



Fulcrum
Therapeutics

ReDUX4, a Phase 2b Clinical Trial with Losmapimod in Facioscapulohumeral Muscular Dystrophy (FSHD)

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June 24, 2021



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Agenda

- **Welcome and Opening Remarks**
- **Background**
- **Phase 2b ReDUX4 Data**
- **Q&A**



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Opening Remarks

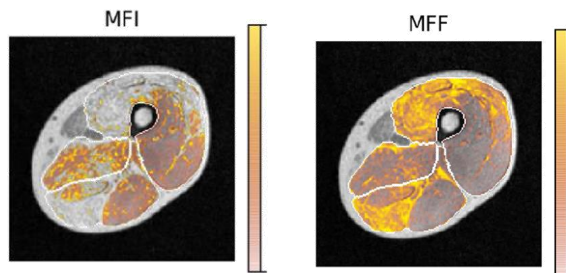
Bryan Stuart, President and Chief Executive Officer

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

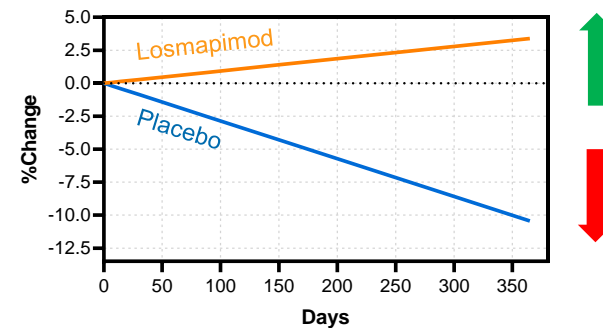
Muscle Health

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

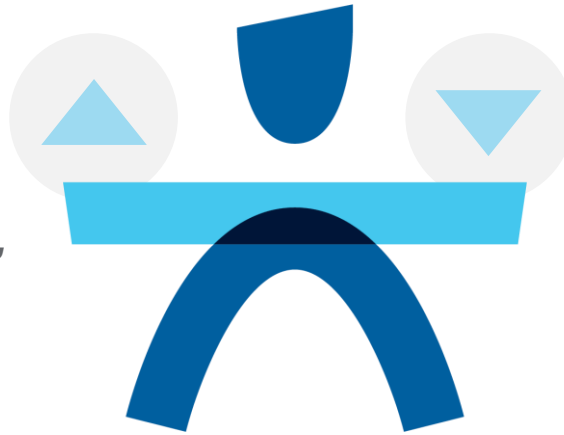
Losmapimod Demonstrated Slowed Disease Progression and Improved Function

- **Primary endpoint, change in DUX4-driven gene expression, which was an experimental biomarker, was not met**
 - Current measurement method insensitive in an interventional clinical trial
 - Downstream benefits of reducing DUX4 activity **were** observed
- **Losmapimod showed statistically significant ($p \leq 0.05^*$) and clinically relevant benefit across multiple structural, functional and patient reported endpoints**
 - **Muscle Health** - Decreased Muscle Fat Infiltration
 - **Function** - Improved Reachable Workspace
 - **Patient Benefit**- Improved Patient Global Impression of Change
- **Favorable safety and tolerability**
- **Positive benefit/risk supports losmapimod's potential to be a transformative therapy**

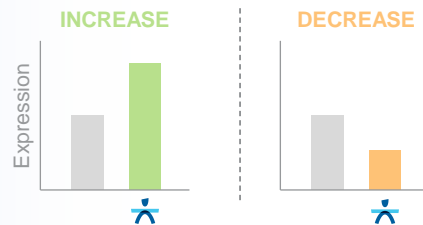
Identification of New Targets that Impact the Root Cause of Disease is Highly Challenging and Rate Limiting in R&D

Fulcrum's patient centric approach systematically & rapidly pinpoints novel intervention points

Fulcrum's Platform identifies targets that have the potential to rebalance monogenic, polygenic, and heterogenous diseases



Treatments that Modulate Monogenic Disease Genes



Treatments that Revert Gene Signatures of Polygenic Diseases



Treatments that Modulate Cell Fate in Complex Diseases



- Our core focus is on patients with diseases of high unmet need
- We use the most relevant cellular models to study a given disease
- We systematically employ target & modality agnostic screening approaches to enable rapid identification of high-quality targets
- Fulcrum's deep and broad approach utilizes state-of-the-art capabilities to comprehensively interrogate diseases and identify disease modifying therapies



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Background

Chris Morabito, MD, Chief Medical Officer

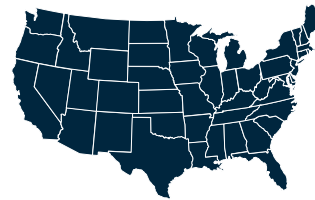
Second Most Common Muscular Dystrophy with Significant Disease Burden and No Current Treatment Options

Characterized by progressive muscle degeneration

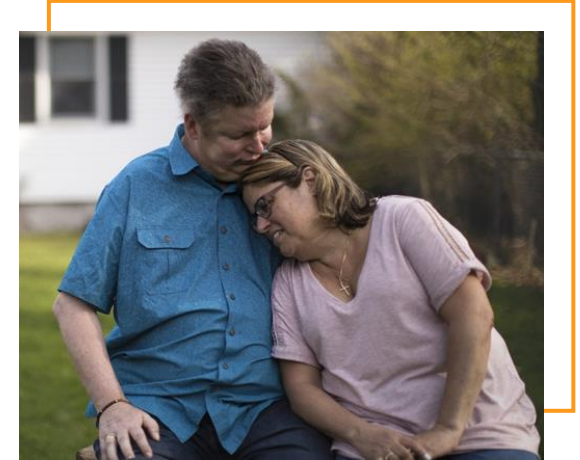
- Skeletal muscle replaced by fat
- Significant impairment of upper extremity function and mobility
- Affects movement of face and eventually the trunk and legs
- Patients report chronic pain, anxiety and depression
- Approximately 2/3 of cases are familial-inherited

Losmapimod Market Opportunity

Estimated US FSHD Population*
16,000-38,000



Estimated Global FSHD Population*
300,000-780,000



“They told me that I was probably going to die from muscular dystrophy at 30 years old—that I would probably roll over and suffocate myself in my sleep.”

“You know how many years it took to get out of that? That’s a scary feeling.”

Voice of the Patient Forum on FSHD – June 29, 2020

Landmark report capturing testimony given to the FDA by patients and family members about the severity of disease symptoms and urgent need for treatment

- “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 hers 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*

FSHD
SOCIETY
LIGHTING THE WAY TO A CURE



Facioscapulohumeral
Muscular Dystrophy (FSHD)

VOICE OF THE PATIENT REPORT



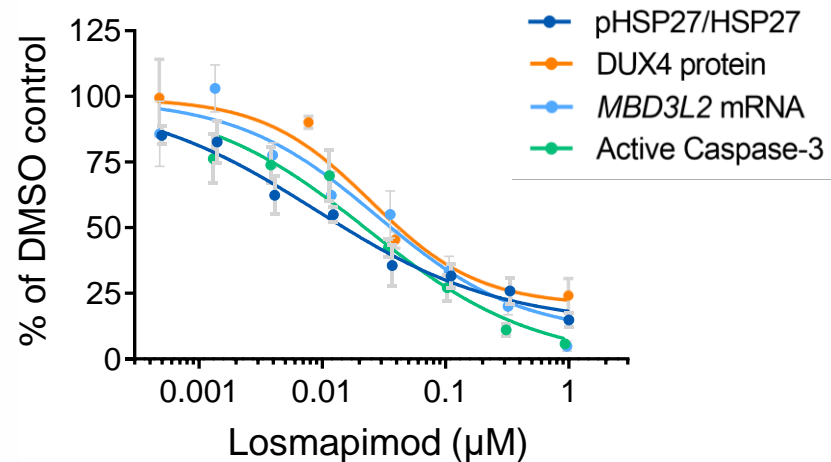
Externally Led
Patient-Focused
Drug Development
Meeting



*This report is dedicated to the individuals
who courageously shared their stories*

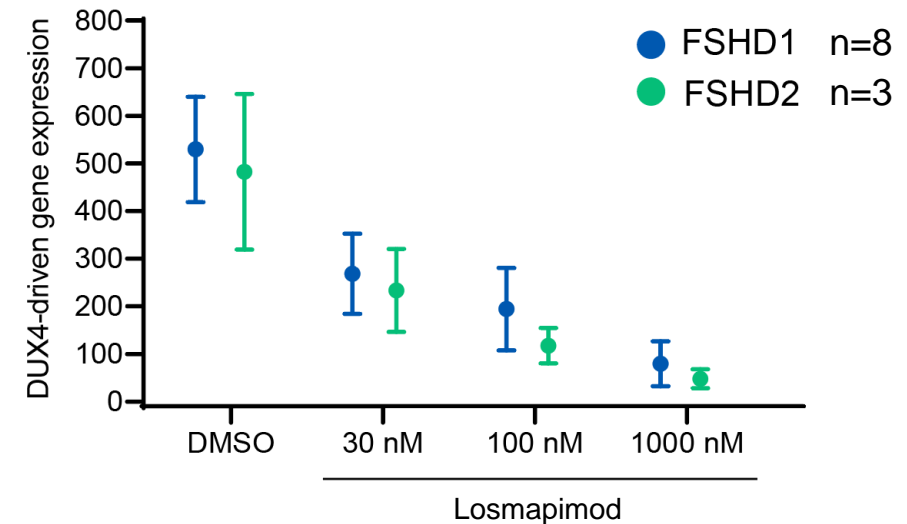
Losmapimod Reduced DUX4 Expression in Preclinical FSHD Studies

