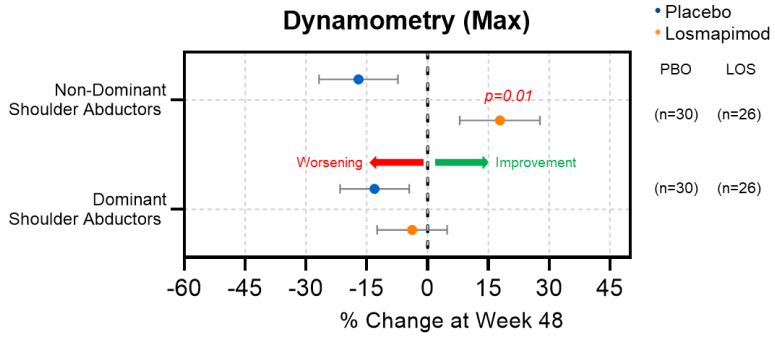
Decreased Muscle Fat Infiltration





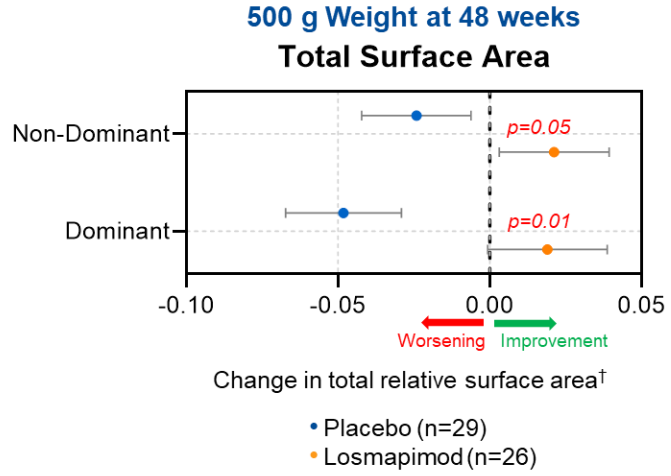
Improved Muscle Strength in Upper Extremities





Observed absolute differences of up >30% between placebo and losmapimod treatment

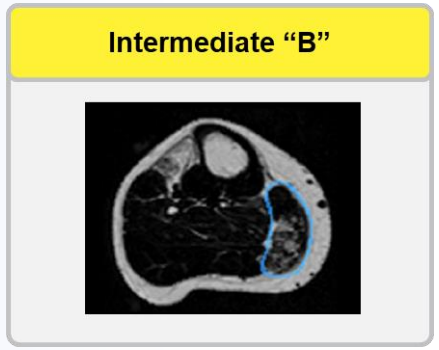
Improved Function in Upper Extremities

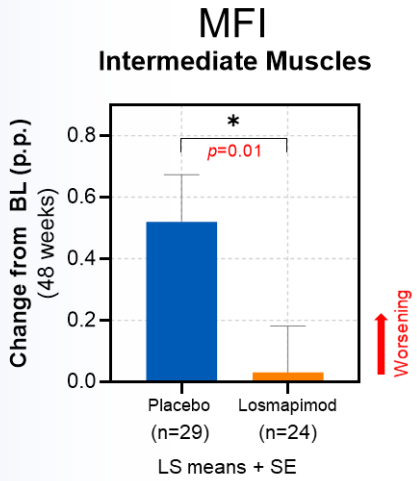


*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).

