Fulcrum Therapeutics

ReDUX4
Assessing losmapimod in FSHD

A phase 2, randomized, double-blind, placebo-controlled, 48-Week study of the efficacy and safety of losmapimod in subjects with FSHD: ReDUX4

Christopher Morabito, MD, Chief Medical Officer, Fulcrum Therapeutics

Disclosure Statement

- Dr. Christopher Morabito is a full-time employee of Fulcrum Therapeutics.

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

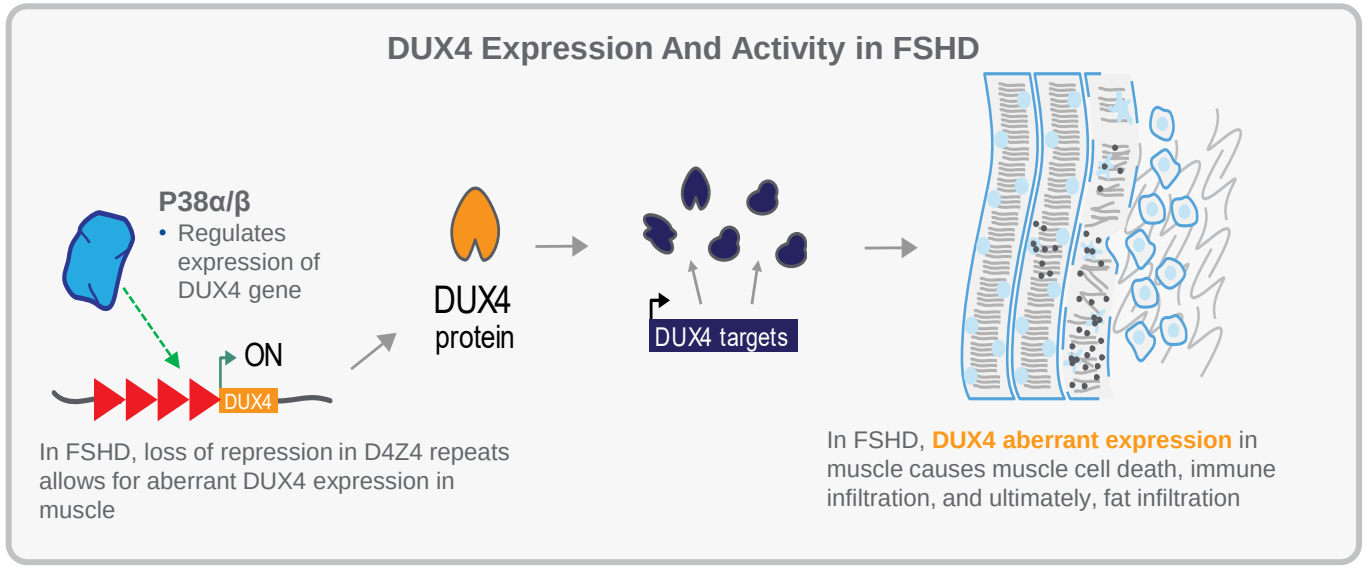
MUSCLE PATHOLOGY leads to accumulation of disability