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

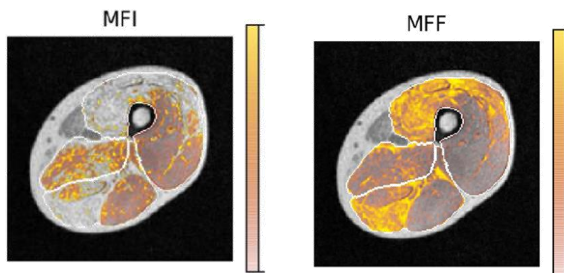


ReDUX4 Hypothesis: Losmapimod Modifies the Course of FSHD

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

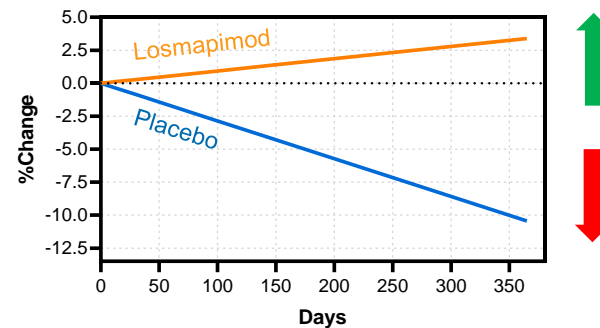
Muscle Health

Decrease of fat replacement in muscle



Function

Preserve and/or improve muscle function

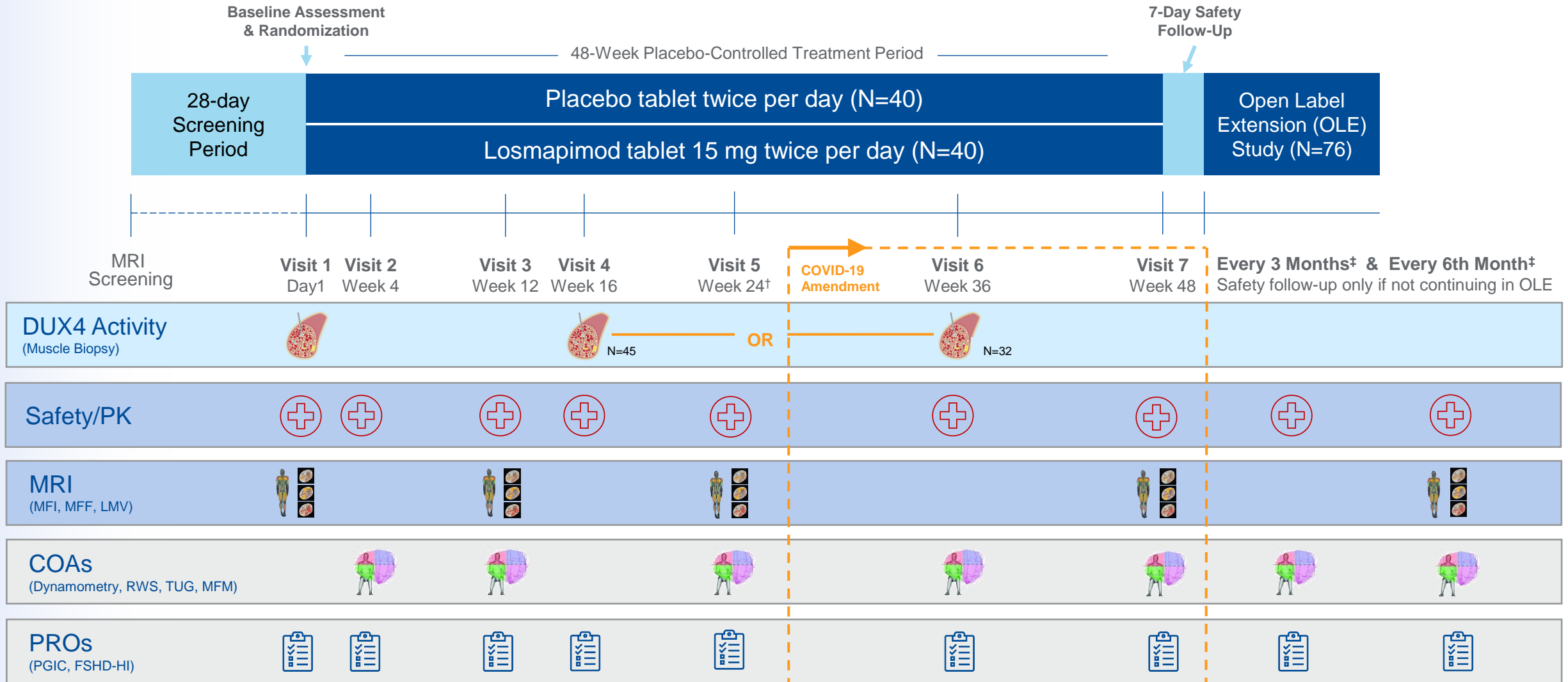


Quality of Life

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

ReDUX4 Trial Design*

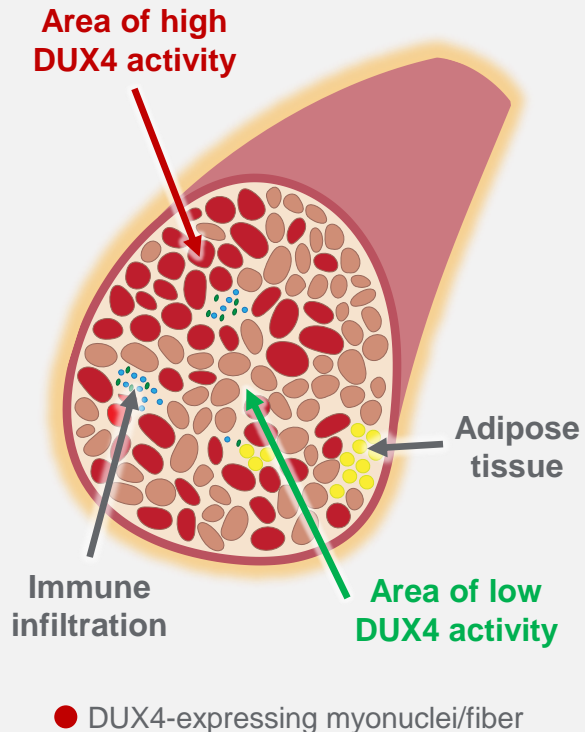


FULCRUM THERAPEUTICS

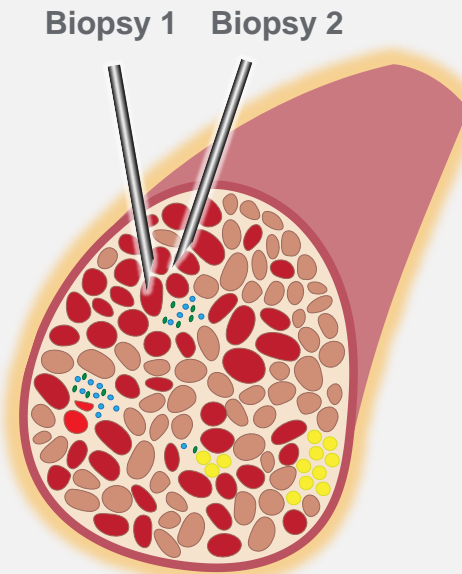
*All analyses were pre-specified in the statistical analysis plan, with the exception of dynamometry, which is now presented as percent change from baseline. [†]Protocol amended due to COVID-19 to allow collection of data to inform study endpoints. 16 subjects had completed the Wk24 visit and had already 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=facioscapulothoracic 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.

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



Biopsy procedure was designed to sample proximal regions in repeated biopsies



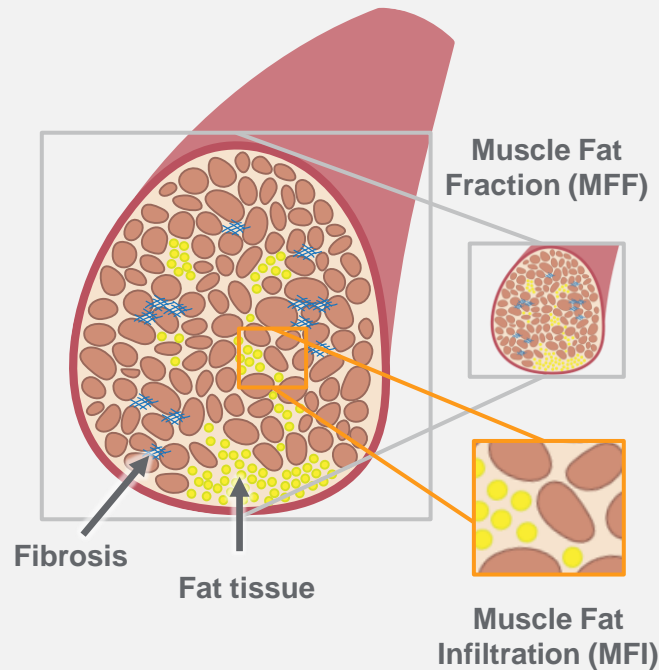
- DUX4-driven gene expression levels represent DUX4 activity
- RT-qPCR assay validated to quantify DUX4 target gene expression*
- Assessed by the mean signal of 6 DUX4 target genes
- Primary analysis performed at 16 or 36 weeks of treatment

- Please see poster: "Evaluating DUX4 Activity in a Phase 2, Randomized, Double-Blind, Placebo-Controlled, 48-Week Study of the Efficacy and Safety of Losmapimod in Subjects with FSHD"

Evaluating Skeletal Muscle Health by Whole Body Musculoskeletal MRI*

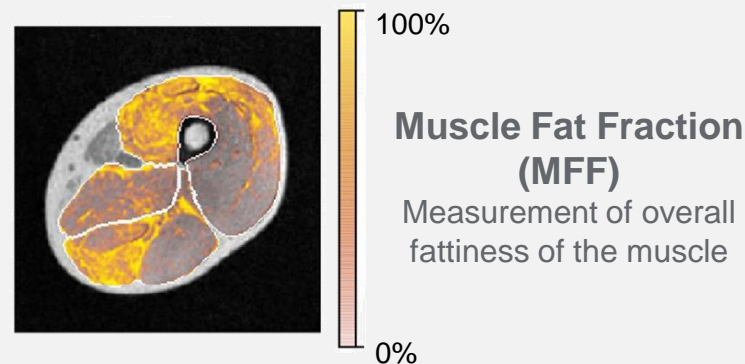
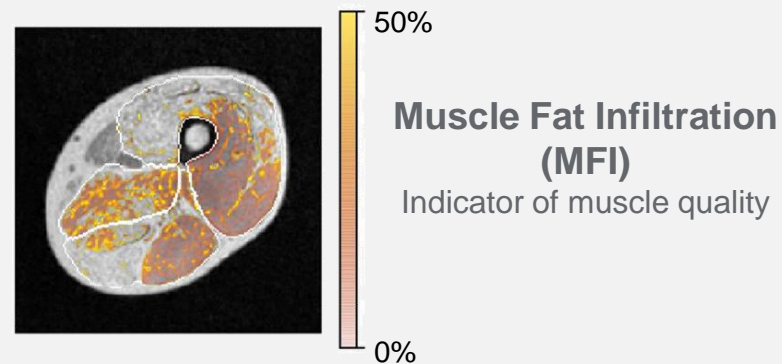
Dystrophic Skeletal Muscle Tissue in FSHD