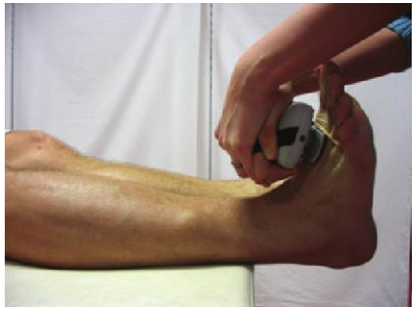
Treatment with Losmapimod Resulted in Improved Muscle Health, Strength, and Function: Timed Up and Go

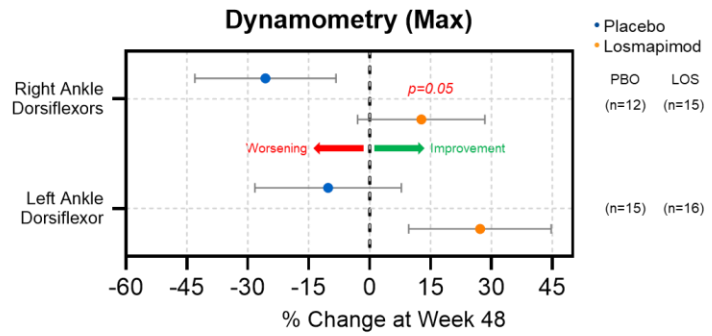
Decreased Muscle Fat Infiltration



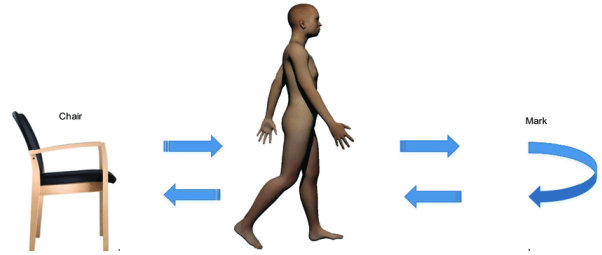


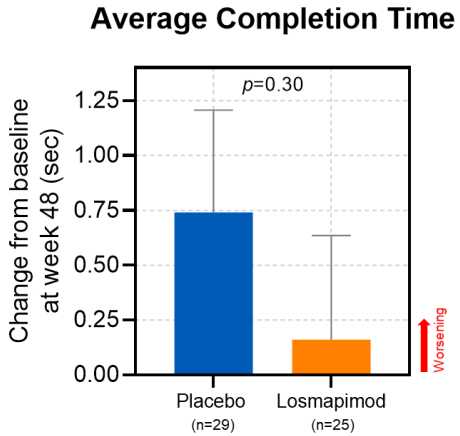
Improved Muscle Strength in Lower Extremities





