Measuring Progression in FSHD: Implications for Clinical Trials

WMS Industry-Supported Symposium

October 12th, 2022

Fulcrum Therapeutics




Agenda

Agenda Topic	Presenter	Duration
Welcome and Introduction	Jennifer Shoskes, PharmD Fulcrum Therapeutics, Inc., United States	10 min
ReDUX4 Overview and MRI Results	Leo H. Wang, MD, PhD University of Washington	25 min
Reachable Workspace (RWS) Overview and Results	Sabrina Sacconi, MD, PhD Nice University Hospital, France	25 min
New Data **96 week ReDUX4 Open Label Extension (OLE)**	Jennifer Shoskes, PharmD Fulcrum Therapeutics, Inc., United States	10 min
Phase 3 REACH Study	Jennifer Shoskes, PharmD Fulcrum Therapeutics, Inc., United States	10 min
Q&A	Panel	10 min

Disclosures

- Leo H. Wang is on advisory boards for Argenx, Roche, Mitsubishi Tanabe, AskBio, Scholar Rock; he is a consultant for Fulcrum Therapeutics, Avidity, PepGen.
- Sabrina Sacconi has been a speaker for Sanofi/Genzyme, LFB, Biogen, Alnylam, Roche, UCB Pharma, Argenx, and Fulcrum Therapeutics; she has received research/scientific funding from BioMarin, Sanofi Genzyme, LFB, Grifols, Santher, Biogen, Roche, UCB Pharma, Dyne Therapeutics, and Argenx; she is a consultant for Fulcrum Therapeutics, Dyne Therapeutics, Sanofi/Genzyme, UCB Pharma, and ARGENX
- Jennifer Shoskes is a full-time employee of Fulcrum Therapeutics

Our Mission is to Treat Root Cause of Rare Genetic Diseases

We aim to

Deliver disease-modifying therapies that improve the lives of people with rare genetic diseases

Three Clinical-Stage Programs

FSHD: Phase 3; positioned to be first-to-market with a disease-modifying therapy that preserves muscle function

Sickle cell disease: Phase 1b patient study; potential first oral functional cure

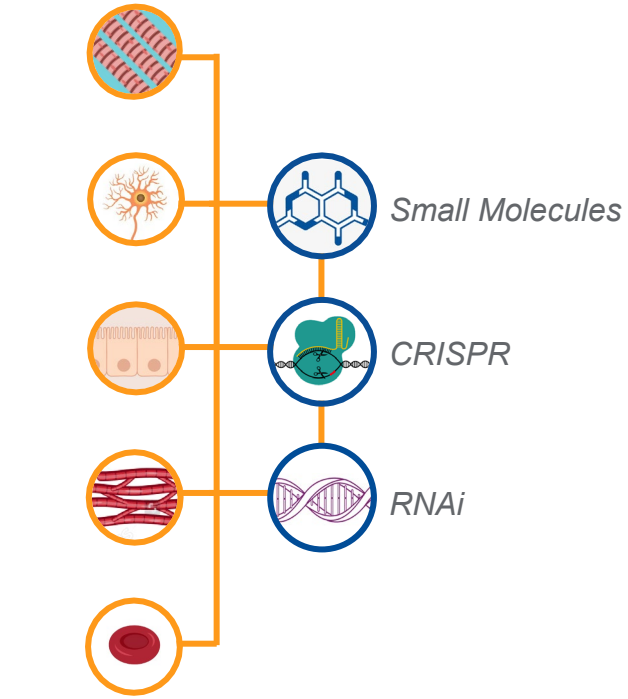
Non-SCD hemoglobinopathies: Phase 1b ready

FulcrumSeek™

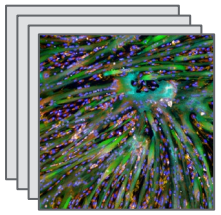
Product engine to systematically identify high-value, de-risked targets at speed and scale for rare genetic diseases

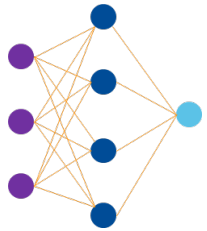
FulcrumSeek™ Systematically Identifies High-value, De-risked Therapeutic Targets for Rare Genetic Diseases

Toolbox of Disease Relevant Cell Models Interrogated with Highly Curated Perturbagens



Insights Harvested from Rich Data Readouts



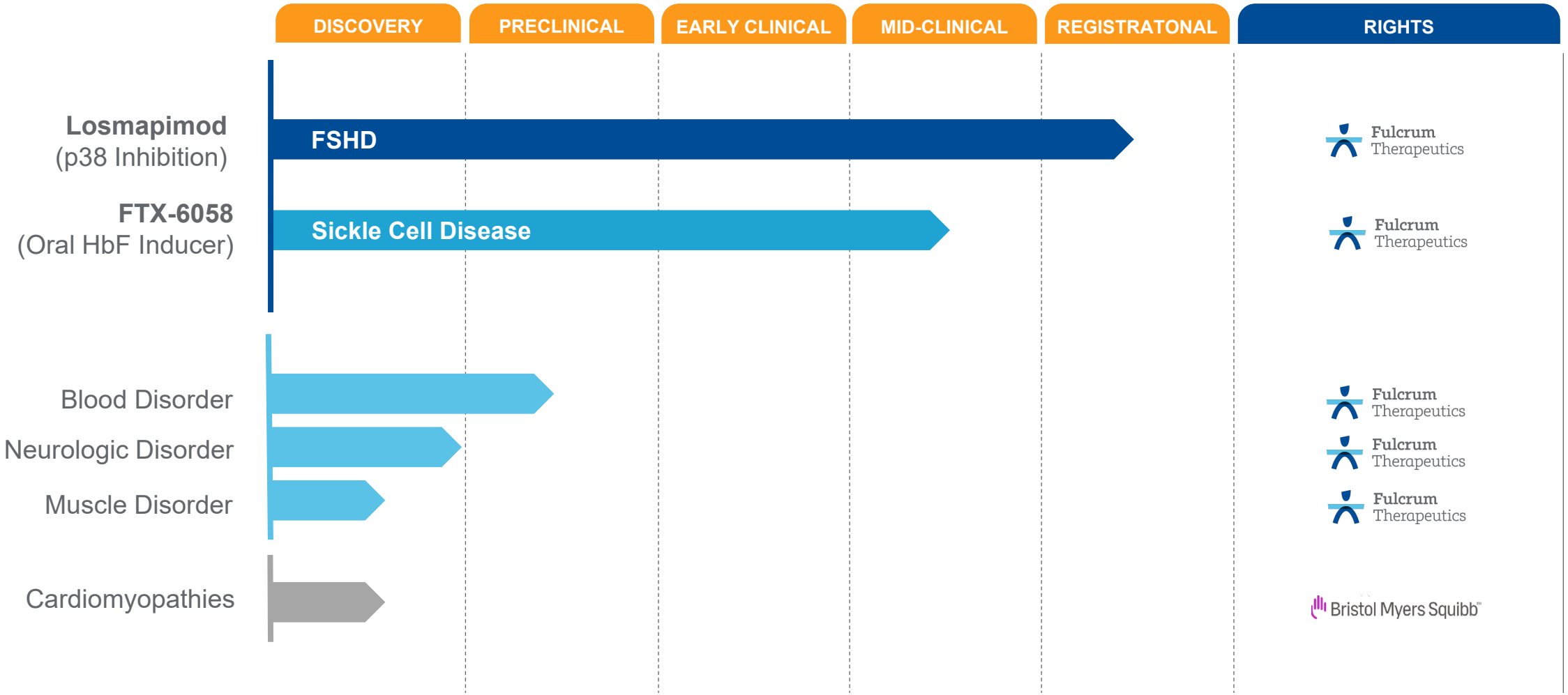


Disease-Modifying Targets and Value-Unlocking Datasets

Targets with **specificity** and **selectivity**

Comprehensive data set that **significantly accelerates development**

Pipeline of Potentially Disease-modifying Therapies



Next IND in 2023

Fulcrum Therapeutics

ReDUX4 Overview and MRI Results

Leo Wang, MD, PhD
University of Washington

Every FSHD Patient Faces Relentless and Accumulating Muscle and Functional Loss

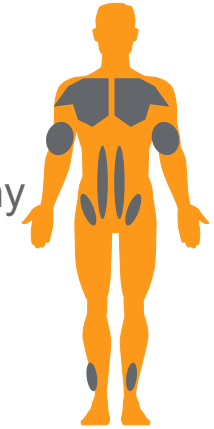
The Disease

Rare, genetic disorder in which skeletal muscle is replaced by fat

Second most common muscular dystrophy

Caused by aberrant expression of DUX4 gene

2/3 of cases are hereditary



Fat infiltrates muscle

Estimated US FSHD Population*

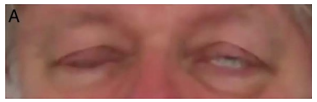
16,000-38,000

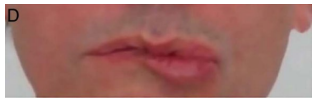
Estimated Global FSHD Population*

300,000-780,000

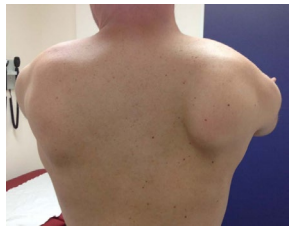
*Deenen, JCW, et al. Neurology. 2014; Preston, MK et al. GeneReviews – FSHD. 2020

FSHD is a genetic disorder defined by the progressive weakening of skeletal muscles, resulting in loss of function and independence

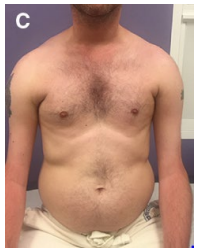


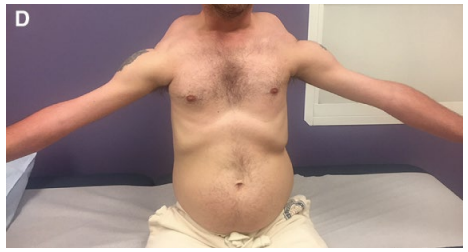


Facial weakness

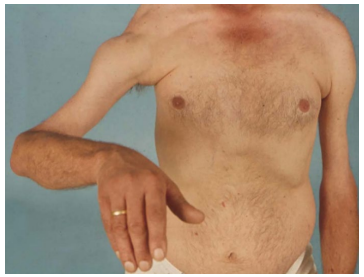


Scapular winging





Impaired ability to raise arms caused by scapular elevation



Wasting of muscles in chest, shoulders, and upper arms; Protuberant abdomen

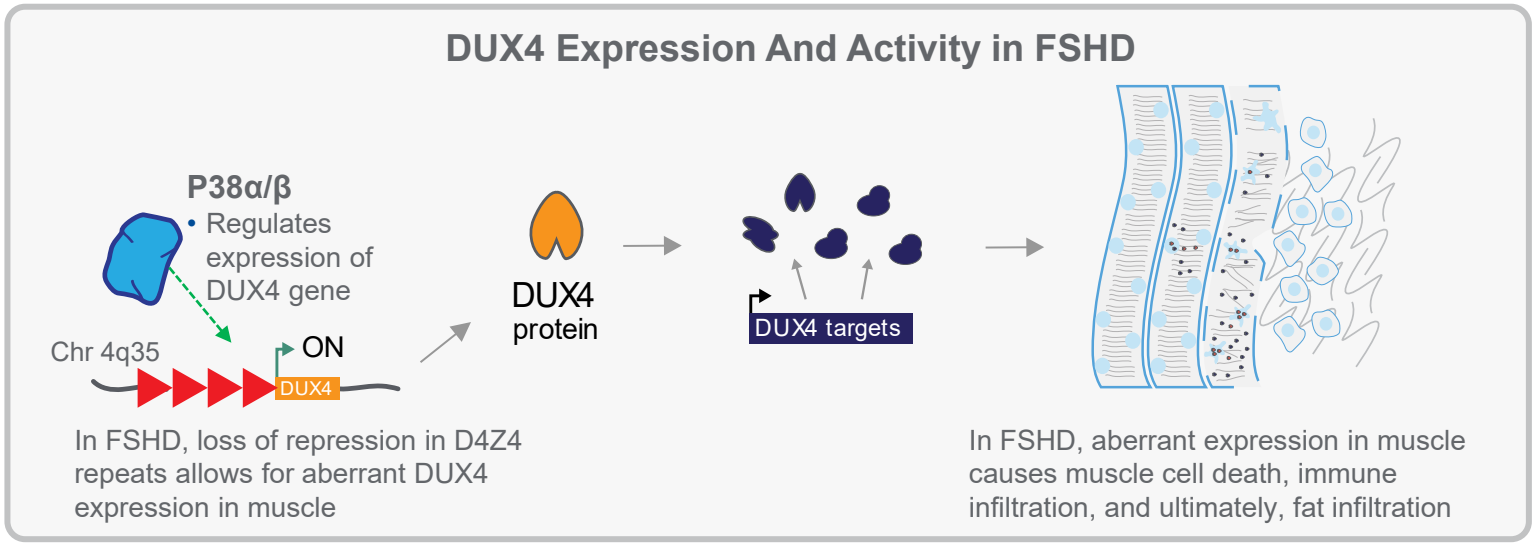
Wheelchair dependence

- **Second** most prevalent adult muscular dystrophy
- **Progressive weakness in muscles** in the face, shoulders, and upper arms; progression to the lower limbs
- Results in **difficulty using arms, frequent falls & injury, impaired mobility, and facial weakness**
- **Over 20% of affected individuals becoming wheelchair-dependent** and many patients **unable to work or live independently**