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

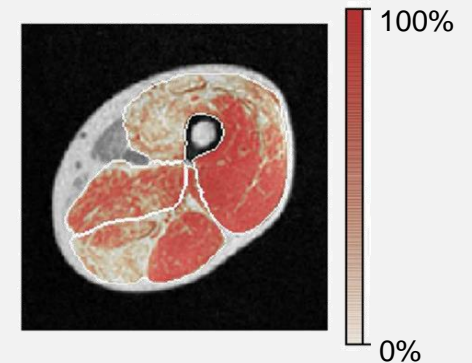


Holistic and Quantitative Picture of Muscle Health

18 muscles were analyzed bilaterally (36 total)



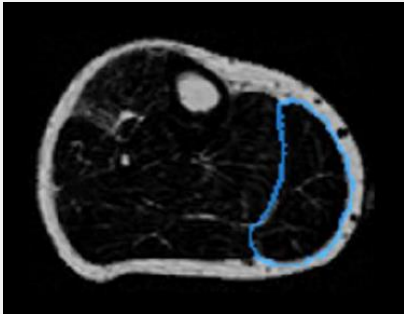
Lean Muscle Volume (LMV)
Measurement of the amount of lean/contractile muscle tissue



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

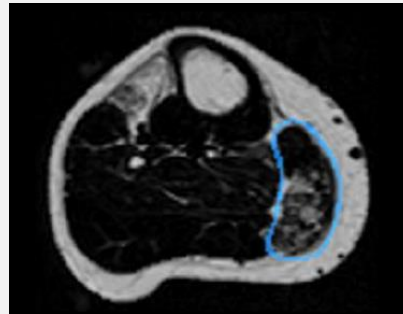
The intermediate “B” class of muscles are at high risk of progression

Normal-Appearing “A”



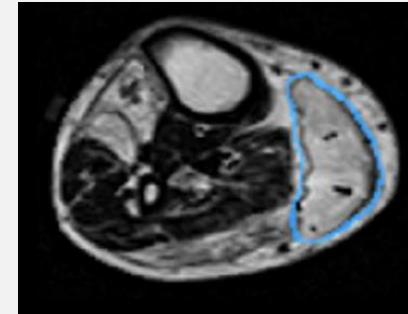
- Muscles do not appear to be affected by disease
- MFI < 10%; MFF < 50%

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%

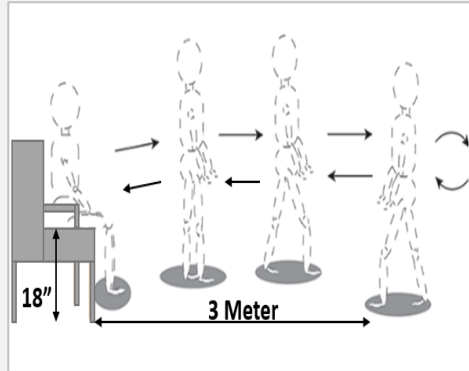
End-Stage “C”



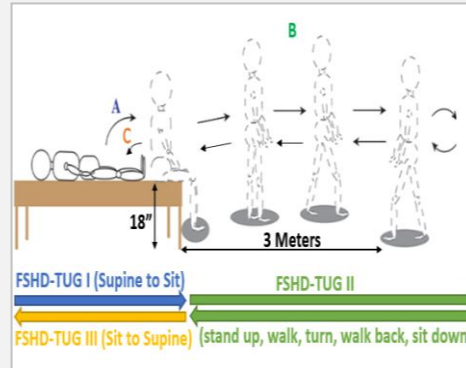
- Muscles severely fat replaced and have likely lost most if not all function
- MFF ≥ 50%

Evaluating Clinical Outcome Assessments (COAs)*

Timed Up and Go (TUG)



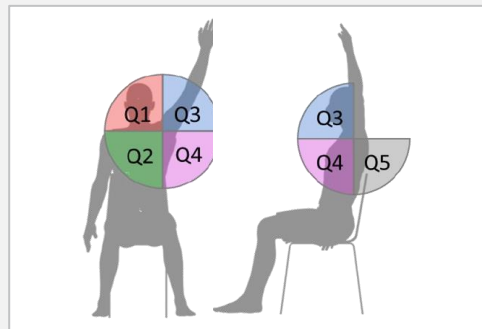
FSHD-TUG



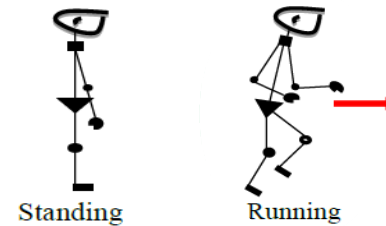
Dynamometry



Reachable Workspace (RWS)



Motor Function Measurement Domain 1



Evaluating Patient Reported Outcomes (PROs)*

Patients' Global Impression of Change (PGIC)

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

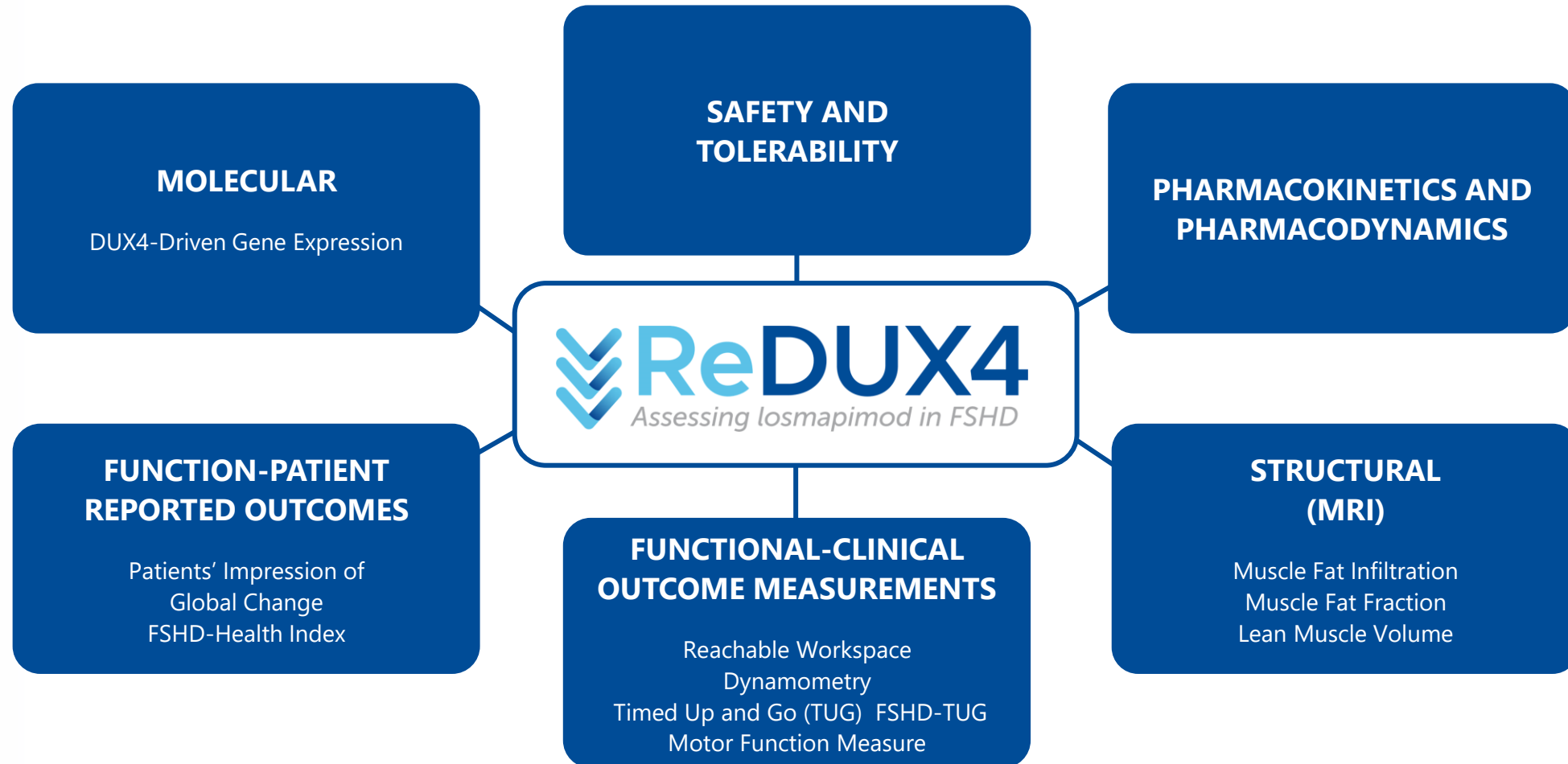
Scores	PGIC
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Worse
6	Much worse
7	Very much worse

FSHD-Health Index (FSHD-HI)

	A	B	C	D
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ReDUX4 Study Was Designed To Capture a Wide Range of FSHD Disease Progression