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

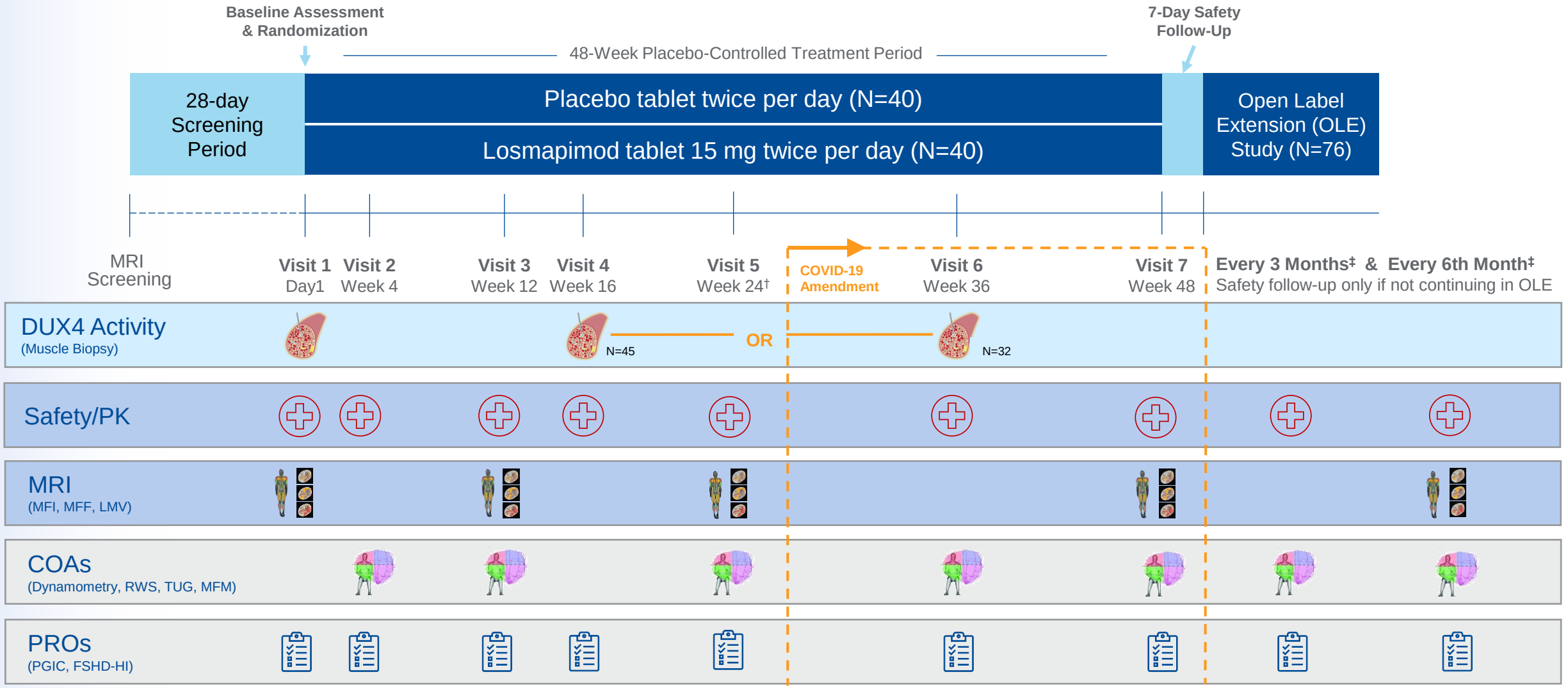
Losmapimod, a selective p38 MAPK inhibitor, blocks DUX4-driven gene expression

FulcrumSeek™ identified losmapimod as drug candidate to treat root cause of FSHD

- Highly selective p38α/β MAPK inhibitor
- Reduced DUX4 expression in preclinical studies
  - Aberrant expression DUX4 gene is known root cause of FSHD
- Generally well-tolerated, with clinical experience in >3,600 people



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.

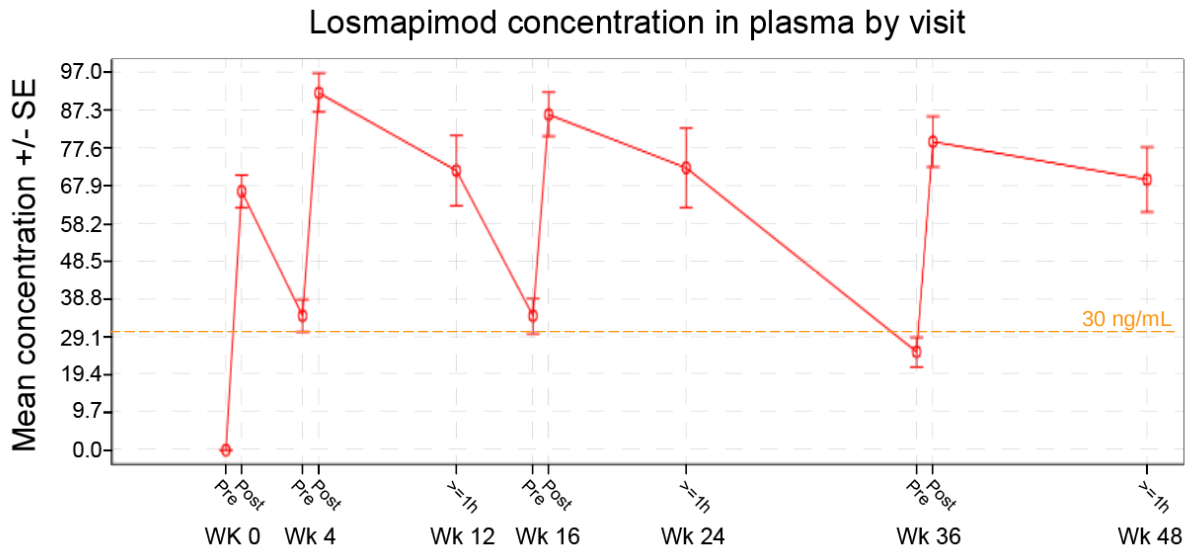
ReDUX4 Study Participant Randomization Was Well Balanced