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

Losmapimod: Most Advanced Development Candidate for the Treatment of FSHD

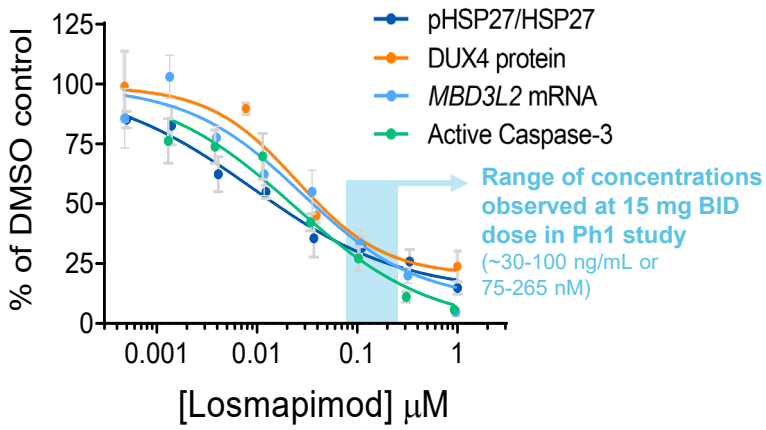
- Losmapimod is a targeted disease-modifying therapy that preserves muscle function
- Highly selective p38α/β MAPK inhibitor
- Reduced DUX4 expression in preclinical studies
  - Aberrant expression DUX4 gene is known root cause of FSHD
- Oral therapy with demonstrated safety data in over 3500 clinical trial participants



24 SEPTEMBER 2010 VOL 329 SCIENCE

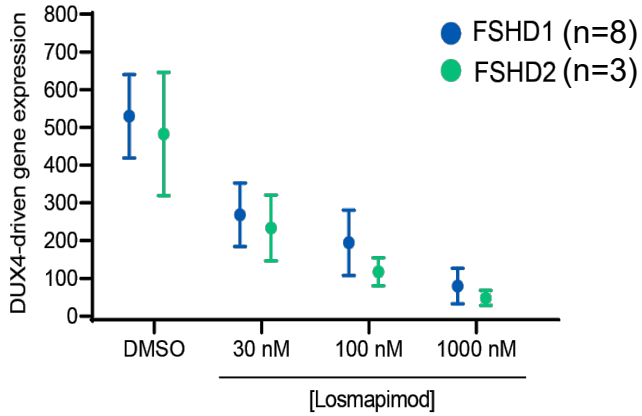
Losmapimod Reduces DUX4, DUX4 Driven Gene Expression, and Muscle Cell Death in Preclinical Models

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

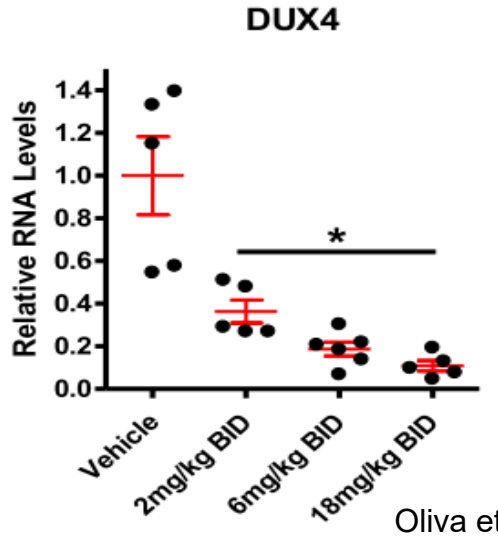


HSP27 is a substrate of p38 MAP kinase pathway
MBD3L2 is a DUX4-target gene
Caspase 3 is an indicator of cell death

Clinical-trial in a dish demonstrates reduction of DUX4 activity across multiple patient-derived FSHD1/2 myotubes



In a xenograft model of acute expression of DUX4, losmapimod reduces DUX4 and its target genes by >50%



Oliva et al, 2019

Losmapimod Clinical Development Program To Date

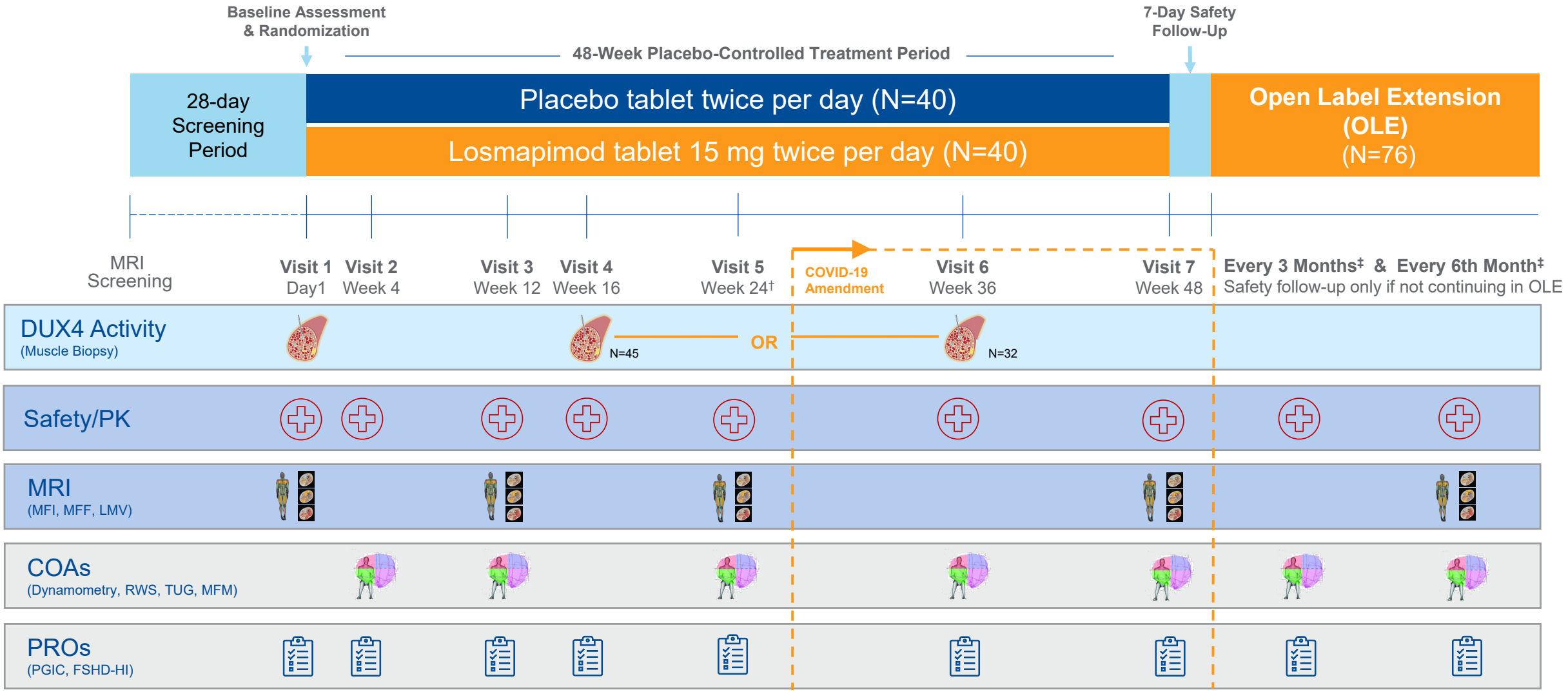
Complete	**Fulcrum Preparatory Studies**	▪ Refined clinical endpoints: DUX4, MRI, Muscle Function, PROs
	Phase 1	▪ Generally well-tolerated in FSHD subjects ▪ Target engagement demonstrated ▪ Losmapimod penetrates FSHD muscle
	Phase 2b ReDUX4 *48-week analysis*	▪ Losmapimod demonstrated disease modifying properties as evidenced by treatment benefit on structural and functional measures of FSHD disease progression
	Phase 2 Open Label Study (OLS) *52-week analysis*	▪ Provides supporting evidence of losmapimod demonstrating disease modifying properties as observed in ReDUX4

Ongoing Studies	**Phase 2b ReDUX4***
	Long Term Open Label Extension (OLE)
		▪ Continued long term evaluation of
		  ▪ Clinical assessments of upper extremity function and mobility
		  ▪ Quantitative whole body musculoskeletal MRI
		  ▪ Patient reported outcomes

	Phase 2 Open Label Study (OLS)* Extension	
	Phase 3 REACH Trial *Pivotal 48-week study*	▪ Global, randomized, double-blind, placebo-controlled, 48-week, parallel-group study of the efficacy and safety of losmapimod

*Main studies complete, long term open-label extensions ongoing

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.

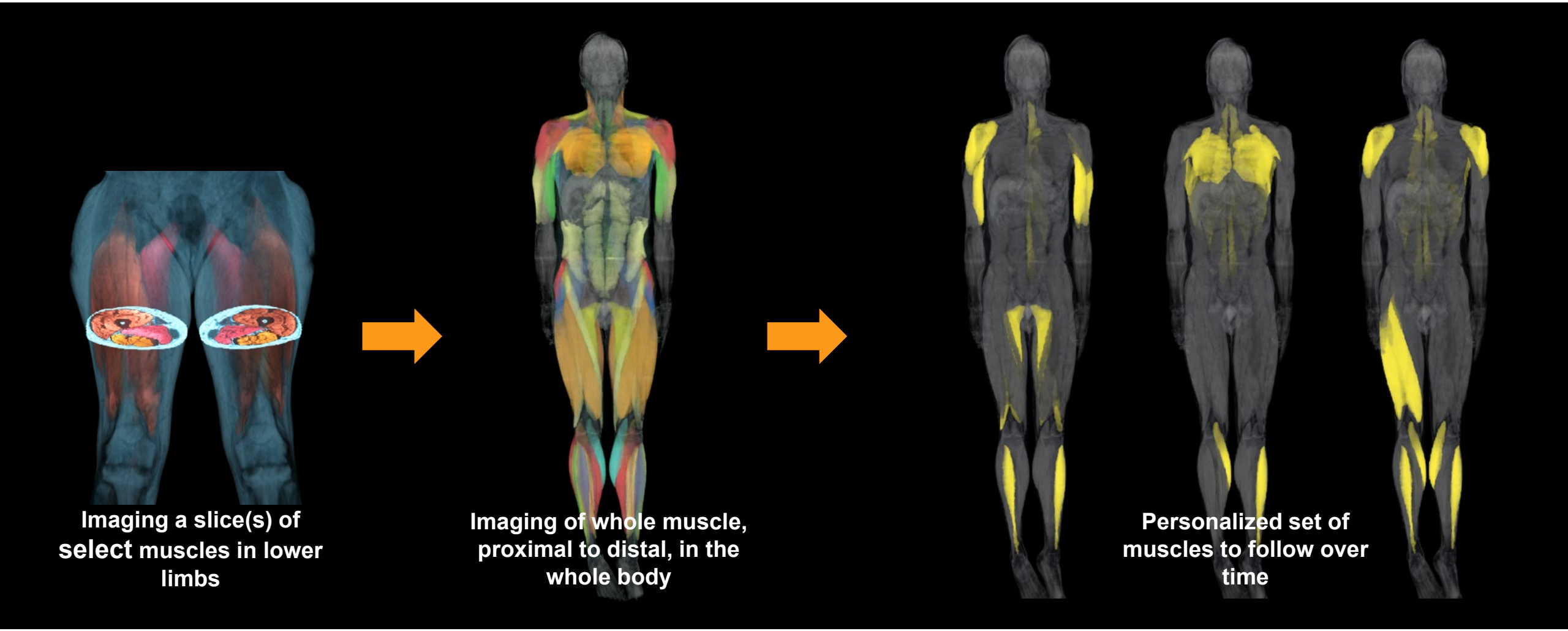
ReDUX4 Study Participant Randomization Was Well Balanced

		Placebo BID (N=40)	Losmapimod 15 mg BID (N=40)
Completed, n (%)		38 (95)	39 (97.5)
Discontinued*, n (%)		2 (5.0)	1 (2.5)
DEMOGRAPHICS			
Age (years)	N	40	40
	Mean (SD)	45.7 (+/- 12.7)	45.7 (+/- 12.4)
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)	26.2 (+/- 4.9)	25.7 (+/- 5.4)
D4Z4 Repeat Category, n (%)	1-3 Repeats	6 (15.0)	7 (17.5)
	4-9 Repeats	34 (85.0)	33 (83.5)
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.