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





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ReDUX4 Data

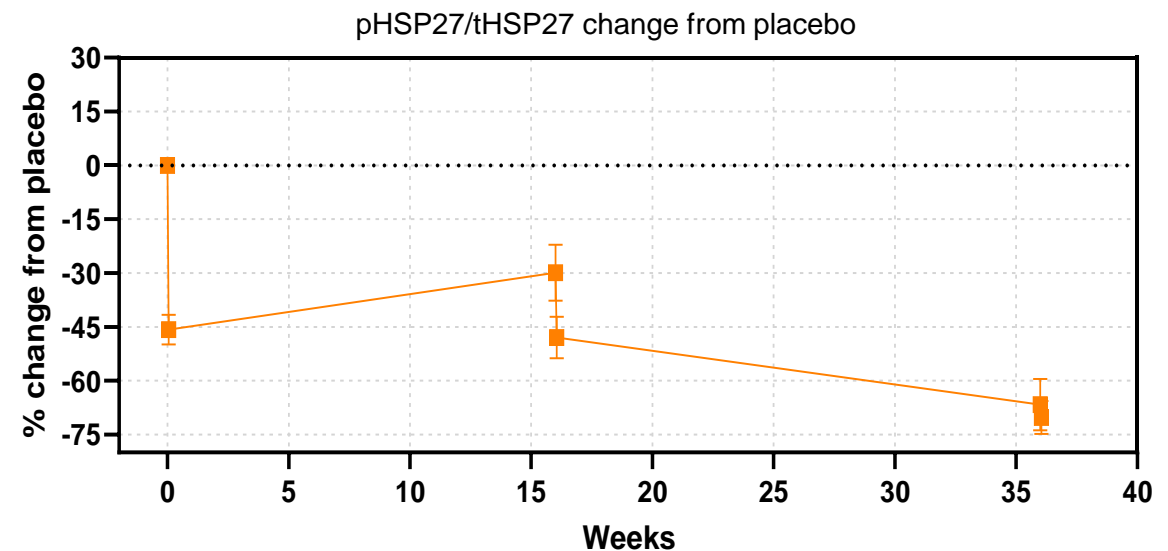
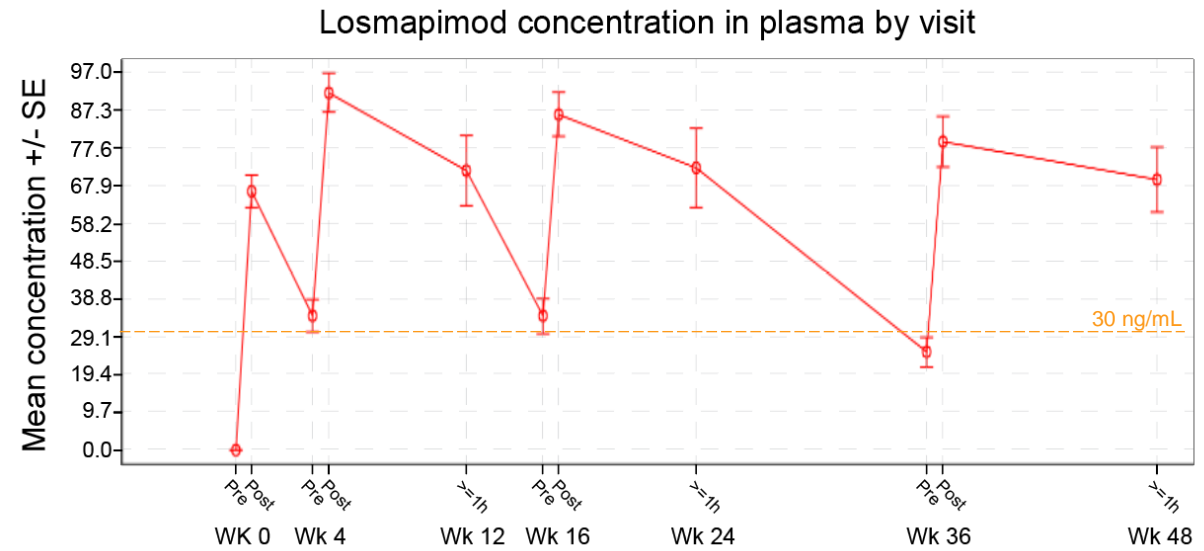
Judith Dunn, Ph.D., President, Research and Development

ReDUX4 Study Participant Randomization Was Well Balanced

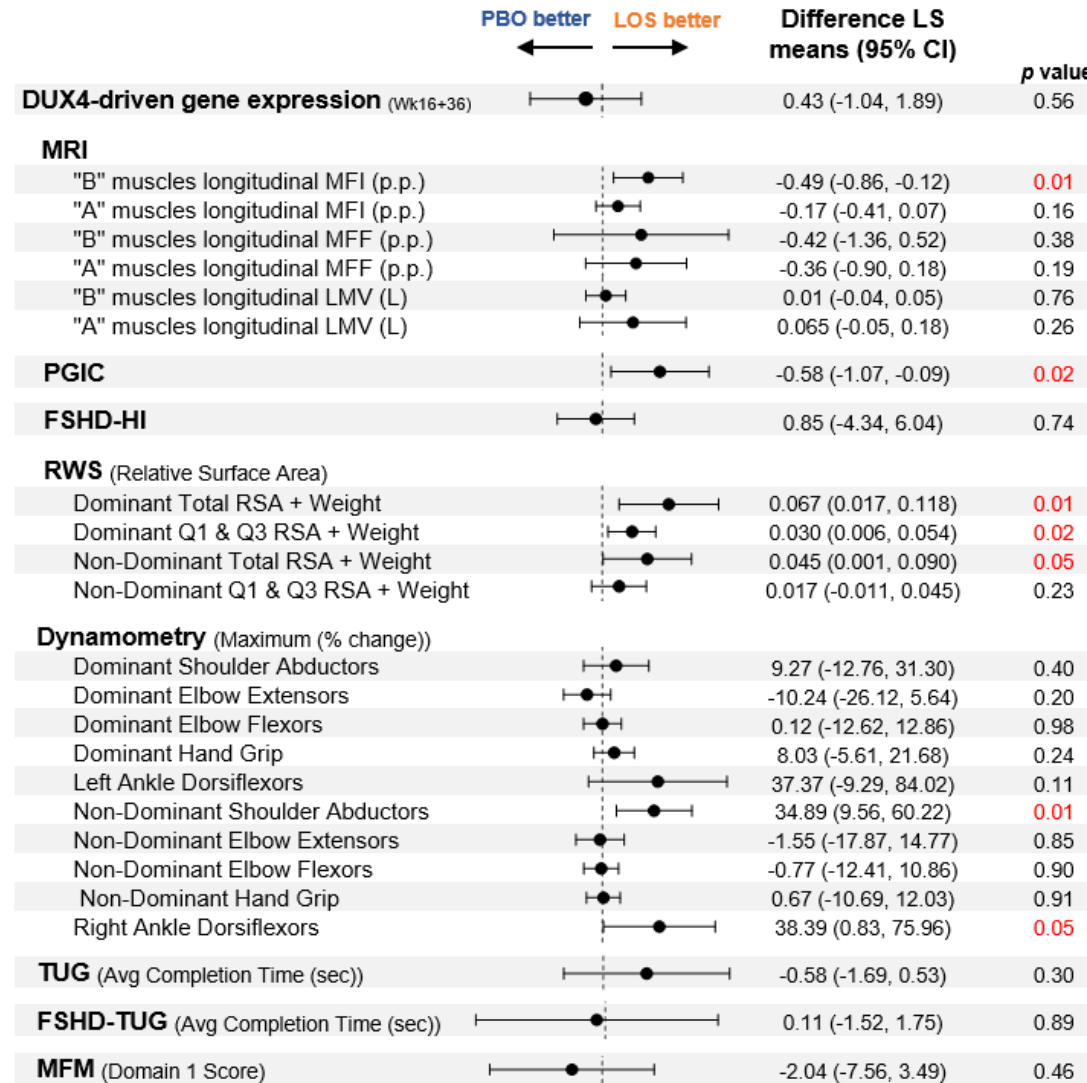
		Placebo BID (N=40)	Losmapimod 15 mg BID (N=40)
Completed		38 (95%)	39 (97.5%)
Discontinued*		2 (5.0%)	1 (2.5%)
DEMOGRAPHICS			
Age (years)	N	40	40
	Mean (SD)	45.7 (+/- 12.69)	45.7 (+/- 12.44)
Race n (%)	White	39 (97.5)	31 (77.5)
	Asian	0	5 (12.5)
	Other	0	1 (2.5)
	Not Applicable	1 (2.5)	3 (7.5)
Ethnicity 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/m²)	N	39	40
	Mean (SD)	26.19 (+/- 4.914)	25.71 (+/- 5.434)
D4Z4 Repeat Unit n (%)	1-3	6 (15.0)	7 (17.5)
	4-6	26 (65.0)	29 (72.5)
	7-9	8 (20.0)	4 (10.0)
D4Z4 Repeat Category n (%)	1-3 Repeats	6 (15.0)	7 (17.5)
	4-9 Repeats	34 (85.0)	33 (83.50)
Ricci Score n (%)	2	0	0
	2.5	7 (17.5)	5 (12.5)
	3	18 (45.0)	19 (47.5)
	3.5	7 (17.5)	11 (27.5)
	4	8 (20.0)	5 (12.5)

Losmapimod Exhibited Expected Pharmacokinetic and Target Engagement in Blood and Muscle as Observed in Previous FSHD Studies

- Blood concentrations consistent with previous studies
- Muscle exposures of losmapimod were within expected range
- Levels of pHSP27/tHSP27 in blood after sorbitol stimulation ex vivo show a reduction of ~35% to 65% at C_{max}



ReDUX4 Demonstrated Clinically Meaningful Impacts on Measures of FSHD Disease Progression*