Improved Function in Lower Extremities

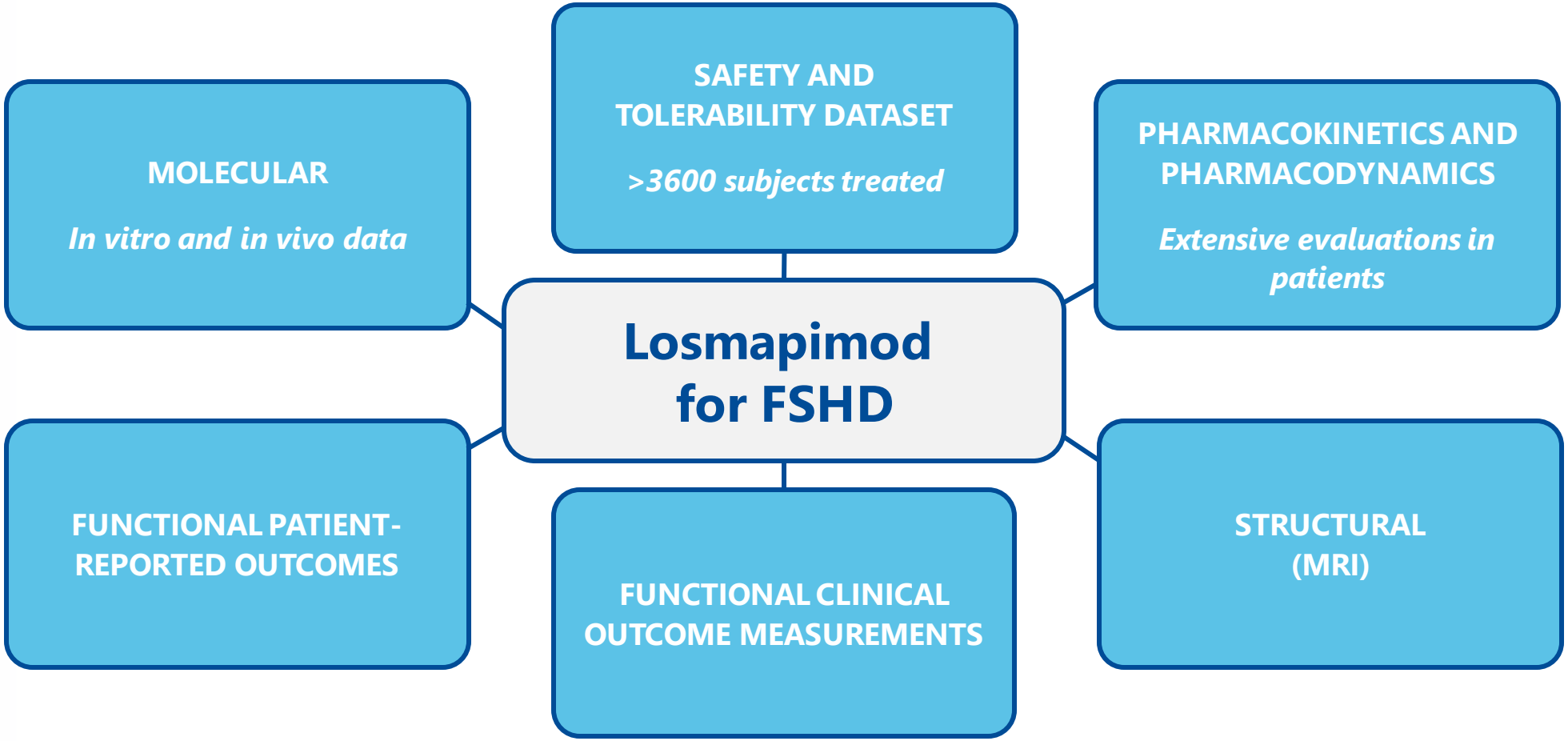




Observed absolute differences of up to 40% between placebo and losmapimod treatment

*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).

The Totality of Evidence Supports Losmapimod as a Potential, Transformative Disease-Modifying Treatment for FSHD



Acknowledgements

ReDUX4
Assessing losmapimod in FSHD

People Living With FSHD Participating in This Study

ReDUX4 Study Sites

ReDUX4 Physical Therapists

ReDUX4 Study Coordinators

Clinical and Scientific Advisors

- Baziel van Engelen, MD, PhD Radboud UMC
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- Lee Sweeney, PhD. UFL
- Leslie Leinwand, PhD. UC Boulder
- Peter Jones, PhD. UNR
- Rabi Tawil, MD. URMC
- Silvère van der Maarel, PhD. LUMC
- Stephen Tapscott, MD, PhD. Fred Hutch

Other Collaborators

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Principal Investigator

Rabi Tawil, MD. URMC

Site Investigators

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- Kathryn Wagner, MD, PhD. KKI*
- Hanns Lochmüller, MD, PhD. CHEO
- Jeffrey Statland, MD. KUMC
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- Nicholas Johnson, MD. VCU
- Nuria Muelas, MD, PhD. Hospital La Fe
- Perry Shieh MD, PhD. UCLA Health
- Sabrina Sacconi, MD, PhD. CHU Nice
- Samantha LoRusso, MD. OSU
- Sub Subramony, MD. UFL
- Summer Gibson, MD. Utah Health

Collaborating Organizations

PPD
AMRA PRECISION FOR DECISION
VIRTUALSCOPICS Imaging for Clinical Trials
IMMUNOLOGIX LABORATORIES
BIONIKS
Q² Solutions a Quintiles Quest Joint Venture

Patient Groups

FSHD SOCIETY
MDA Muscular Dystrophy Association
friends of FSH research
NORD National Organization for Rare Disorders

Fulcrum Therapeutics

ReDUX4
Assessing losmapimod in FSHD

Q&A / Discussion

Fulcrum Therapeutics

ReDUX4
Assessing losmapimod in FSHD

Thank you!