New Paradigm of Image Analysis in NMD

Imaging of whole muscle, proximal to distal, in the whole body



Skeletal Muscle MRI
Muscles Studied- 18 muscles bilaterally; 36 in total

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)

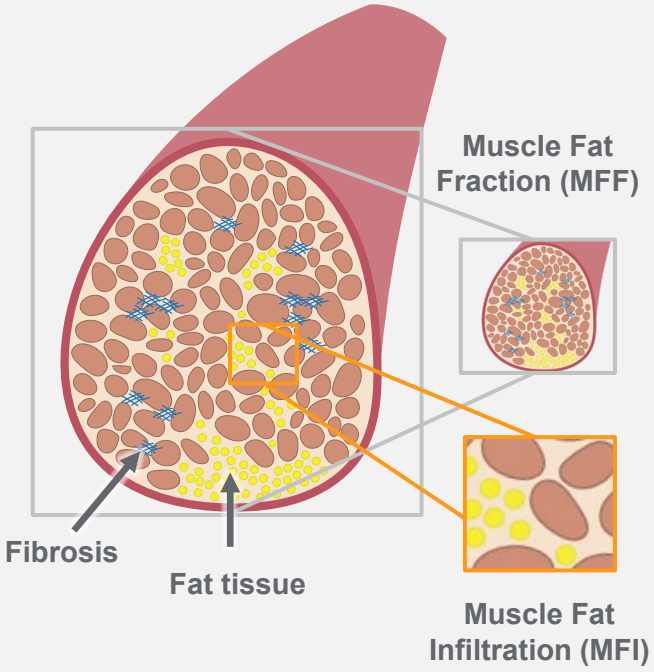
Arm

- Deltoid
- Biceps Brachii
- Triceps Brachii

Evaluating Skeletal Muscle Health by Whole Body Musculoskeletal MRI

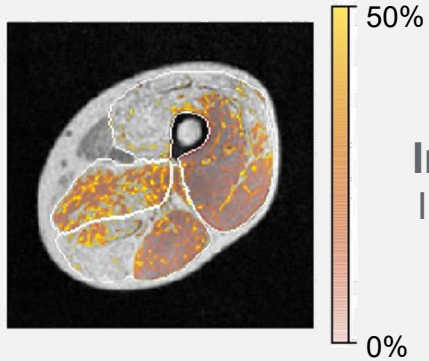
Dystrophic Skeletal Muscle Tissue in FSHD

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

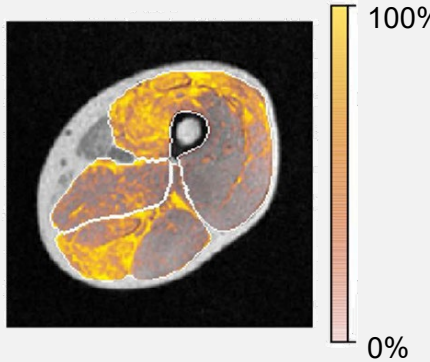


Holistic and Quantitative Picture of Muscle Health

18 muscles were analyzed bilaterally (36 total)

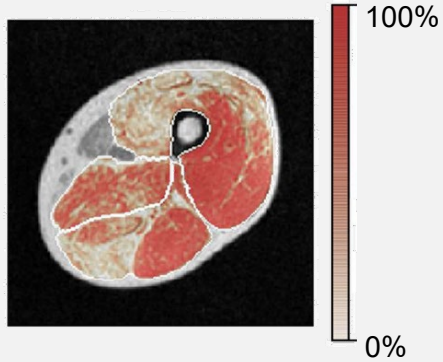


Muscle Fat Infiltration (MFI)
Indicator of muscle quality

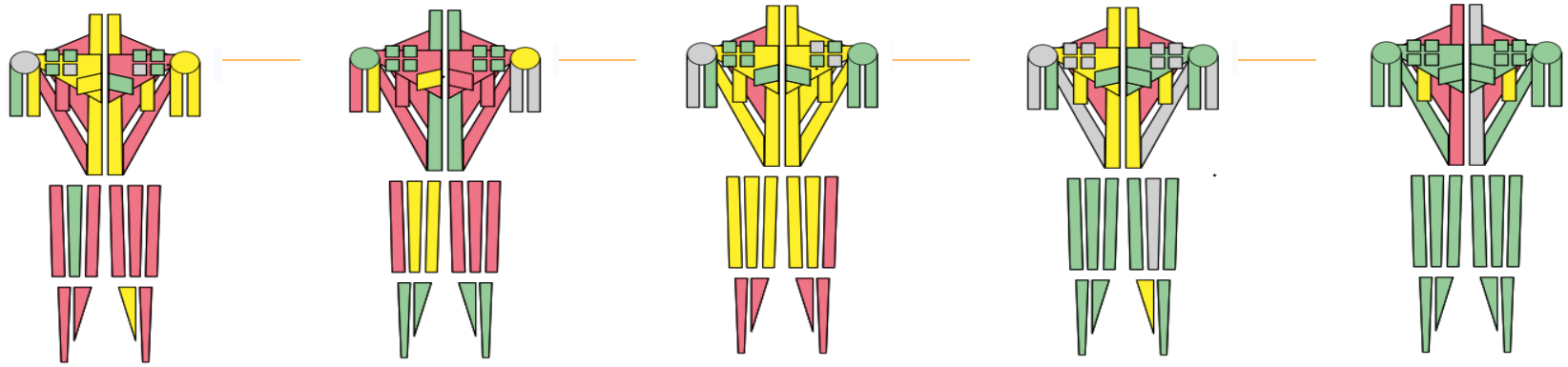


Muscle Fat Fraction (MFF)
Measurement of overall fattiness of the muscle

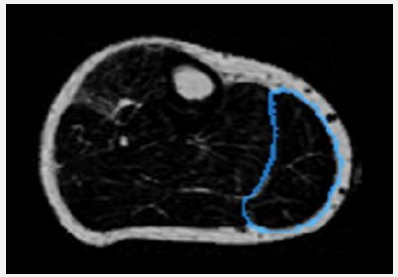
Lean Muscle Volume (LMV)
Measurement of the amount of lean/contractile muscle tissue



Muscle Categorization Captures FSHD Disease Heterogeneity

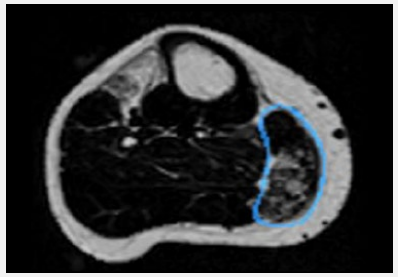


Normal-Appearing "A"



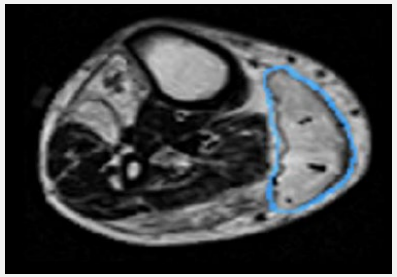
- Muscles do not appear to be affected by disease
- MFI < 10%; MFF < 50%

Intermediate "B"



- Muscles clearly affected by disease, but not so severely fat replaced to have lost all function
- Included in the longitudinal composite score because they are most likely to progress
- MFI ≥ 10%; MFF < 50%

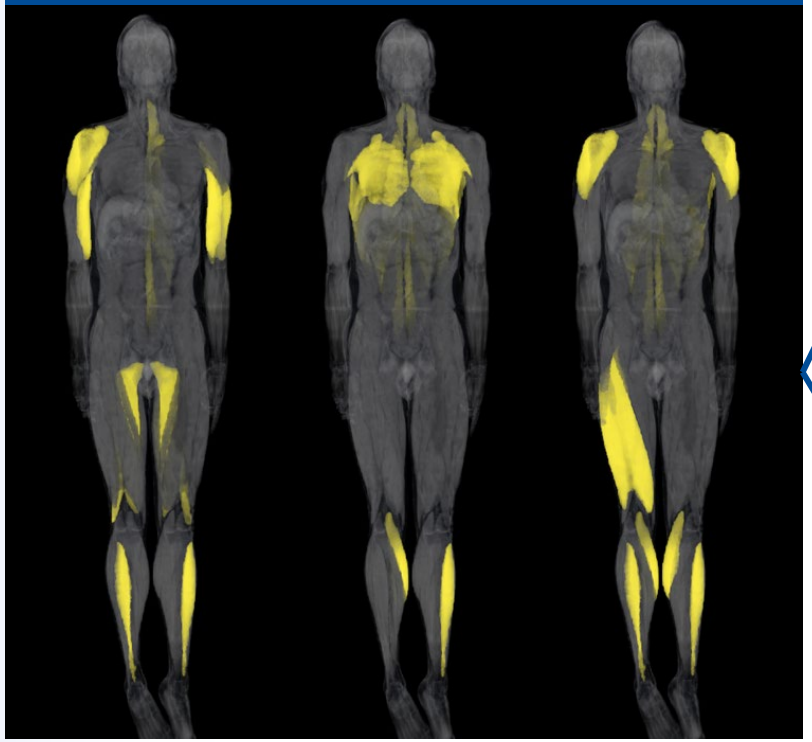
End-Stage "C"



- Muscles severely fat replaced and have likely lost most if not all function
- MFF ≥ 50%

Composite Measurement to Evaluate Treatment Efficacy and Correlations with FSHD relevant COAs

Whole Body MRI



WB Longitudinal Composites

- Measure treatment effect
- Only include B muscles
- No SQI are allowed at either time point

MFI_{tot}
Average MFI, weighted by lean volume of each muscle

MFF_{tot}
Average MFF, weighted by total volume of each muscle

LMV_{tot}
Sum of all LMV

Functional Correlation Composites

- Cross-sectional analysis
- Functional correlation
- All muscle categories
- Minor SQI are allowed

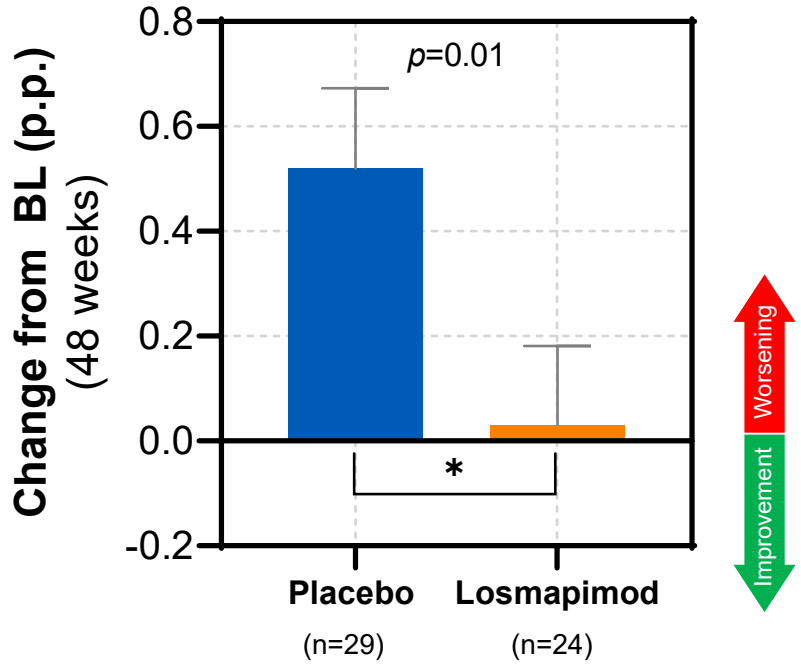
MFI_{tot}

MFF_{tot}

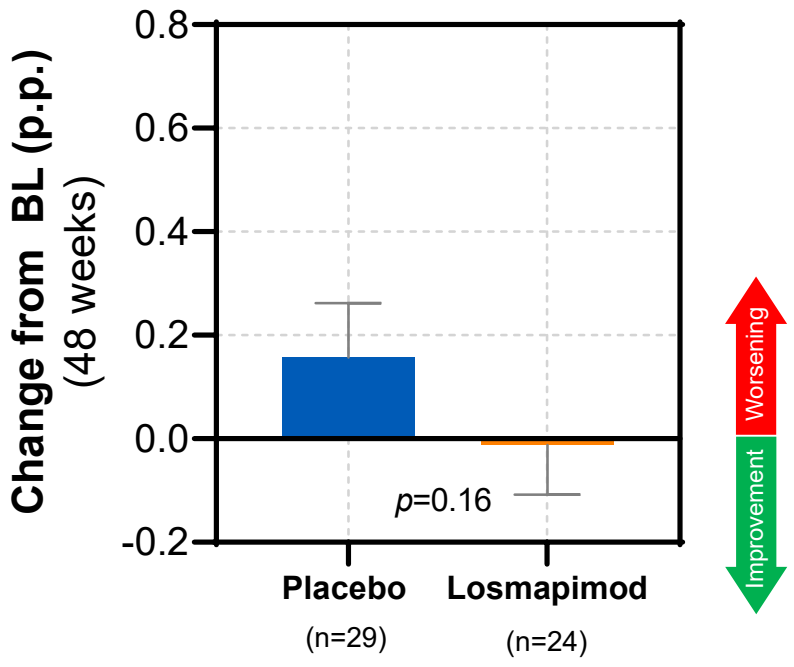
*Analyses at 48 weeks. LMV_{tot}=lean muscle volume total; MFF_{tot}=muscle fat fraction total; MFI_{tot}=muscle fat infiltration total; SQI=Signal Quality Index.