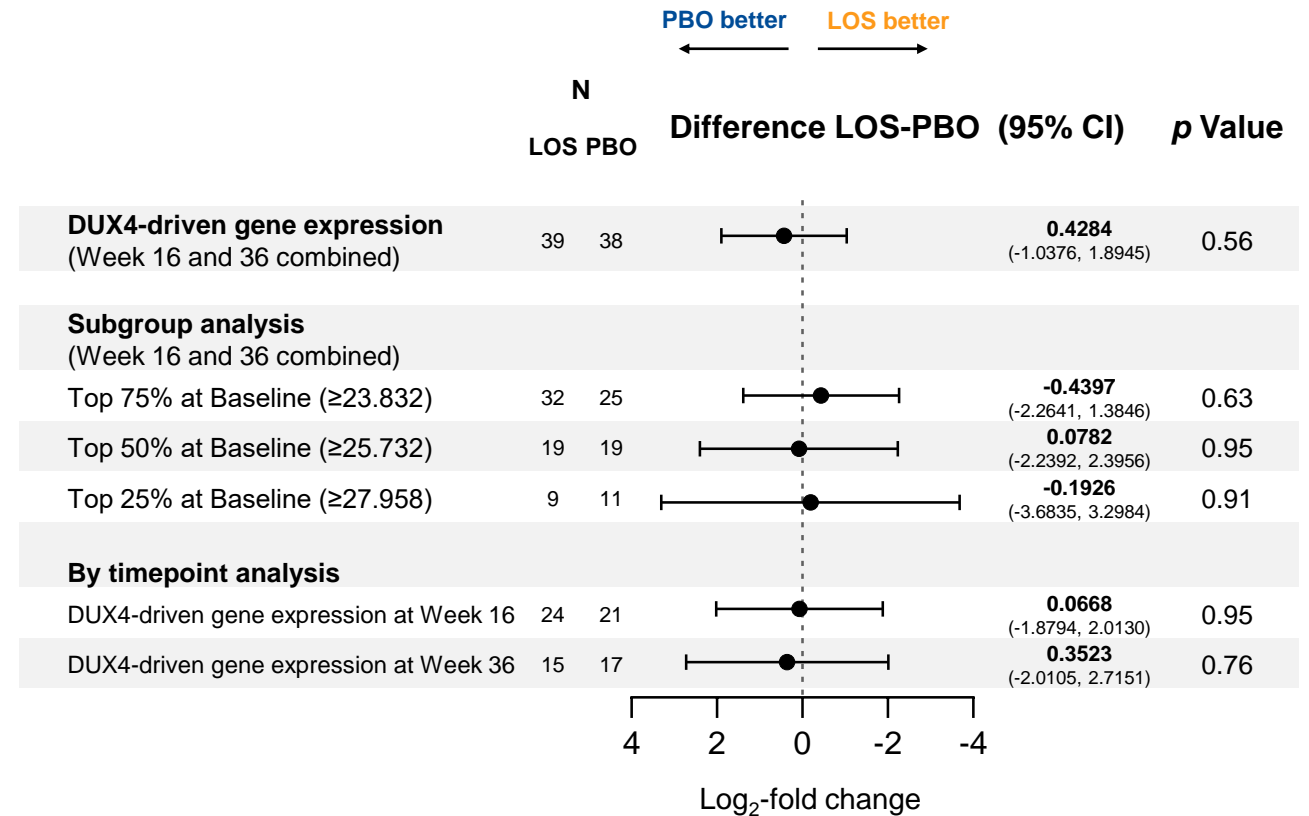
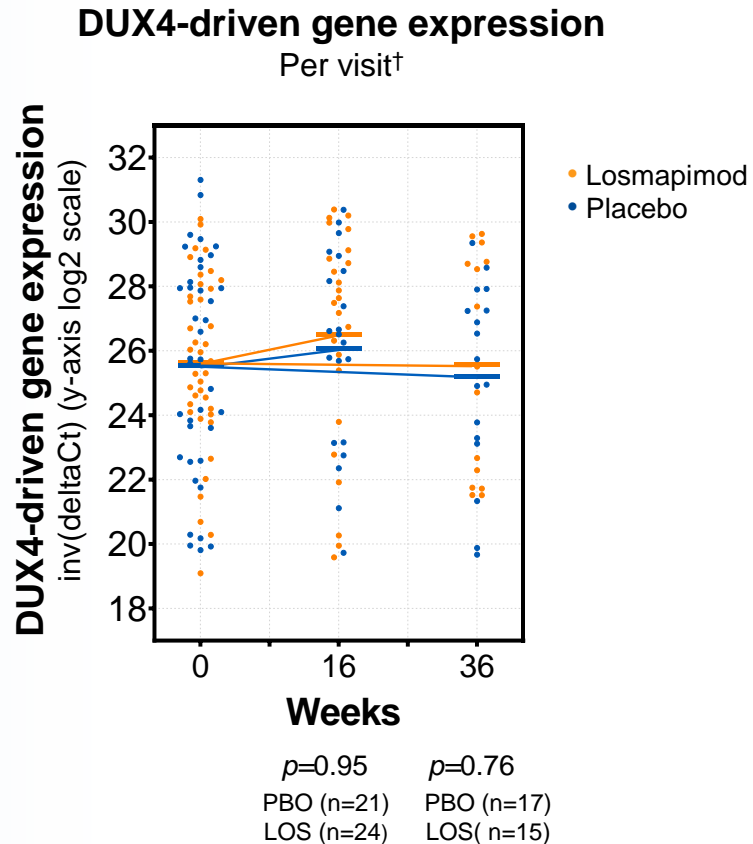


- ✓ Structure
- ✓ Patient Outcome
- ✓ Function

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

Did not observe changes in either group during 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



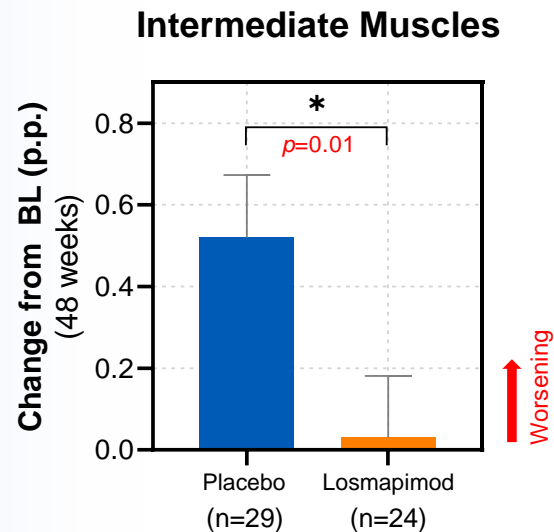
Limitations of DUX4 Experimental Biomarker

- 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 heterogeneous 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

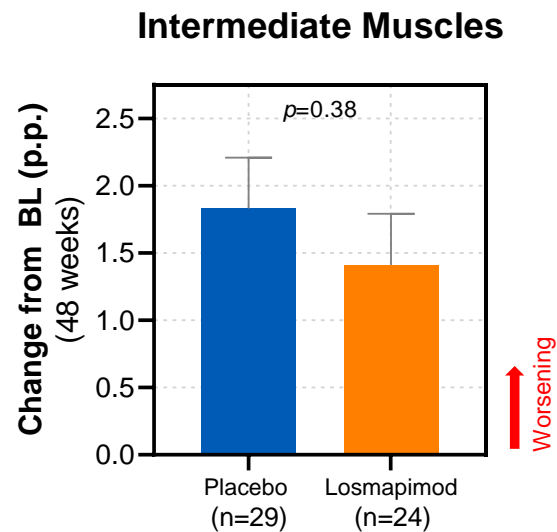
ReDUX4 Showed Downstream Benefits of DUX4 Reduction

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

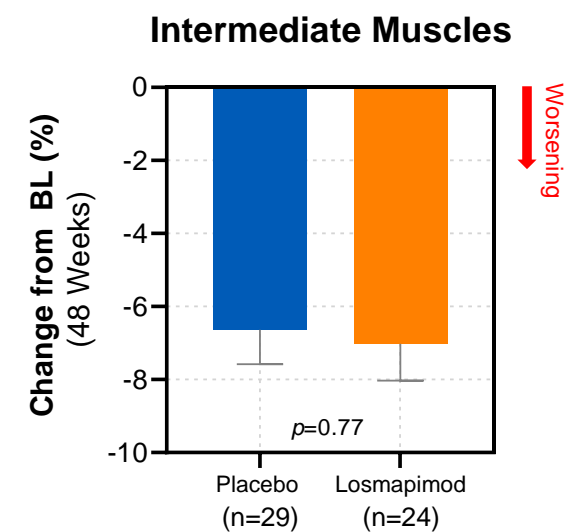
Muscle Fat Infiltration (MFI)



Muscle Fat Fraction (MFF)



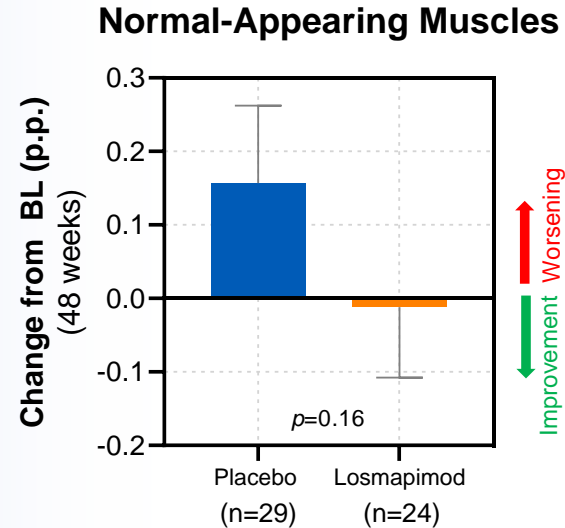
Lean Muscle Volume (LMV)



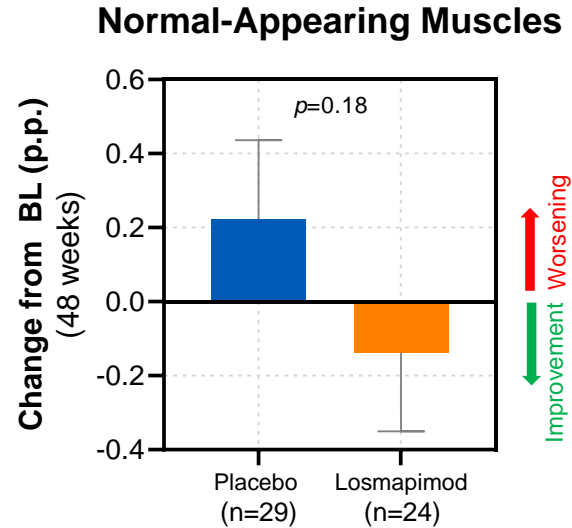
*Please see poster: "Quantitative Muscle Analysis in FSHD Using Whole-Body MRI: Composite Muscle Measurements for Cross-Sectional Analysis".