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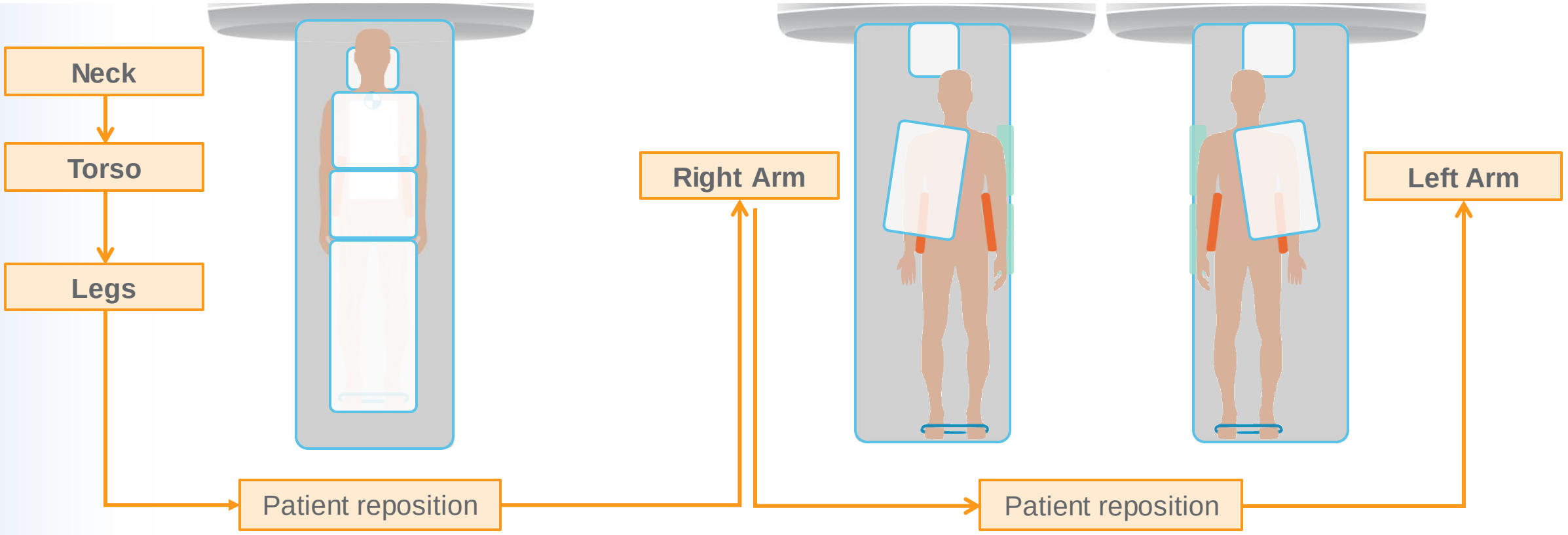
Fulcrum Therapeutics