In ReDUX4, Losmapimod Slowed Additional Muscle Fat Infiltration (MFI)

Losmapimod slowed fat infiltration in muscles already affected by disease (B muscles)



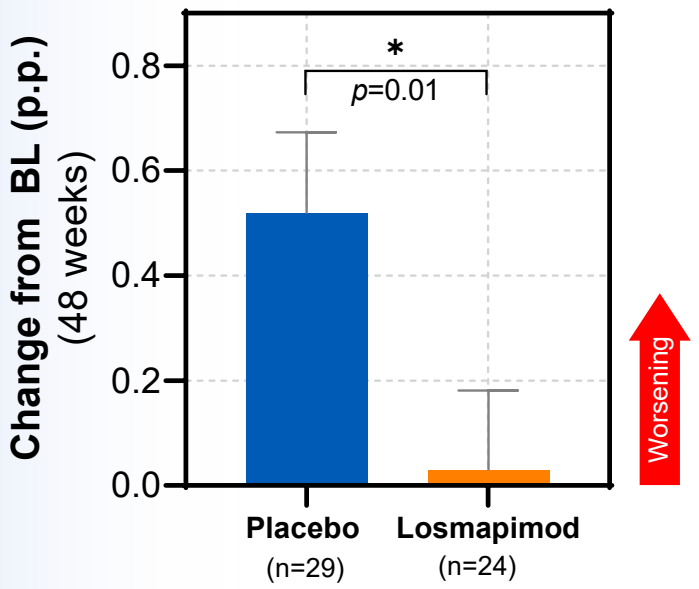
Losmapimod preserved health of normal-appearing muscles (A muscles)



*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%.

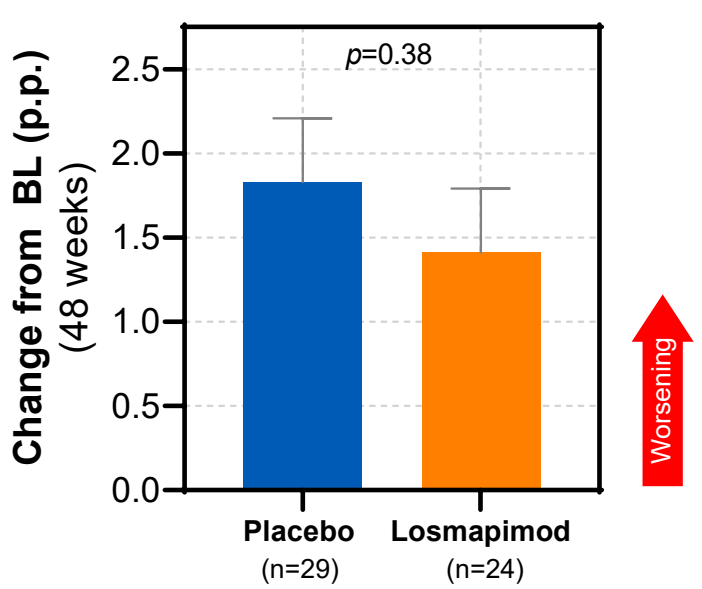
Losmapimod Treated Participants Showed Significantly Less Muscle Fat Infiltration (MFI) vs Placebo in Intermediate (B) Muscles*

Muscle Fat Infiltration (MFI)



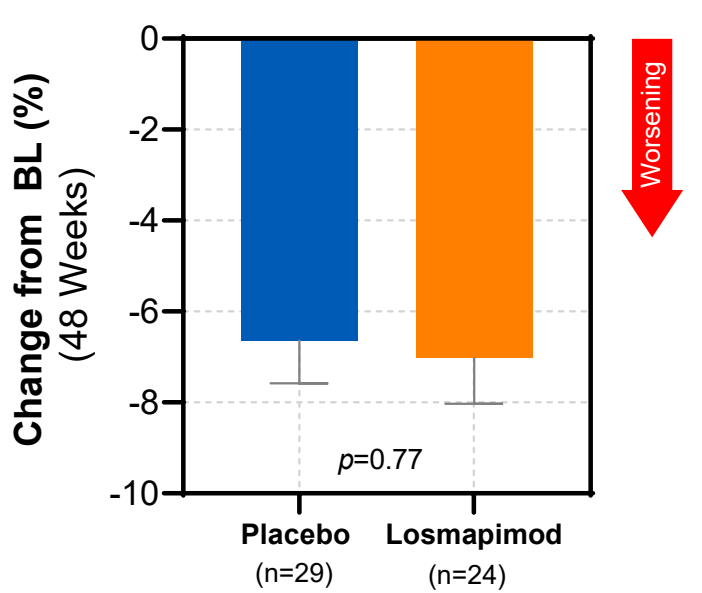
LS means + SE

Muscle Fat Fraction (MFF)



LS means + SE

Lean Muscle Volume (LMV)



LS means + SE

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Fulcrum Therapeutics

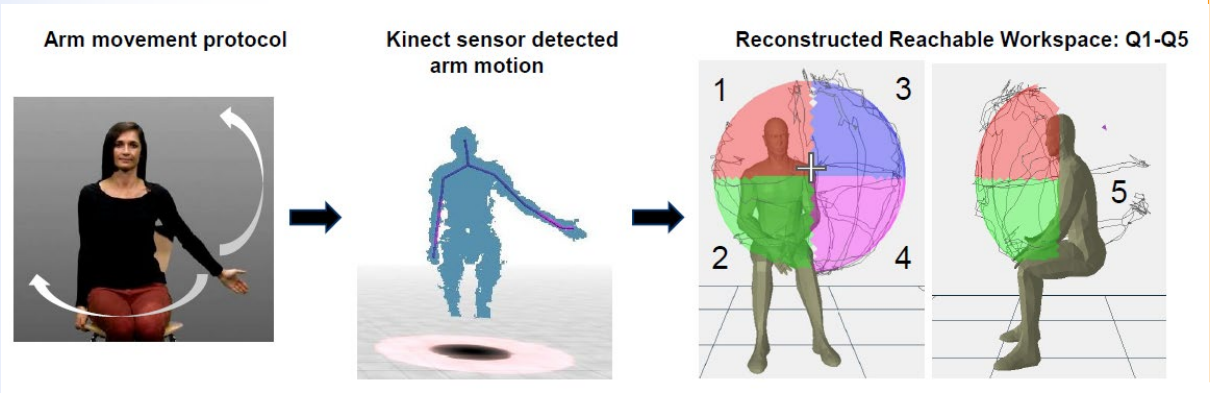
Reachable Workspace (RWS) Overview and Results

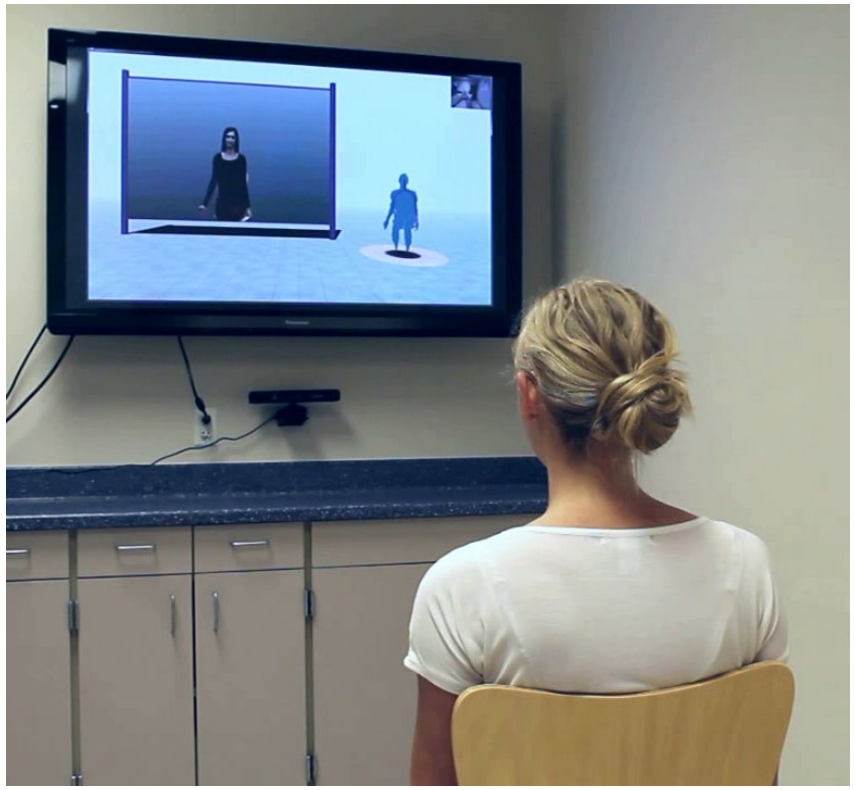
Sabrina Sacconi, MD, PhD
Nice University Hospital, France

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
- Subjects sit in front of Microsoft Kinect sensor and undergo standardized upper extremity movement protocol
- Reliable and sensitive to change
- Evaluation performed with and without weights



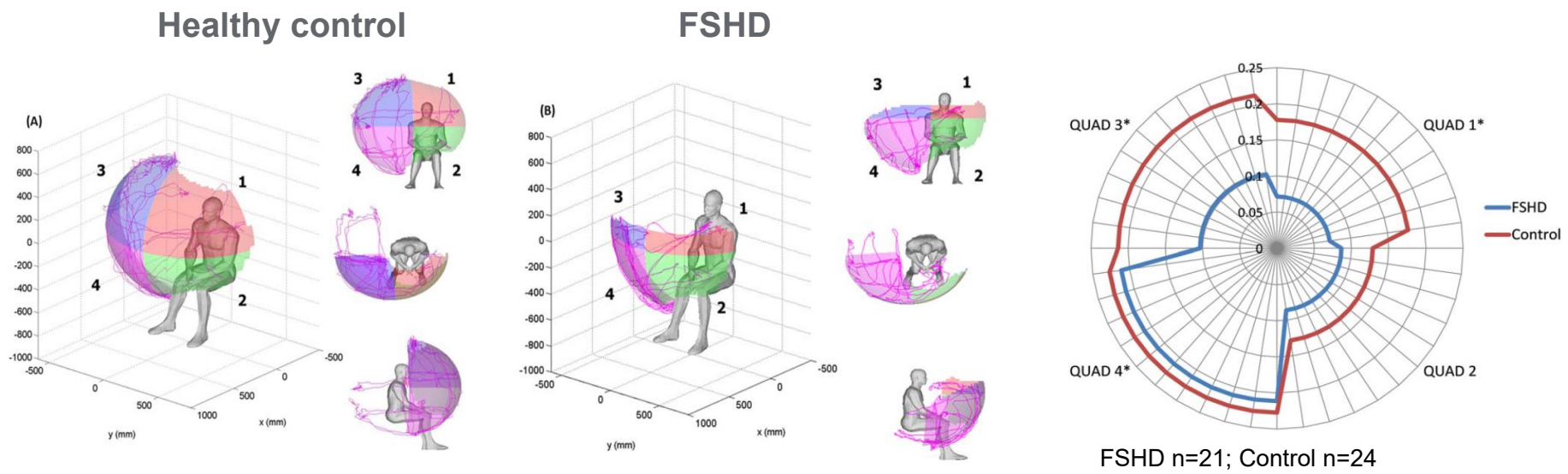


Han et al., 2015 "Reachable workspace reflects dynamometer-measured upper extremity strength in facioscapulohumeral muscular dystrophy"