Normal-Appearing Muscles Appear Preserved With Losmapimod vs Placebo*

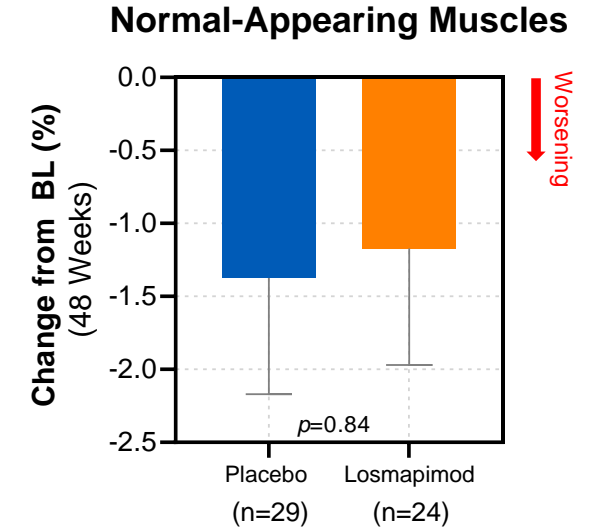
Muscle Fat Infiltration (MFI)



Muscle Fat Fraction (MFF)

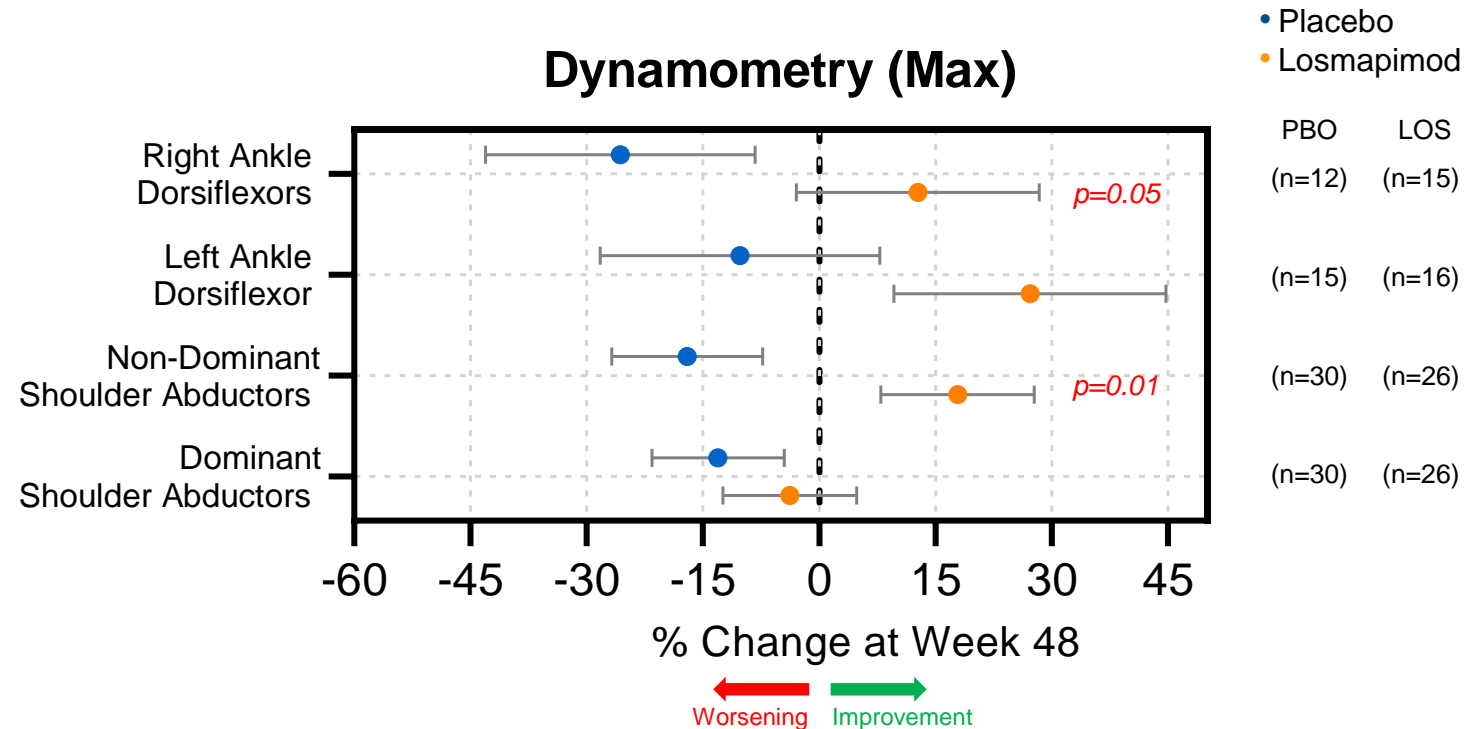


Lean Muscle Volume (LMV)



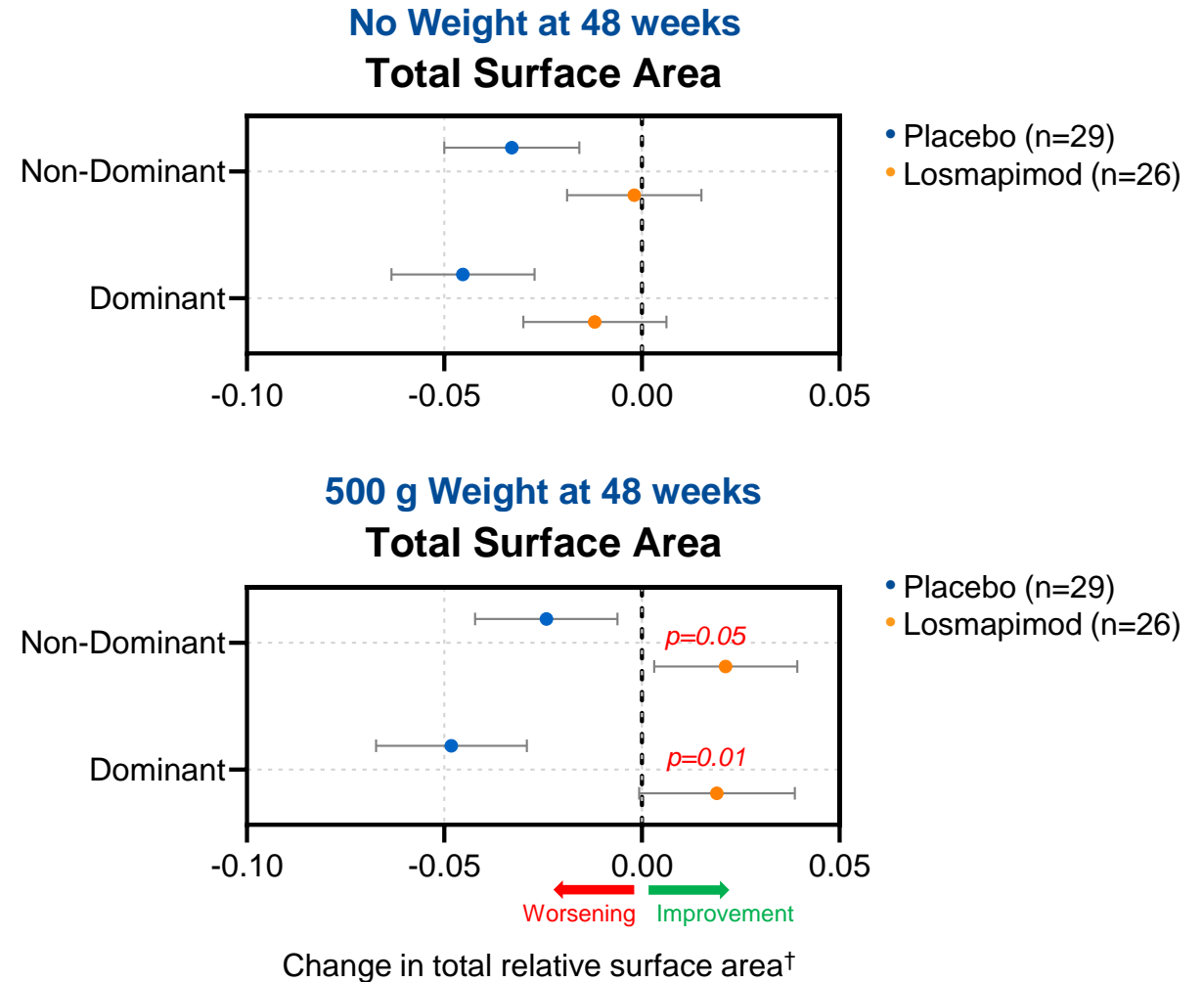
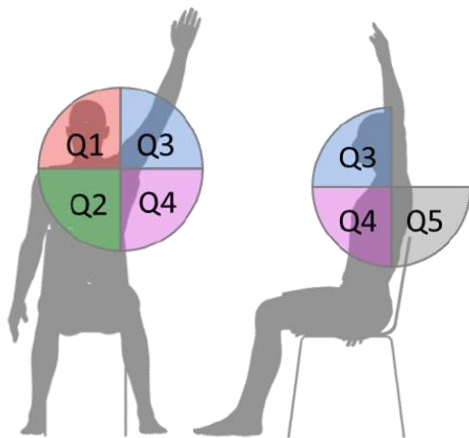
Losmapimod Showed Improved Muscle Strength vs Placebo*