Back-up

Imaging Protocol for Whole Body MRI

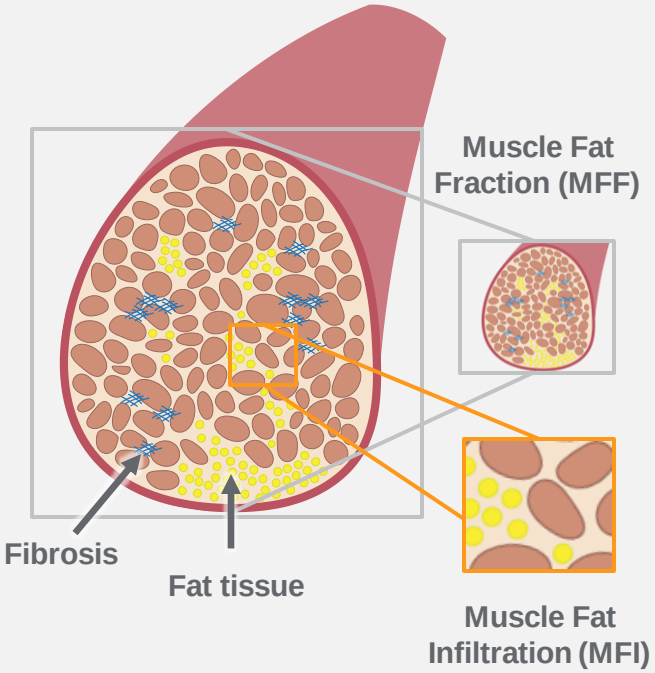


Total examination time ~30 min

Evaluating Skeletal Muscle Health by Whole Body Musculoskeletal MRI*

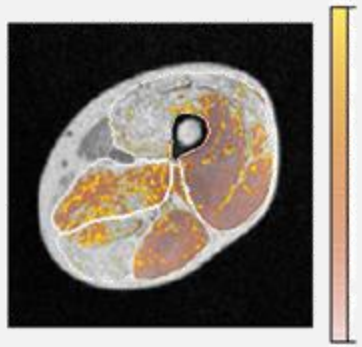
Dystrophic Skeletal Muscle Tissue in FSHD

Fatty and fibrotic tissue infiltration contribute to the loss of function by altering muscle biomechanical properties

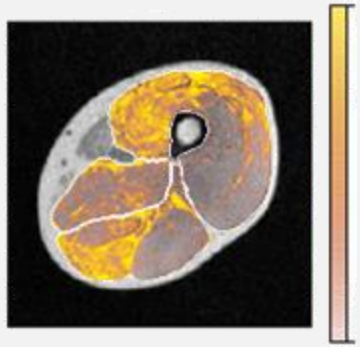


Holistic and Quantitative Picture of Muscle Health

18 muscles were analyzed bilaterally (36 total)

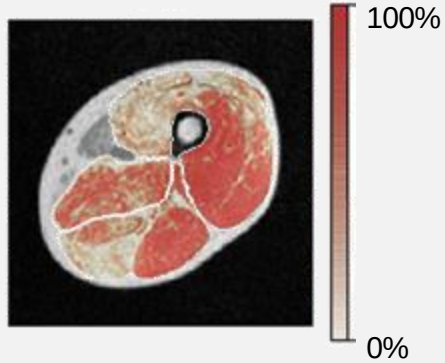


Muscle Fat Infiltration (MFI)
Indicator of muscle quality



Muscle Fat Fraction (MFF)
Measurement of overall fattiness of the muscle

Lean Muscle Volume (LMV)
Measurement of the amount of lean/contractile muscle tissue



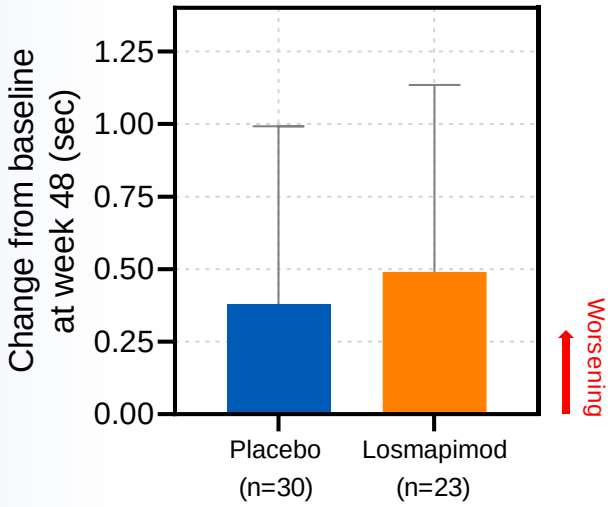
*Please see poster: "Quantitative Muscle Analysis in FSHD Using Whole-Body MRI: Composite Muscle Measurements for Cross-Sectional Analysis".