Reachable Work Space (RWS): FSHD

Valid and Reliable Assessment of RSA in both FSHD and HV control

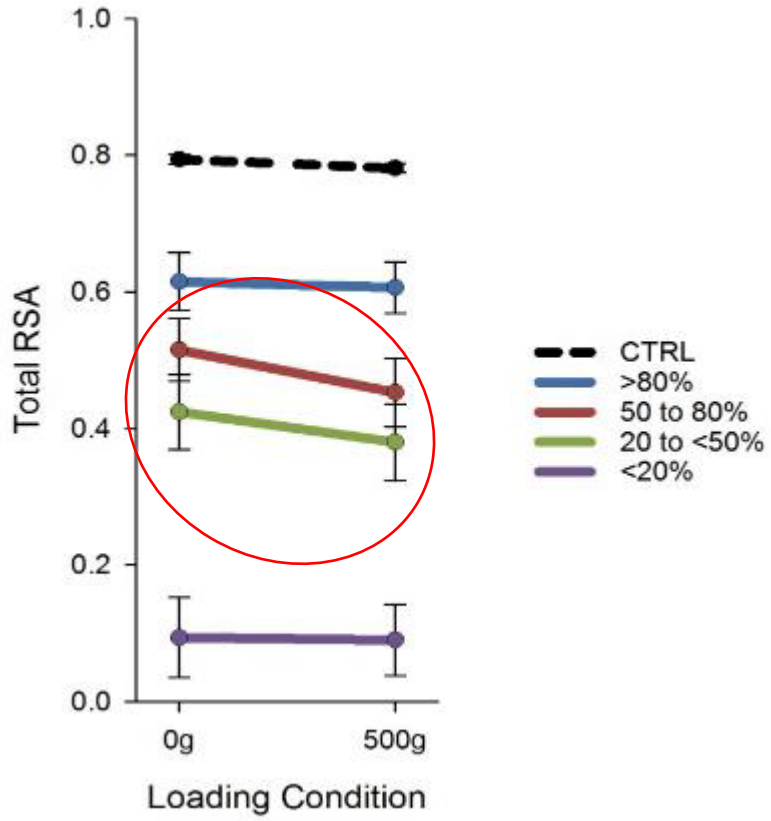
Test re-test reliability: R=0.952 (p<0.001)



FSHD n=21; Control n=24

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

Weighted Assessment with RWS: FSHD



Subtle strength impairments can be differentiated

RSA declines with loading condition in moderately impaired individuals

No significant changes are observed in either very strong or extremely weak individuals

Natural History in FSHD Shows Progression in Annualized RWS Over Time

- Natural history longitudinal study
- N=18
- Up to 5 years observation
  - Range 8mo – 5 years
  - Average 2.5 yrs

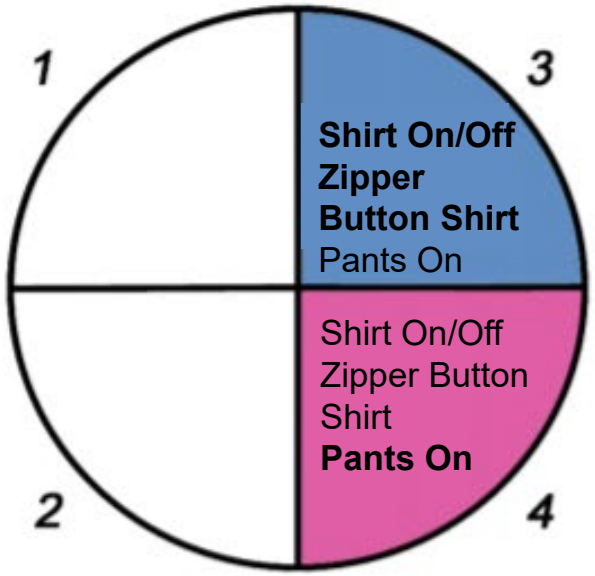
Annualized Change (%RSA change/year)

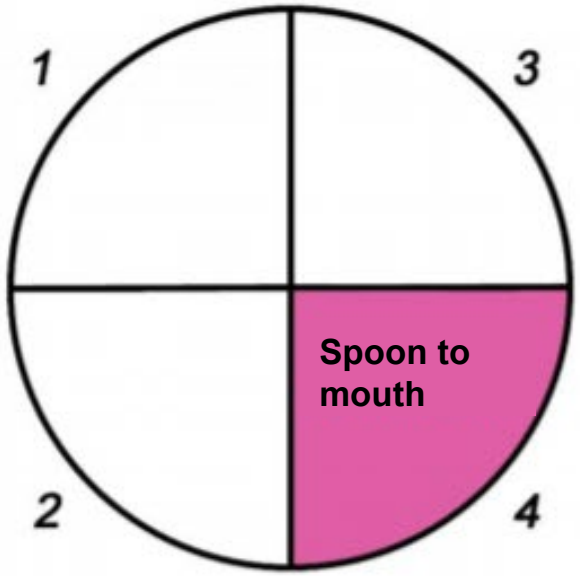
Quadrant	With 500g Weight	Without Weight
	Arms were averaged	
Q1	**-7.20**	**-6.62**
Q2	1.40	1.91
Q3	**-8.09**	**-9.25**
Q4	-0.76	-0.74
Q5	Not done	
Q1+Q3	Not done	
Total RSA*	**-1.82**	**-1.63**

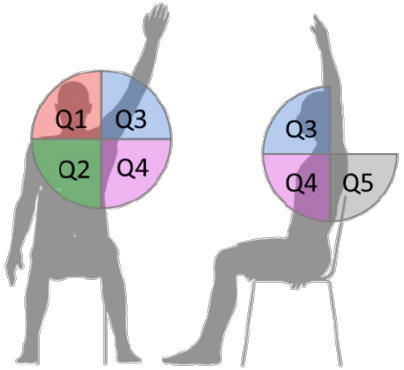
*not including Q5

Hatch et al. Longitudinal Study of Upper Extremity Reachable Workspace in FSHD. Neuromuscular Disorders (2019).

RWS Assessment Can Map to Activities of Daily Living (ADL) Function





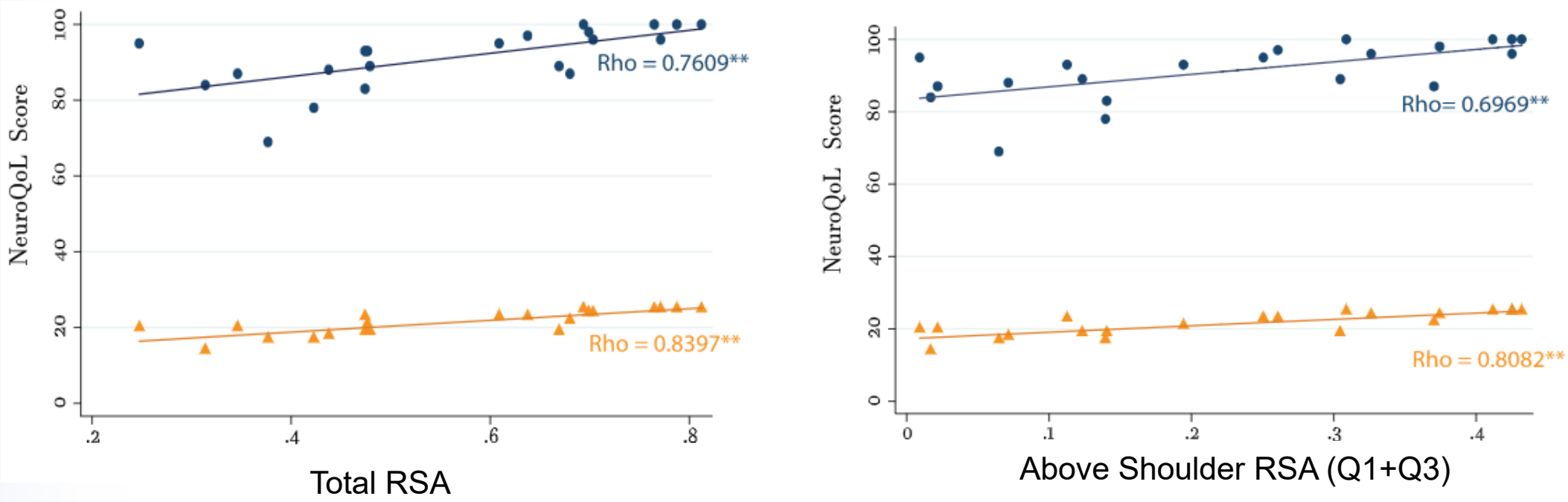


Hatch et al 2021 Muscle Nerve

Strong Association Between Total NeuroQoL UE Scores and Total RSA

- Summed Scores from all NeuroQoL Questions
- Summed Scores from sub-NeuroQoL Questions

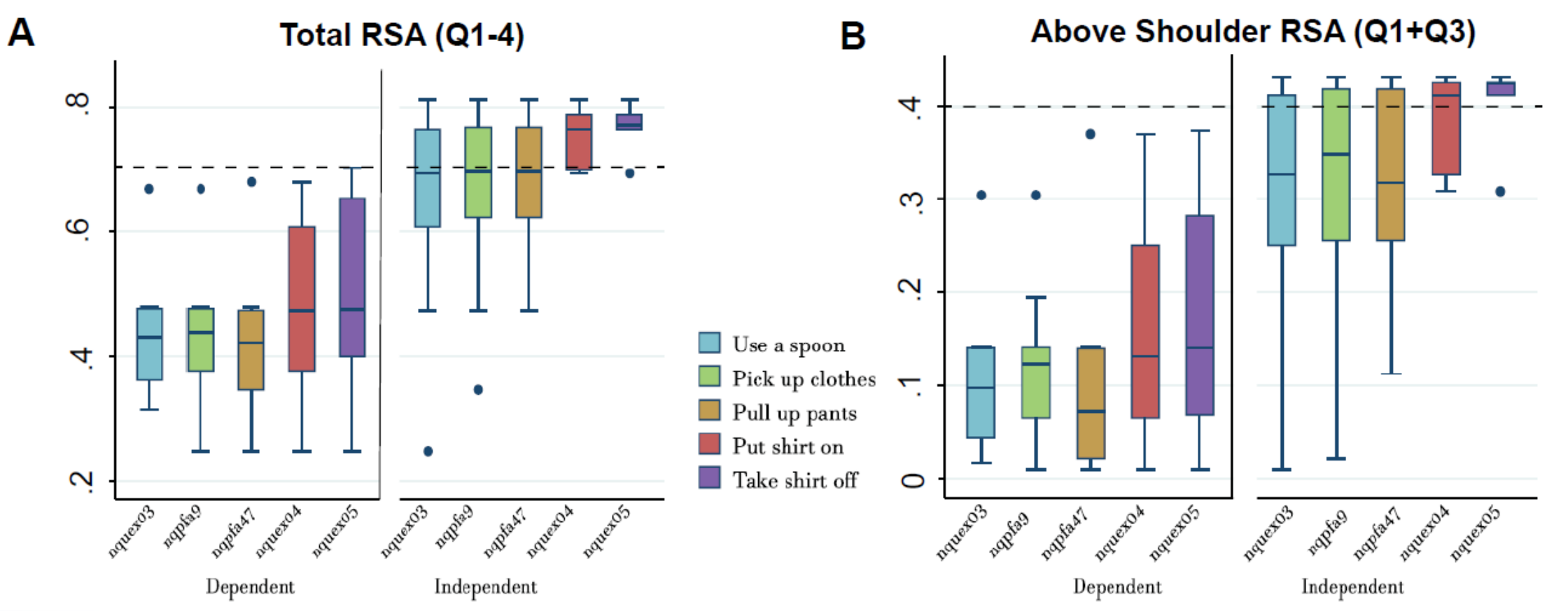
Correlation Between RWS and ADLs



Spearman's correlations against total, and above shoulder RSAs identified five proximal and shoulder related items with at least a moderate spearman's coefficient (ρ ≥ 0.60) for both.

Hatch M, et al. Muscle &Nerve. 2021; 63:250-257. Han J, et al. Muscle & Nerve 2015; 52(3):344-55