- 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

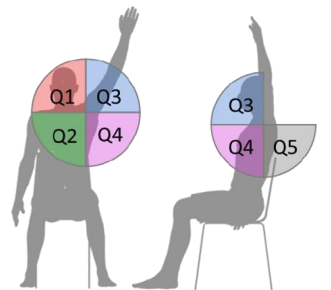
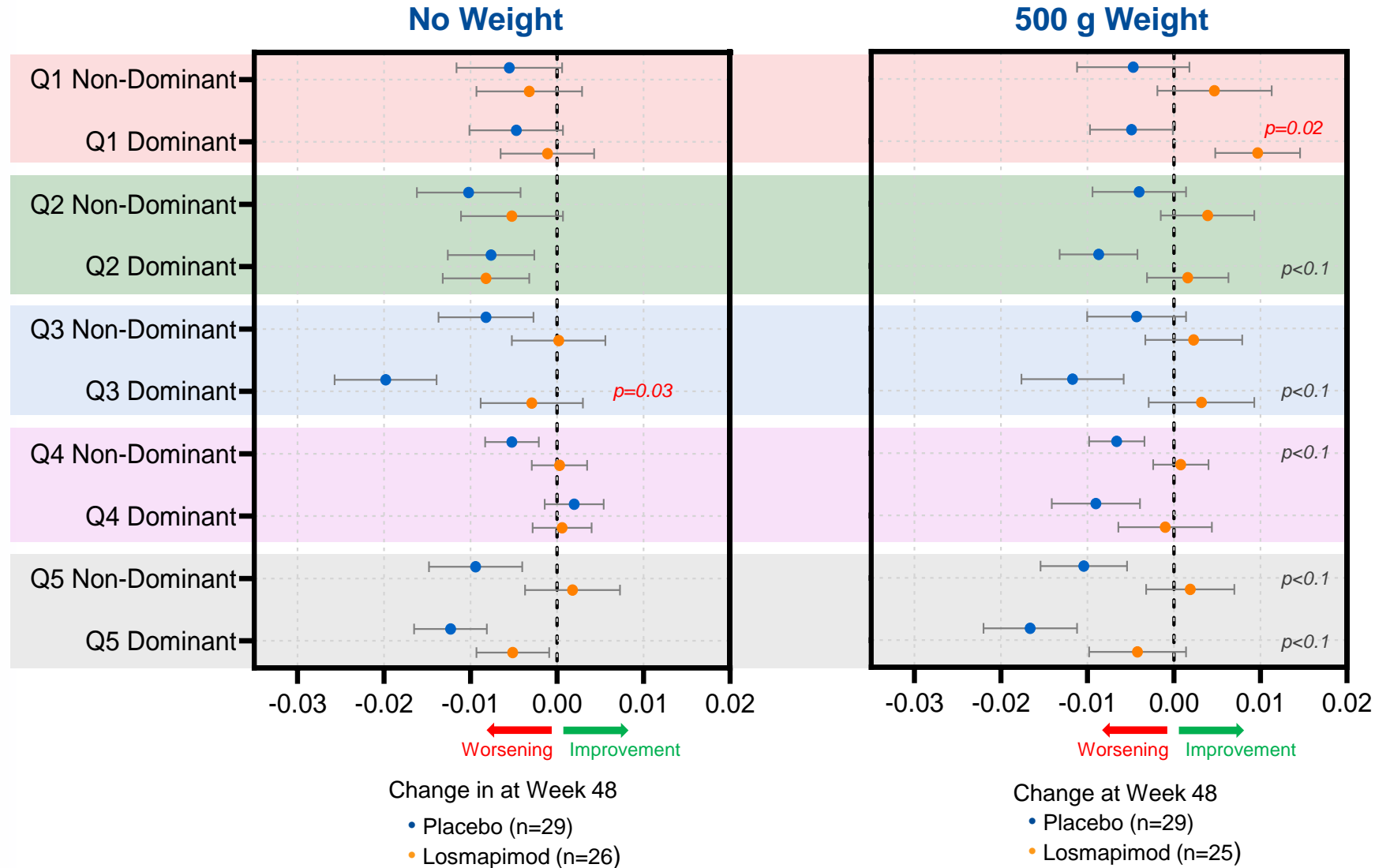


Losmapimod Showed Significant Improvement in Total Surface Area by Reachable Workspace*

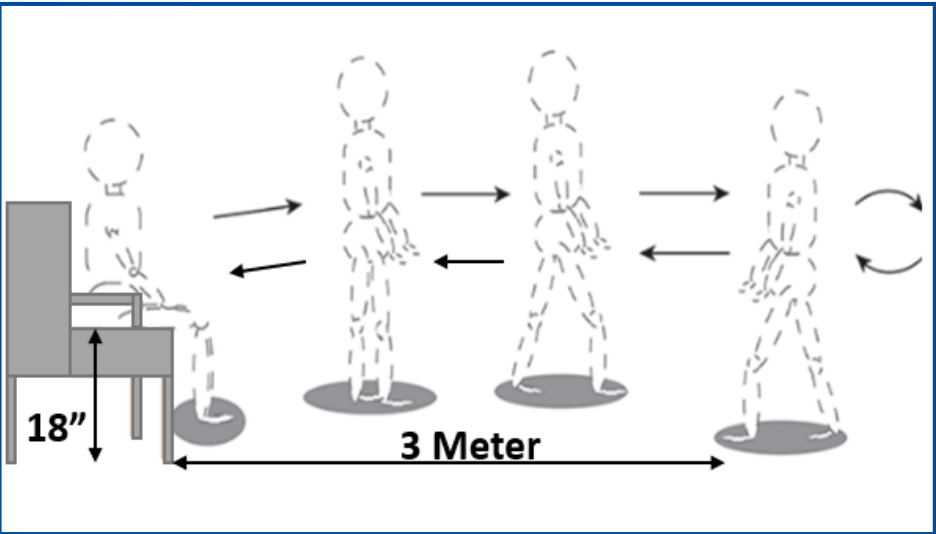
- Placebo group lost about 2% to 4% of Total Surface Area (with and without weight)
- Losmapimod group showed trends of slower disease progression as well as improvements of up to 1.5% in surface area with weight



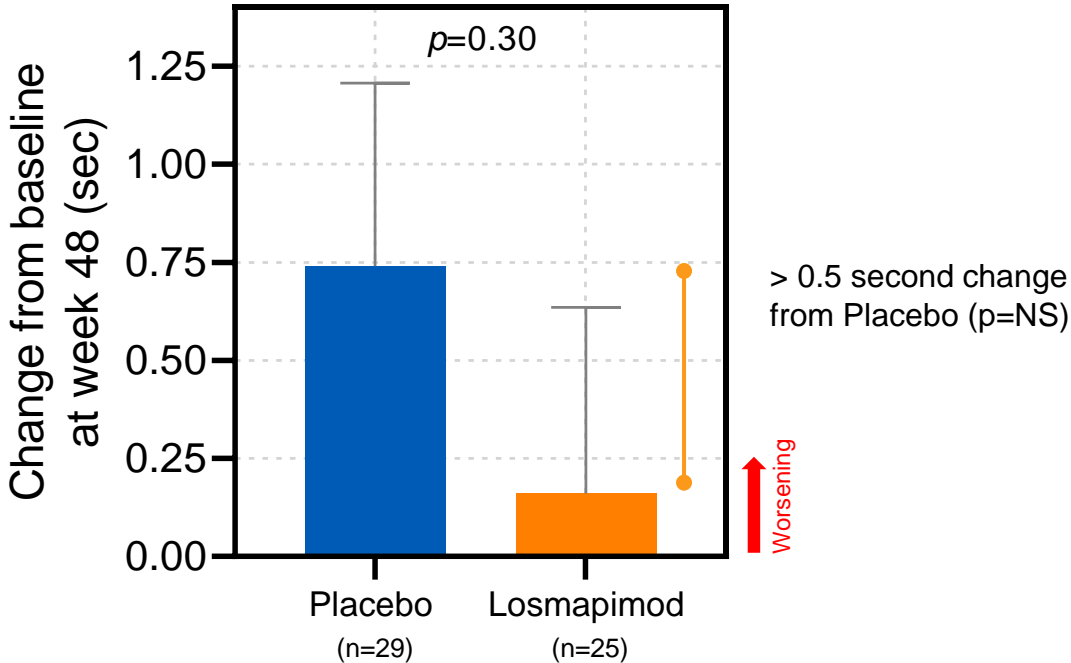
Improvement in Total Surface Area Was Seen in Trends of Slowed Disease Progression and Improvement on Multiple RWS Metrics*