FSHD-TUG, Motor Function Measurement, and FSHD-HI Did Not Demonstrate Differences Between Losmapimod and Placebo*

The placebo results suggest that these measures did not detect progression

FSHD-TUG

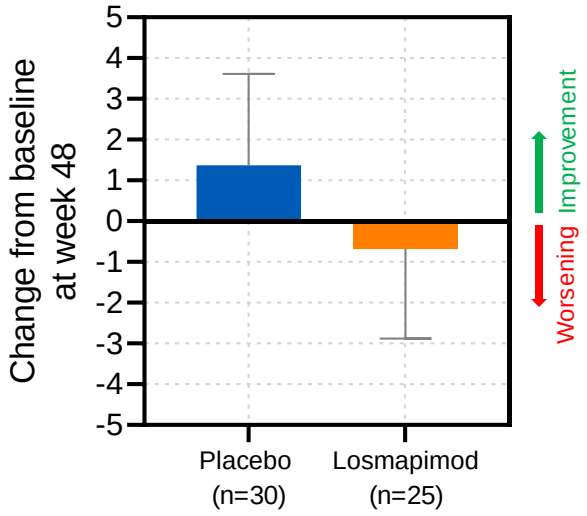
Average Completion Time



LS means + SE

Motor Function Measure

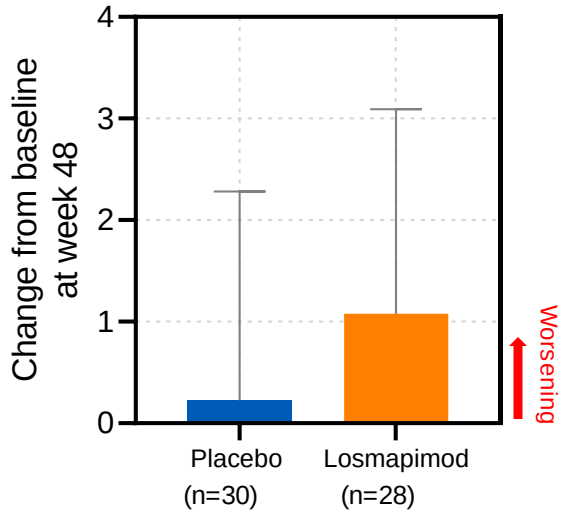
MFM Domain 1 Score



LS means + SE

FSHD Health Index (FSHD-HI)