Relative Surface Area (RSA) Values Correlate with Independence

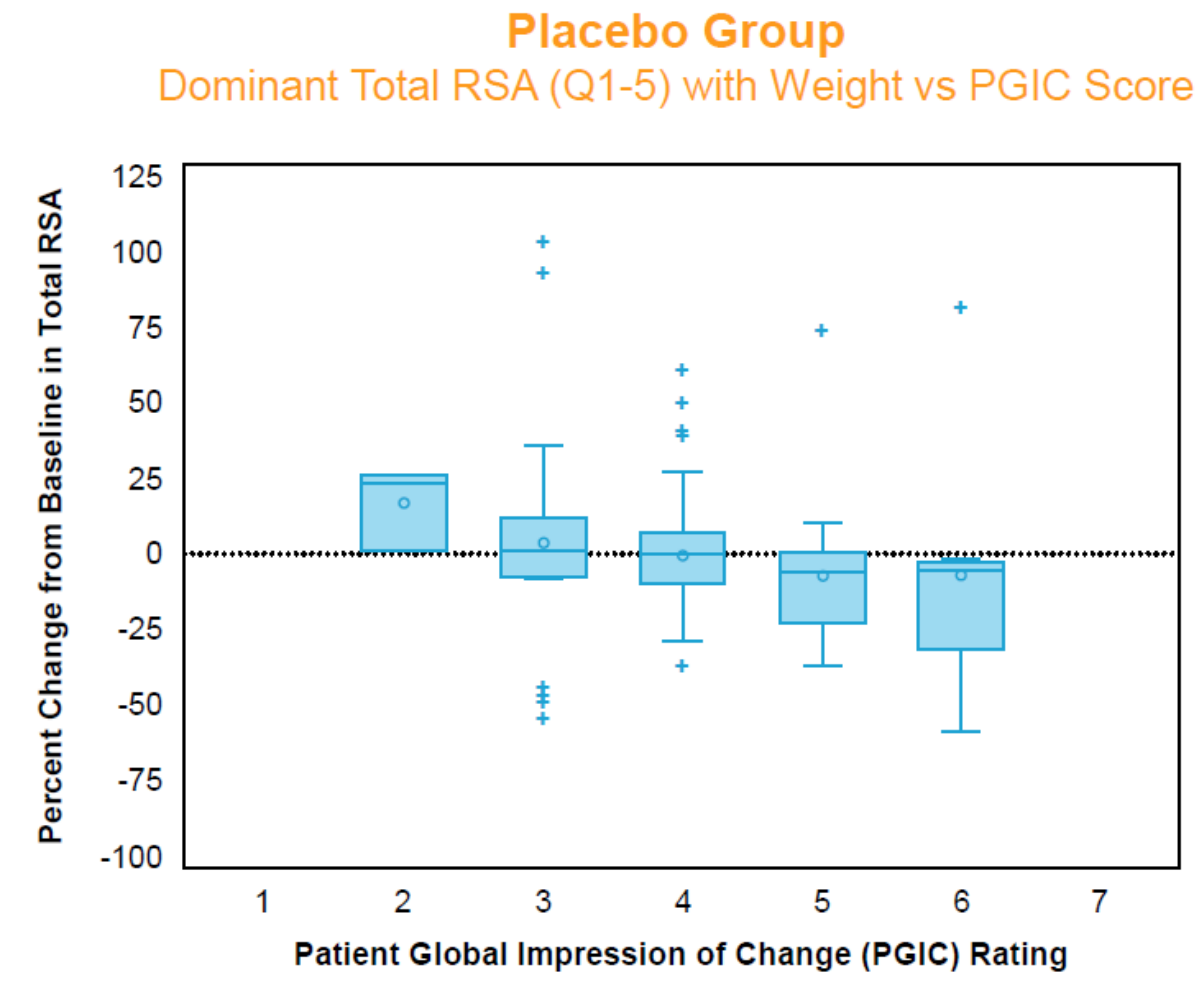


Patients with Total RSA >0.7 are Independent
PPV: 83%
NPV: 100%

Patients with Above Shoulder RSA >0.4 are Independent
PPV: 100%
NPV: 94%

Source: Hatch et al., 2020

Direct Relationship Between RWS and How Patients Feel



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

7: Very much worse

6: Much worse

5: Minimally worse

4: No change

3: Minimally improved

2: Much improved

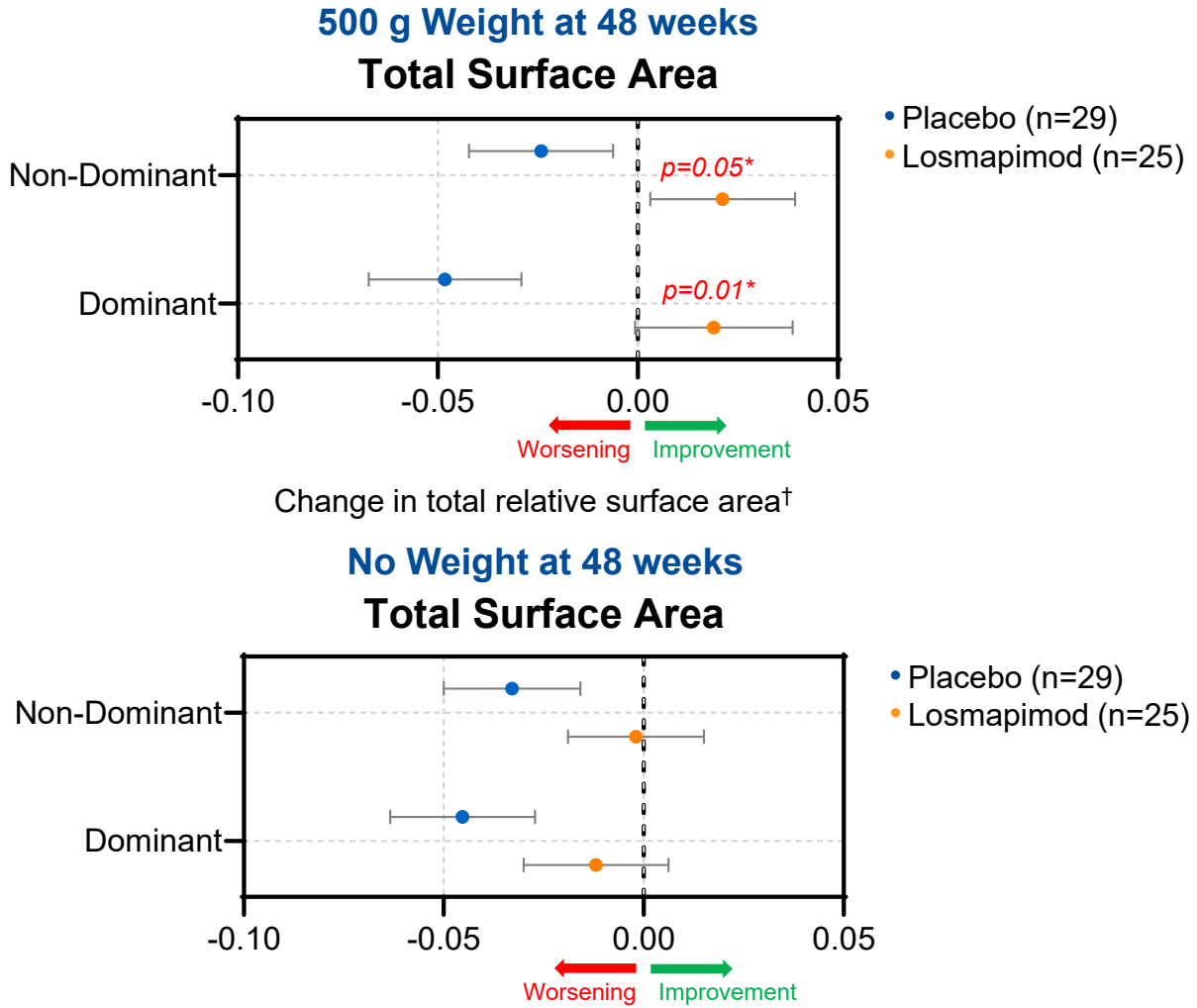
1: Very much improved

Analysis of data from ReDUX4 trial

Losmapimod Showed Nominally Significant Improvement in Total Surface Area by Reachable Workspace in ReDUX4

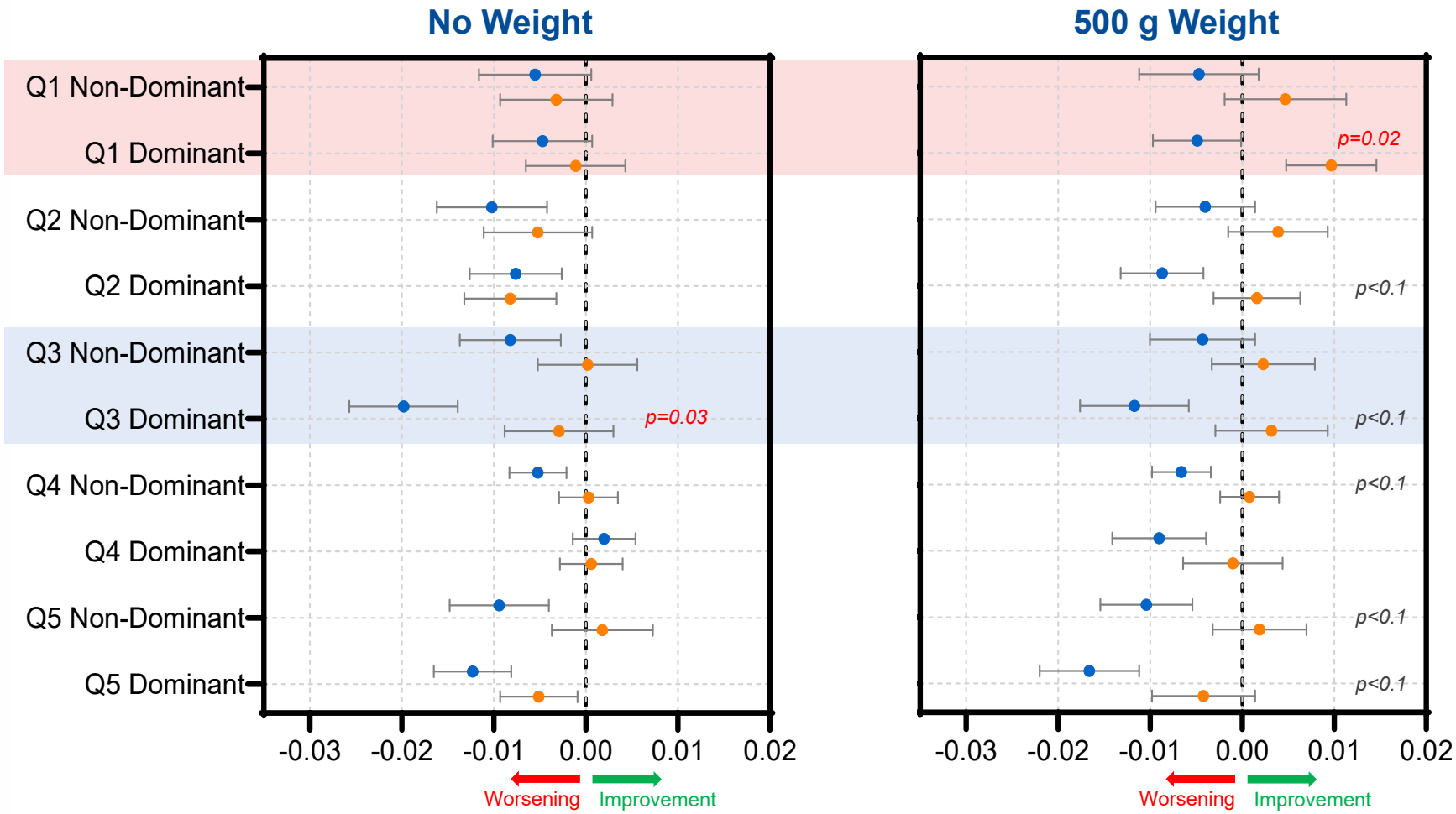
- Placebo group lost about 2% to 4% of Total Surface Area (with and without weight)
- Losmapimod group showed trends of slower disease progression as well as improvements of up to 1.5% in surface area with weight

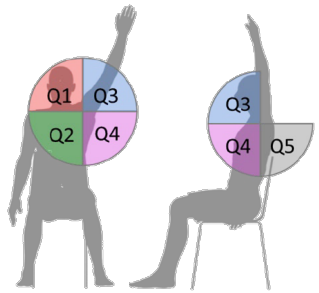
Baseline	Total RSA (Q1 to Q5)	
	Dominant	Non-Dominant
Losmapimod, n=40		
Without Weights, n=39	0.56 (0.24)	0.62 (0.26)
With Weights, n=39	0.51 (0.23)	0.55 (0.27)
Placebo, n=40		
Without Weights, n=40	0.57 (0.24)	0.60 (0.25)
With Weights, n=40	0.53 (0.25)	0.55 (0.26)



*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.