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



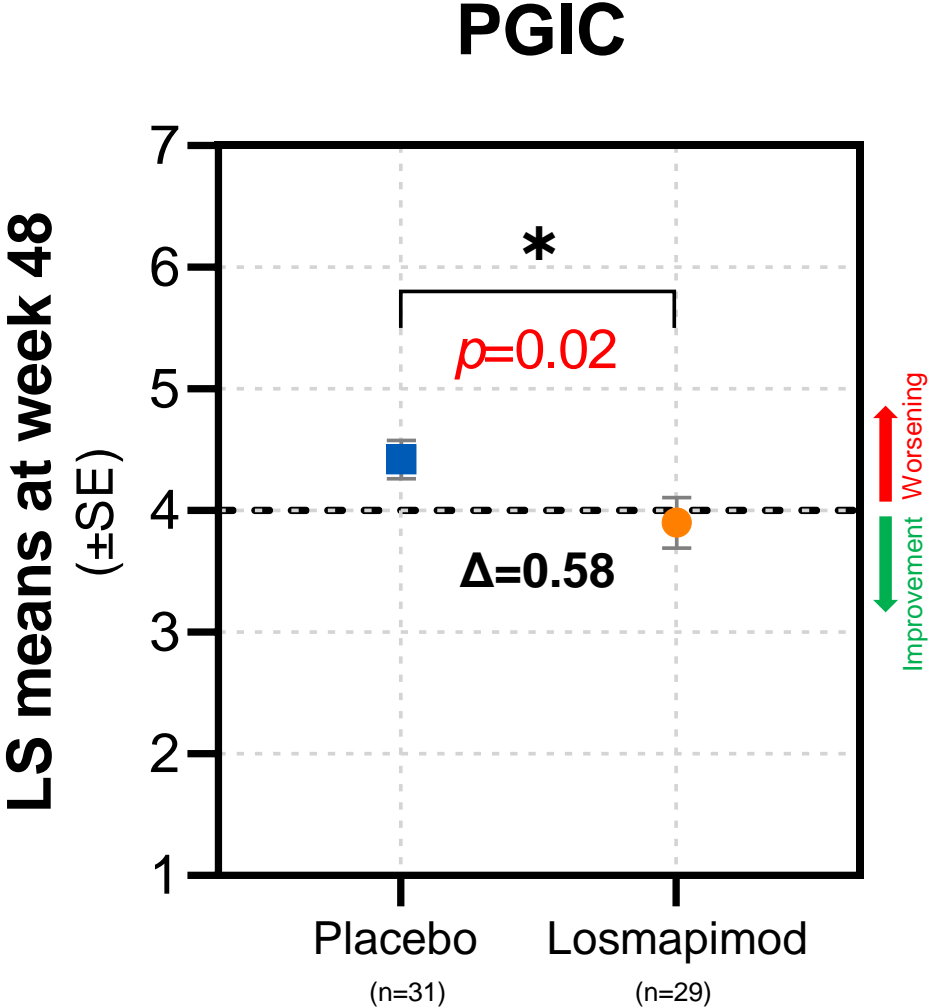
Average Completion Time



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

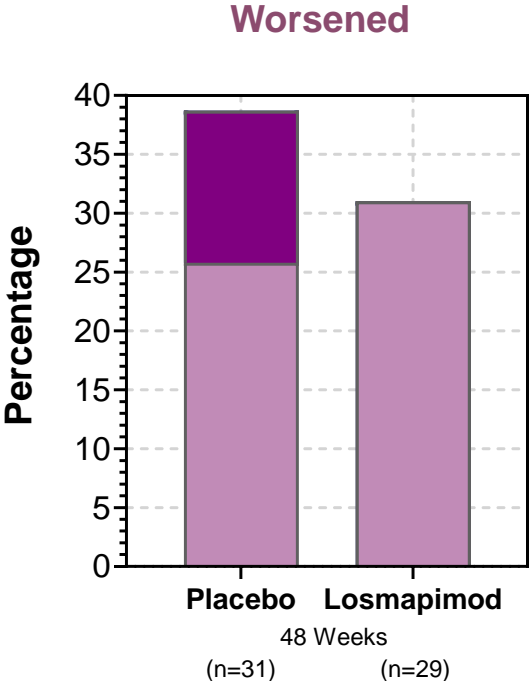
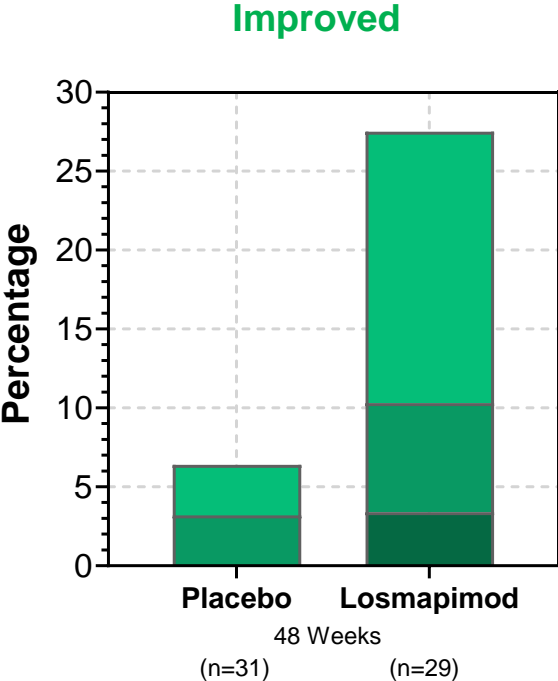


Fewer Participants Reported Worsening on Losmapimod vs Placebo*

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

▲ More study participants reported improvement

▼ Fewer study participants reported worsening



PGIC Rating:

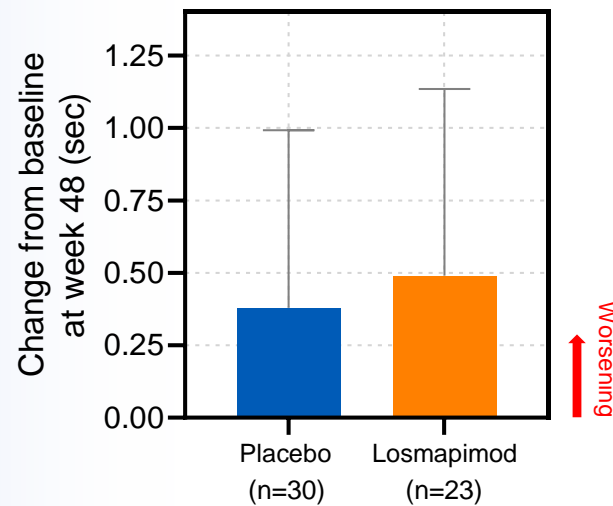
- 7: Very much worse
- 6: Much worse
- 5: Minimally worse
- 4: No Change
- 3: Minimally improved
- 2: Much improved
- 1: Very much improved

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

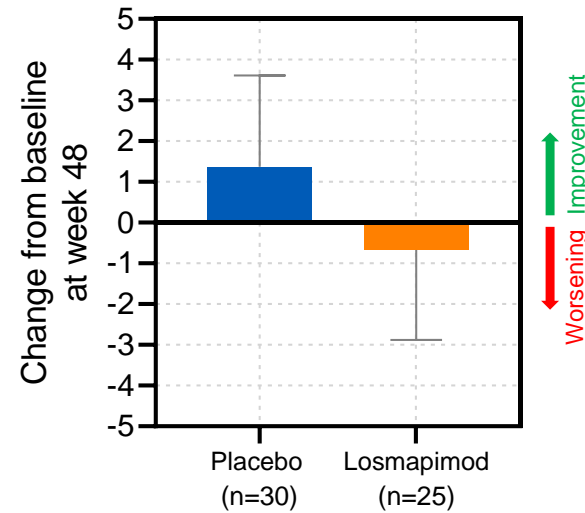
Average Completion Time



LS means + SE

Motor Function Measure

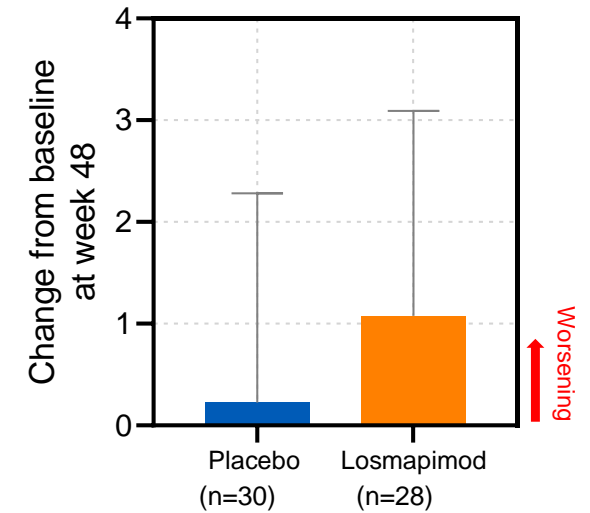
MFM Domain 1 Score



LS means + SE

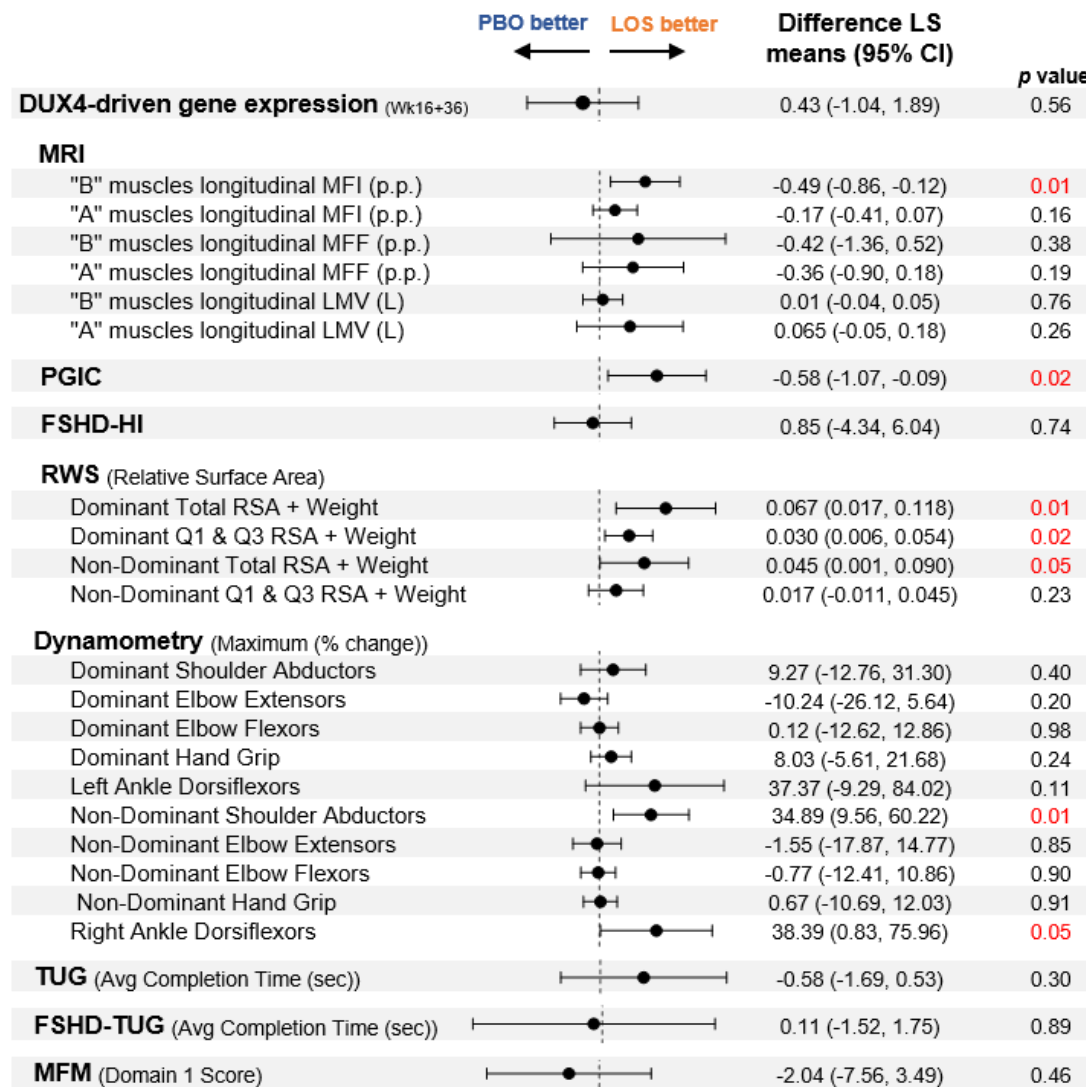
FSHD Health Index (FSHD-HI)

Total FSHD-HI Score



LS means + SE

ReDUX4 Demonstrated Clinically Meaningful Impacts on Measures of FSHD Disease Progression*



- ✓ Structure
- ✓ Patient Outcome
- ✓ Function

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 dose¹

Summary and Next Steps

- **Positive benefit/risk supports losmapimod's potential to be a transformative therapy**
- **Fulcrum is committed to advancing losmapimod for the treatment of FSHD**
- **Planning to meet with health authorities, including the U.S. FDA, in 2H 2021**



Fulcrum
Therapeutics

Q&A

Bryan E. Stuart, President and Chief Executive Officer

Chris Morabito, MD Chief Medical Officer

Judith Dunn, Ph.D., President, Research and Development

Chris Moxham, Ph.D., Chief Scientific Officer

Michelle Mellion, MD, Senior Medical Director