Total FSHD-HI Score

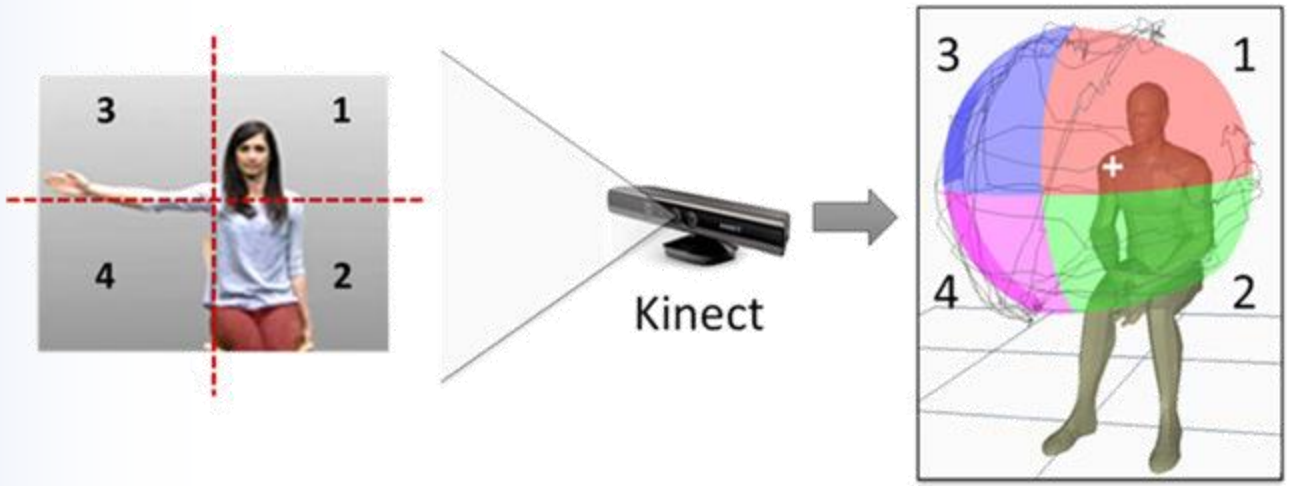


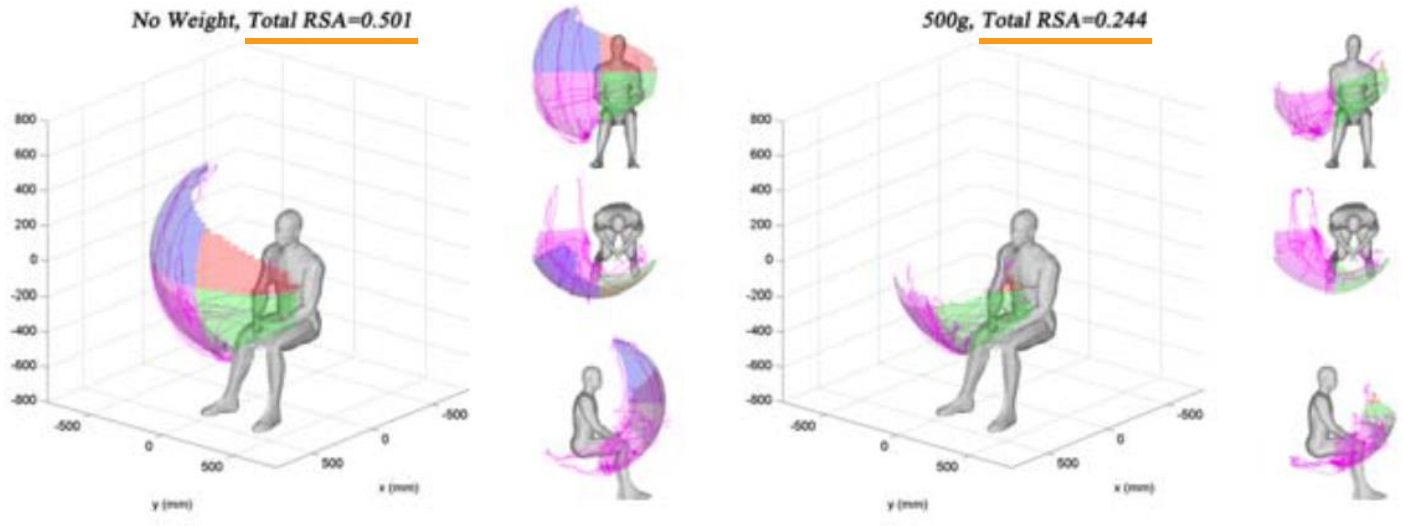
LS means + SE

*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint). Mixed-Effects Model for Repeated Measures (MMRM) analysis. FSHD-TUG was pre-specified for hypothesis testing.