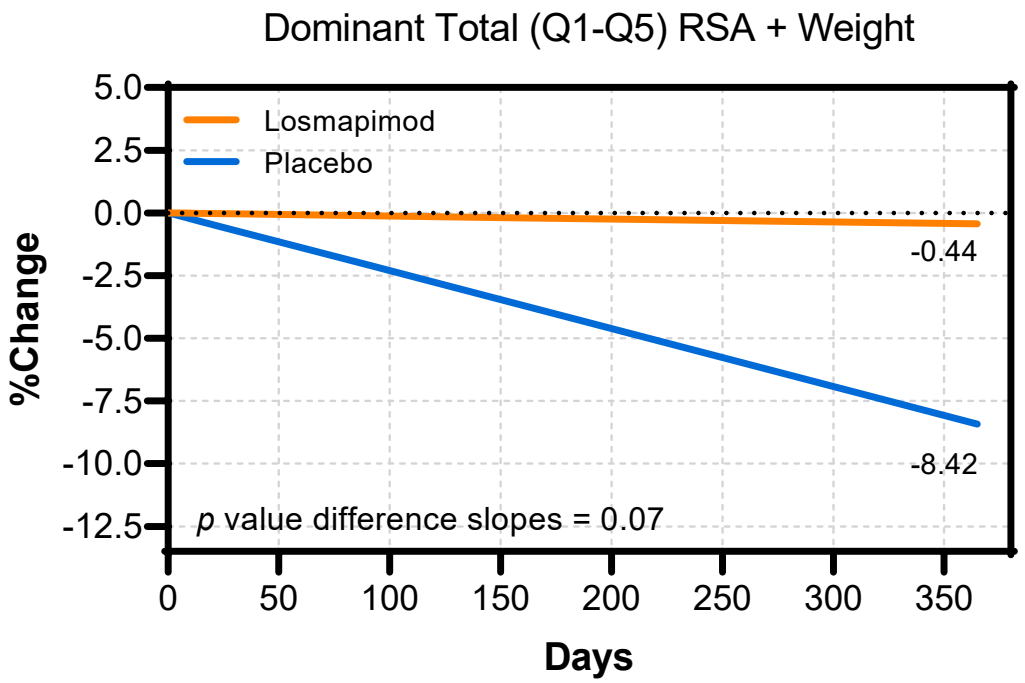
Improvement in Total Surface Area Was Seen in Trends of Slowed Disease Progression and Improvement on Multiple RWS Metrics*



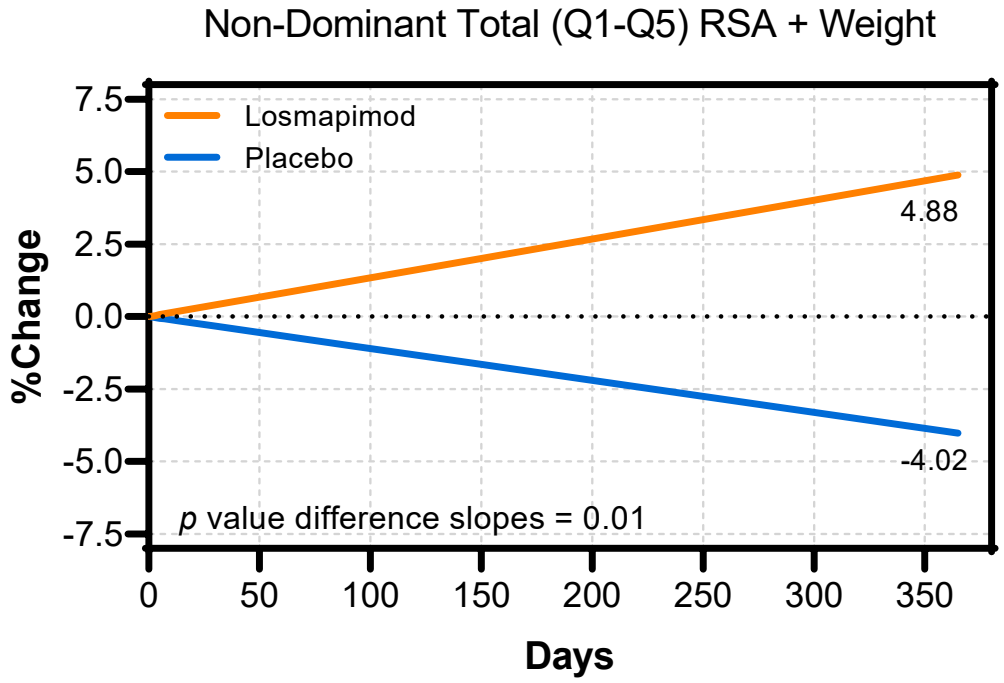


*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint). Total relative area for the 5 quadrants used to calculate the approximate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

In ReDUX4, Annualized Rate of Change Shows that Losmapimod Slows Disease Progression



	LOS	PBO
Slope (SE)	-0.002 (0.02)	-0.044 (0.02)



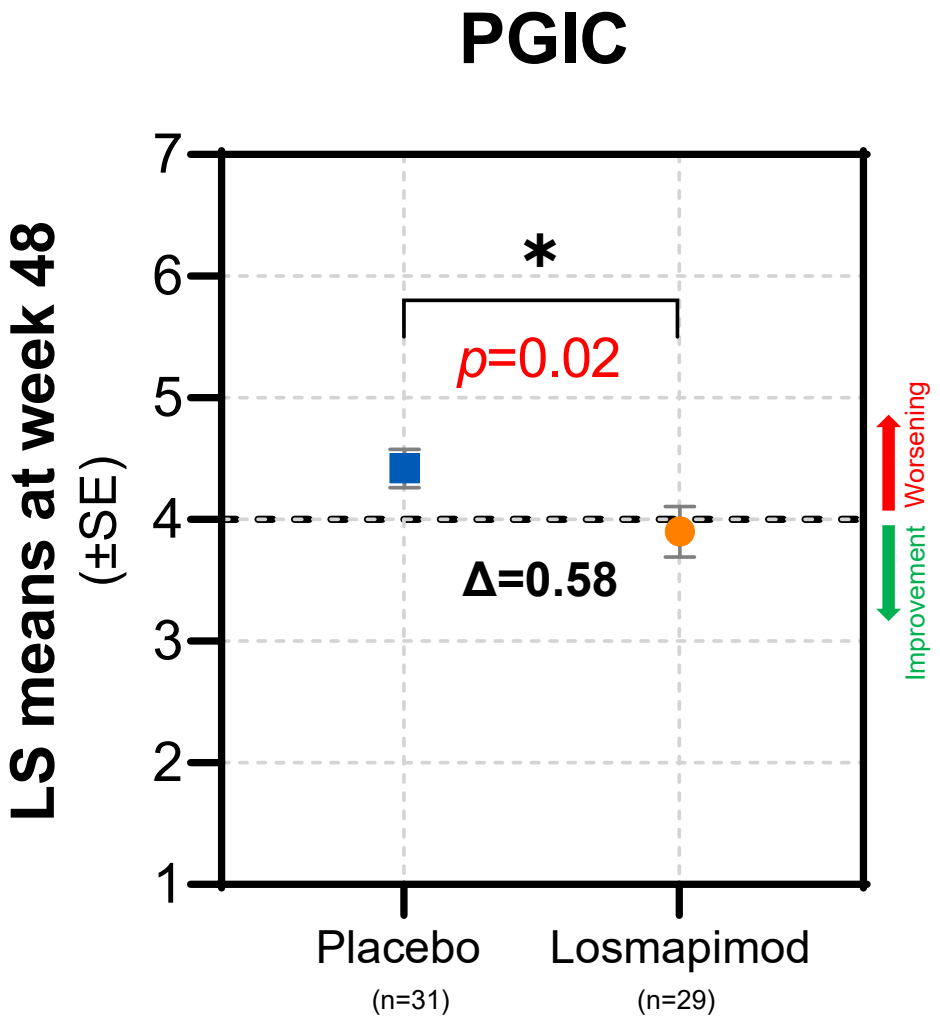
	LOS	PBO
Slope (SE)	0.03 (0.01)	-0.02 (0.01)

Note: Annualized rate of change (%) was calculated using a linear mixed-effects model to estimate percent change per year (y-axis)
RSA = relative surface area; Q = quintant

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

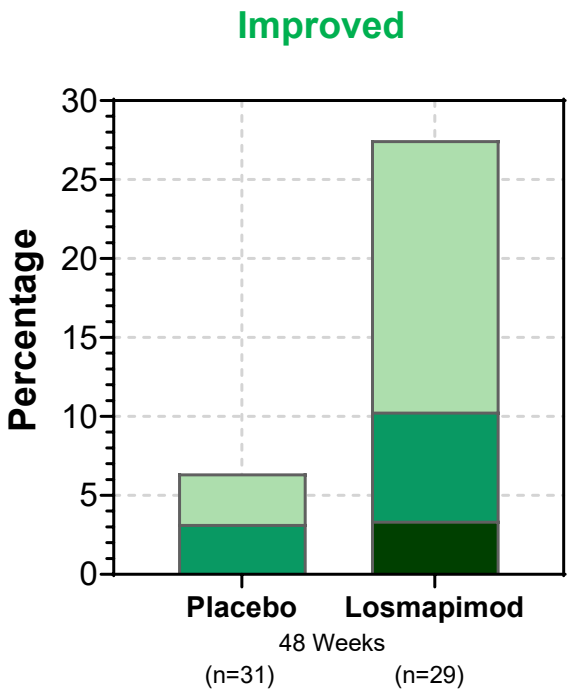


*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).

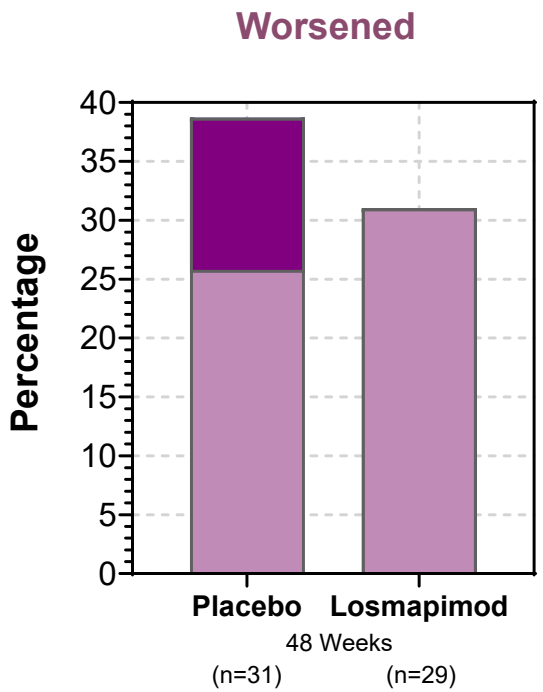
Fewer participants reported worsening on Losmapimod vs Placebo*

- 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 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).

Favorable Safety and Tolerability Dataset

- Majority of treatment-emergent adverse events (TEAEs) were mild or moderate
- No TEAE led to treatment discontinuation or study withdrawal
- No significant changes in vital signs, laboratory studies, or electrocardiogram were observed
- Majority of TEAEs assessed as unlikely related or not related to study drug
- Most common AEs: fall, procedural pain, back pain, and headache
- Majority of AEs resolved with continued dosing
- Observed safety and tolerability data are consistent with prior losmapimod experience in over 3,600 clinical study participants

Losmapimod has been generally well-tolerated with no serious treatment-related adverse events

In the Phase 2b ReDUX4 Study, Losmapimod Demonstrated Nominally Statistically Significant Benefits on Key Endpoints

ReDUX4
Assessing losmapimod in FSHD

Function

Preserved or improved muscle function as measured by **RWS**

Muscle Health

Decreased fat infiltration in muscle as measured by **MFI**

Quality of Life

Patients reported feeling better as measured by **PGIC**

Safety and Tolerability

Clinical experience in ~3,600 people

Fulcrum Therapeutics

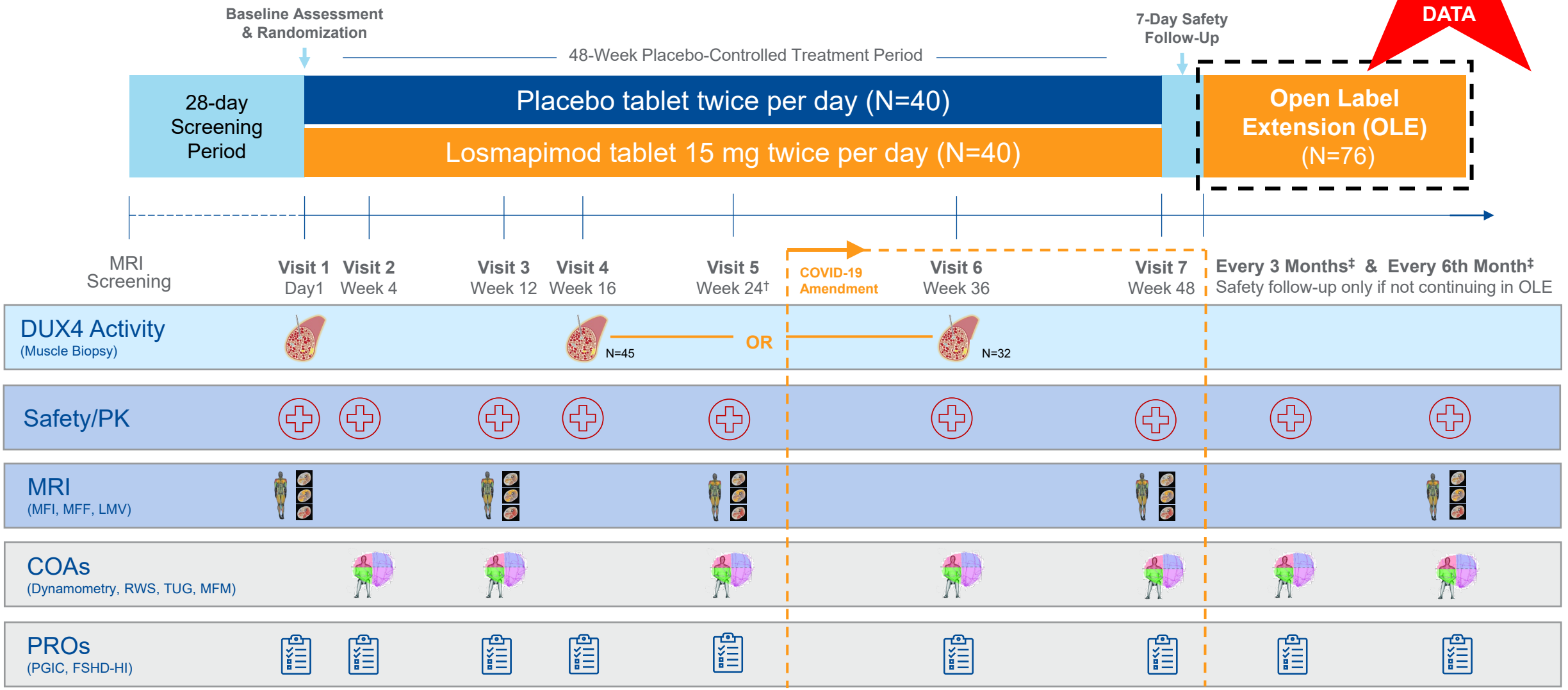
ReDUX4 Week 96 Topline Results

Jennifer Shoskes, PharmD
Fulcrum Therapeutics, Inc. United States

See Late-Breaker Virtual Poster: LSVP.17 ***Results from 96 Weeks Open-Label Extension of a Phase 2 Trial of Losmapimod in Subjects with FSHD: ReDUX4***
Wang L, Han J, Shoskes J, Dunn J, Jiang J, Tawil R

ReDUX4 Trial Design*

96 WEEK DATA



*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.

>97% Retention in OLE

	Losmapimod / Losmapimod (LOS/LOS) (N=39)	Placebo / Losmapimod (PBO/LOS) (N=37)	Total N=76
Treatment / Study Status			
Discontinued	1 (2.6%)	1 (2.7%)	2 (2.6%)
Ongoing	38 (97.4%)	36 (97.3%)	74 (97.4%)

Reasons for discontinuation were unrelated to safety

- **Average Exposure**
  - LOS/LOS: 96 weeks
  - PBO/LOS: 47 to 72 weeks, depending on when they entered the OLE due to implementation of the COVID-19 protocol amendment

No additional safety signals observed with up to 96 weeks of losmapimod 15 mg BID dosing

- No Drug-related SAEs or TEAEs leading to study discontinuation or death
- Most adverse events were mild in severity

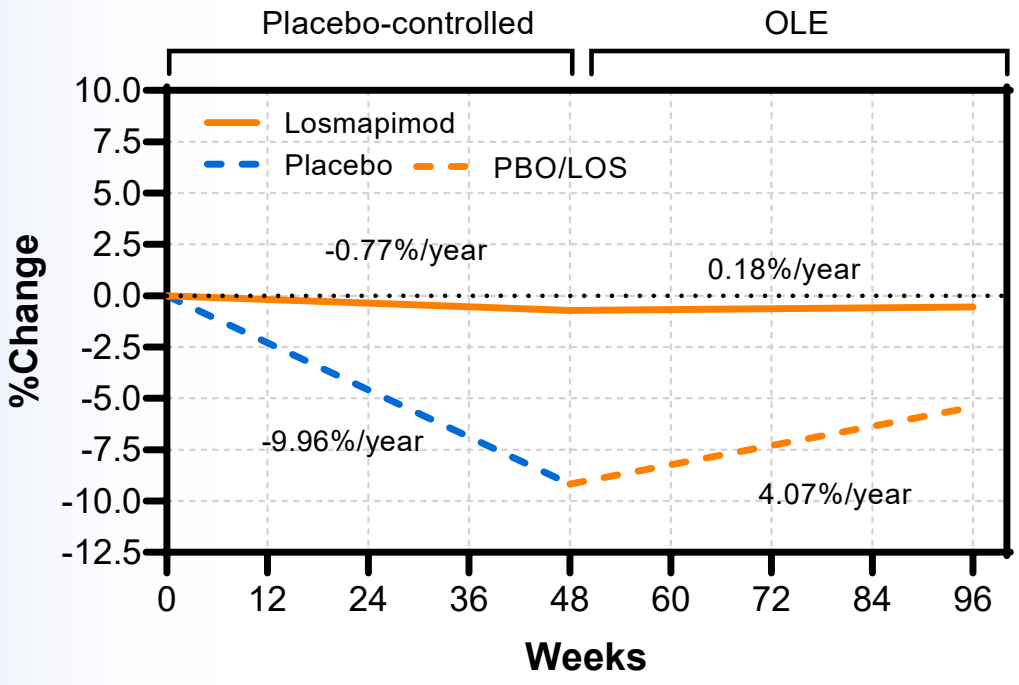
n (%)	LOS / LOS (N=39)	PBO / LOS (N=37)
Any TEAE	31 (79.5)	30 (81.1)
Any Study Drug-related TEAE	10 (25.6)	5 (13.5)
Any SAE	3 (7.7)	1 (2.7)
Any Study drug related SAE	0	0

- Most Common TEAEs (n>5 across groups): Fall, headache, arthralgia, back pain, pain in extremities, nasopharyngitis, pyrexia

RWS Slopes of Annualized Change RCT vs. OLE

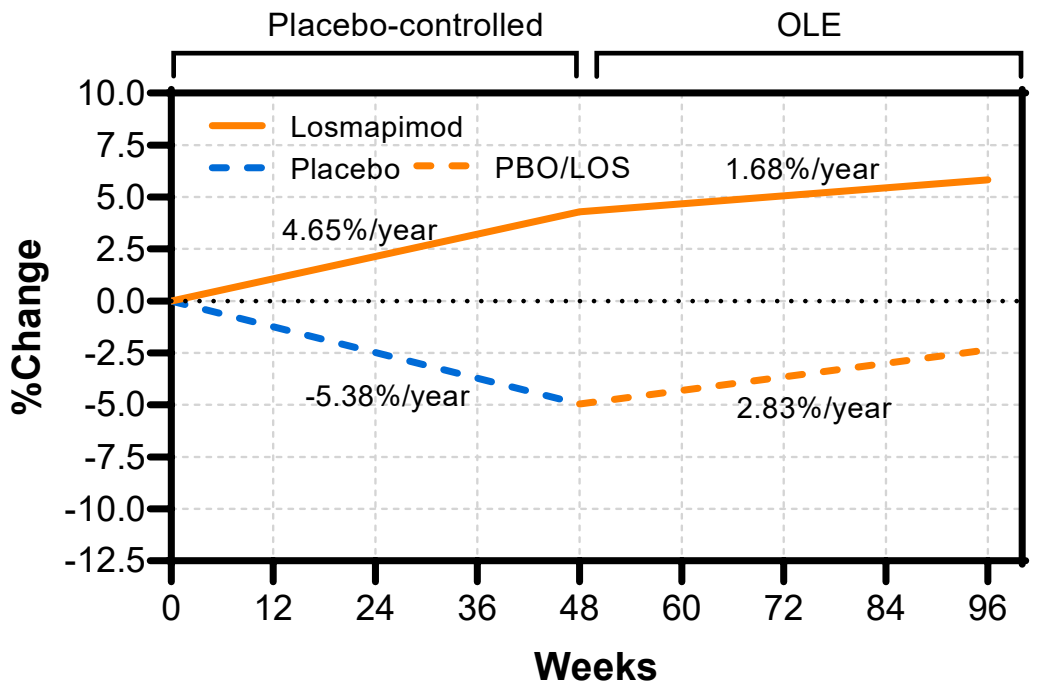
Stabilization or improvement seen in subjects continuing therapy and subjects starting LOS from PBO

Dominant Total (Q1-Q5) RSA + Weight



Slope (SE)	LOS (n=30)	PBO (n=30)
RCT	-0.004 (0.02)	-0.050 (0.02)
OLE	0.001 (0.02)	0.019 (0.02)

Non-Dominant Total (Q1-Q5) RSA + Weight



Slope (SE)	LOS (n=30)	PBO (n=30)
RCT	0.022 (0.02)	-0.026 (0.01)
OLE	0.008 (0.01)	0.013 (0.01)

Summary

- FSHD is a disease of relentless and accumulating muscle and functional loss
- Losmapimod is a targeted disease modifying therapy that preserves muscle function
- RWS is a valid and reliable assessment of RSA that demonstrates slowed disease progression in the losmapimod arm vs placebo over 48 weeks
- Week 96 data supports the finding that losmapimod modifies disease progression in clinical outcome measures:
  - Participants who crossed over from placebo at week 48 demonstrate slowing/stopping of disease progression on assessments of upper extremity function by RWS
  - Participants who remained on losmapimod continued to experience slowing/stopping of progression or improvement on RWS demonstrating treatment durability
- Safety profile with 96 weeks of dosing is consistent with that previously observed – generally safe and well tolerated

See Late-Breaker Virtual Poster: LSVP.17 ***Results from 96 Weeks Open-Label Extension of a Phase 2 Trial of Losmapimod in Subjects with FSHD: ReDUX4***

Fulcrum Therapeutics

Phase 3 REACH Study

Jennifer Shoskes, PharmD
Fulcrum Therapeutics, Inc. United States

REACH Trial Design Leverages Learnings from ReDUX4

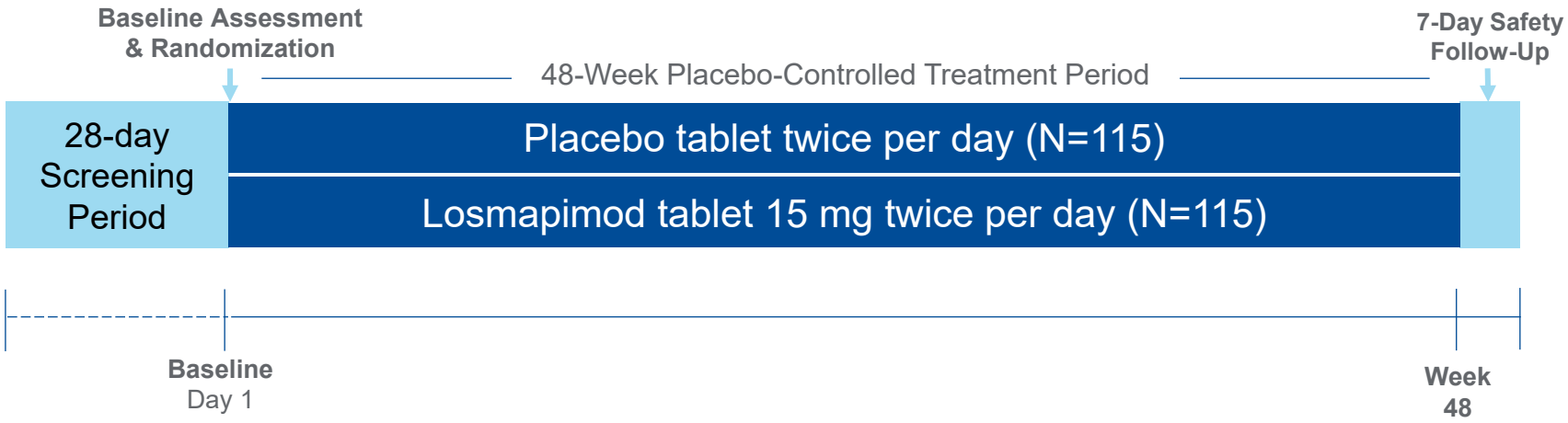
What we know from ReDUX4	REACH Phase 3 Trial Design
Losmapimod demonstrated measurable impact on disease progression at 48 weeks of treatment	48-week treatment duration
Reachable Workspace (RWS) is a reliable and quantifiable measure of function and disease progression	RWS is primary endpoint
Muscle Fat Infiltration (MFI) is a sensitive measure of muscle health most susceptible to disease pathology	MFI is secondary endpoint
Patient-reported outcomes are effective measure of disease progression and activities of daily living in FSHD	Patient-reported outcomes (PGIC and Neuro-QoL) are secondary endpoints

REACH: A Phase 3 Trial of Losmapimod in FSHD

Study Population

~230 subjects with FSHD1 and FSHD2, 18-65 years old, at clinical sites in the US, Canada, UK and Europe

Study Design



Study Endpoints

Primary

RWS quantification of total relative surface area with 500g wrist weight in dominant arm

Secondary

- MFI
- Neuro-QoL Upper Extremity
- PGIC
- Safety and tolerability

Healthcare Utilization

- Healthcare utilization questionnaire
- EQ-5D questionnaire

How to contact us for Phase 3 Study (REACH)

ClinicalTrials.gov website

- https://clinicaltrials.gov/ct2/show/NCT05397470

REACH website

- https://www.reachfshdstudy.com/

Contact

- clinicaltrials@fulcrumtx.com

Acknowledgements

ReDUX4
Assessing losmapimod in FSHD

People Living With FSHD Participating in This Study

ReDUX4 Study Sites

ReDUX4 Physical Therapists

ReDUX4 Study Coordinators

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- Hanns Lochmüller, MD, PhD. CHEO
- Jeffrey Statland, MD. KUMC
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- Jordi Diaz Manera, MD, PhD. HSCSP
- Jorge Alonso-Perez, MD. HSCSP
- Lawrence Hayward, MD, PhD. UMMS
- Leo Wang, MD, PhD. UW Medicine
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- Nicholas Johnson, MD. VCU
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- 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
NORD National Organization for Rare Disorders
friends of FSH research

Fulcrum Therapeutics

Thank you. Questions?

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