Reachable Work Space (RWS)

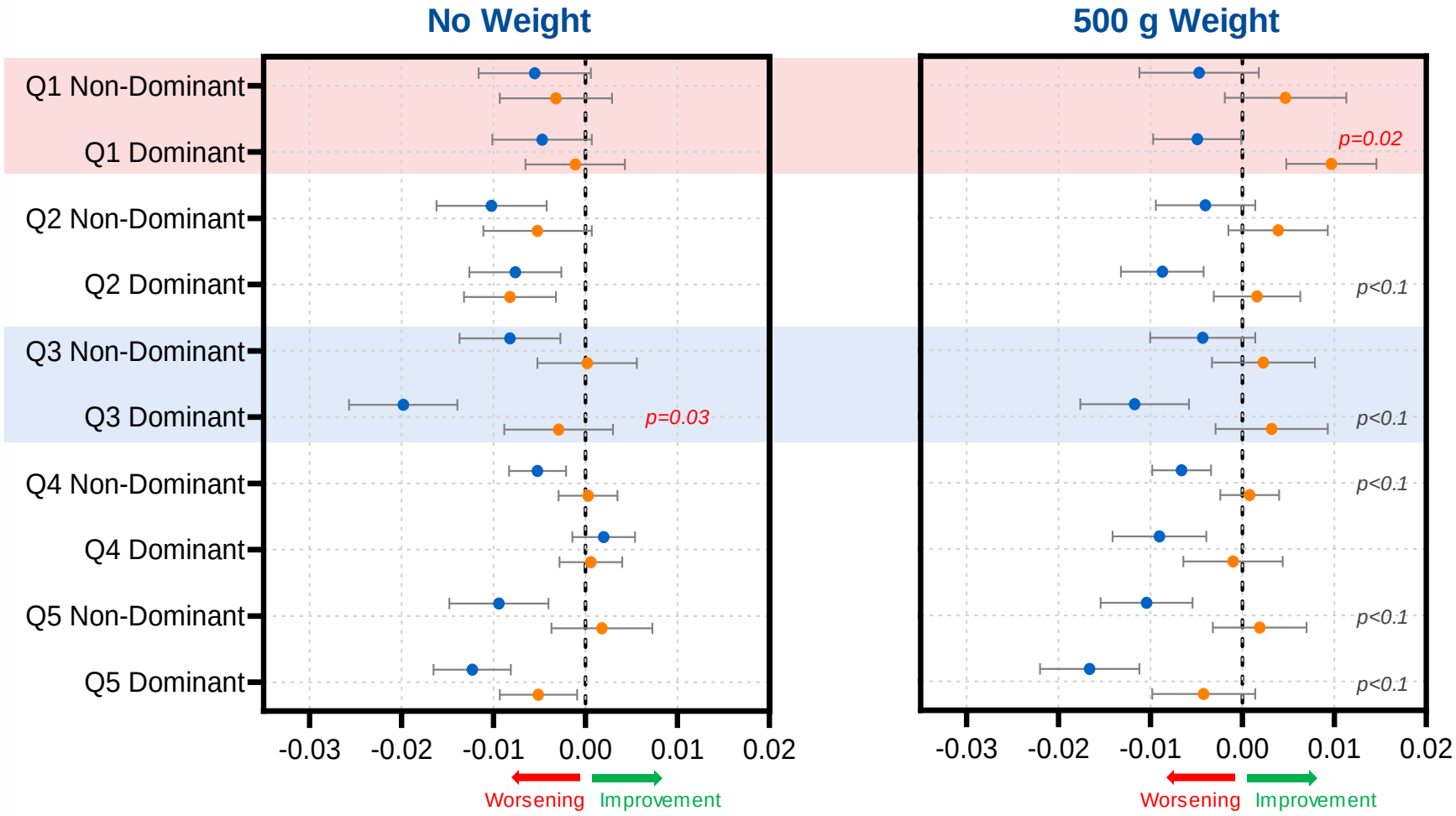
Evaluating Upper Arm and Shoulder Function in FSHD subjects





[1]Han et al., 2015 "Reachable workspace reflects dynamometer-measured upper extremity strength in facioscapulohumeral muscular dystrophy"

Improvement in Total Surface Area Was Seen in Trends of Slowed Disease Progression and Improvement on Multiple RWS Metrics*



*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).
Total relative area for the 5 quadrants used to calculate the approximate percentages of total area that participants experienced change on was 1.25. LS means ± SE.