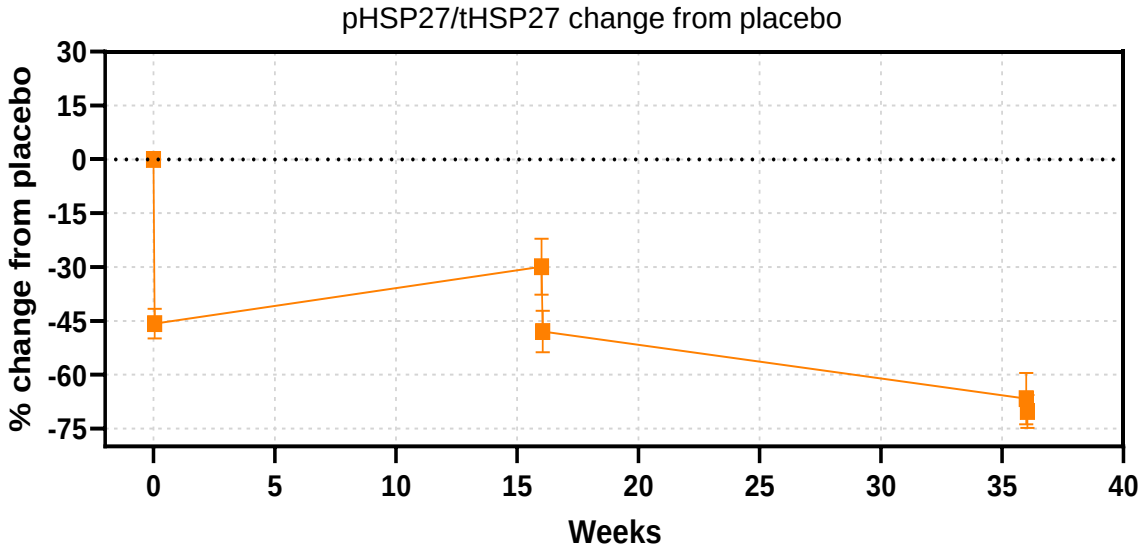
		Placebo BID (N=40)	Losmapimod 15 mg BID (N=40)
Completed		38 (95%)	39 (97.5%)
Discontinued*		2 (5.0%)	1 (2.5%)
DEMOGRAPHICS			
Age (years)	N	40	40
	Mean (SD)	45.7 (+/- 12.69)	45.7 (+/- 12.44)
Race n (%)	White	39 (97.5)	31 (77.5)
	Asian	0	5 (12.5)
	Other	0	1 (2.5)
	Not Applicable	1 (2.5)	3 (7.5)
Ethnicity 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 (+/- 3.914)	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.

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}

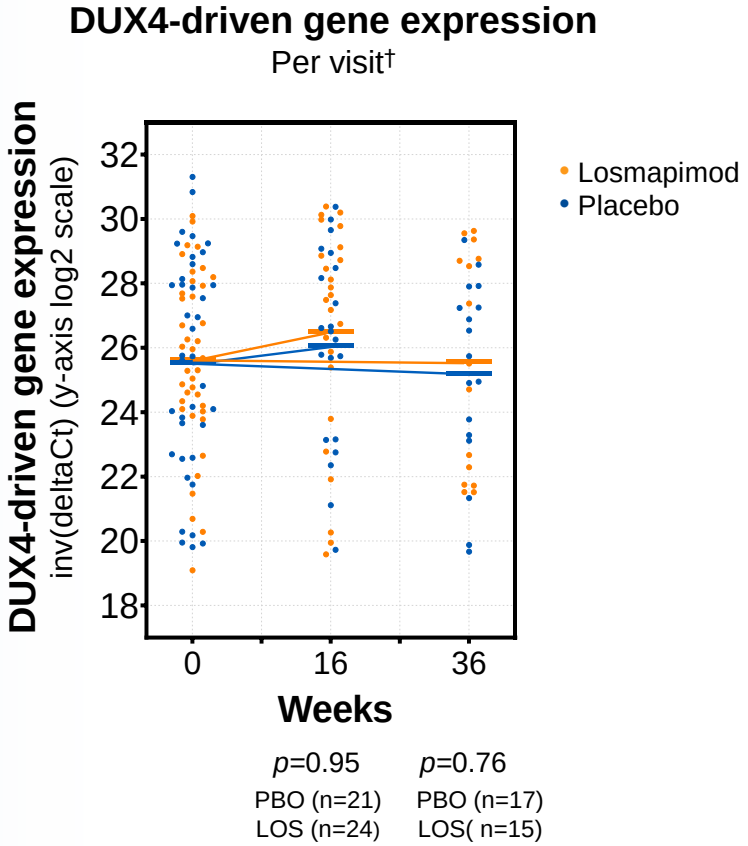


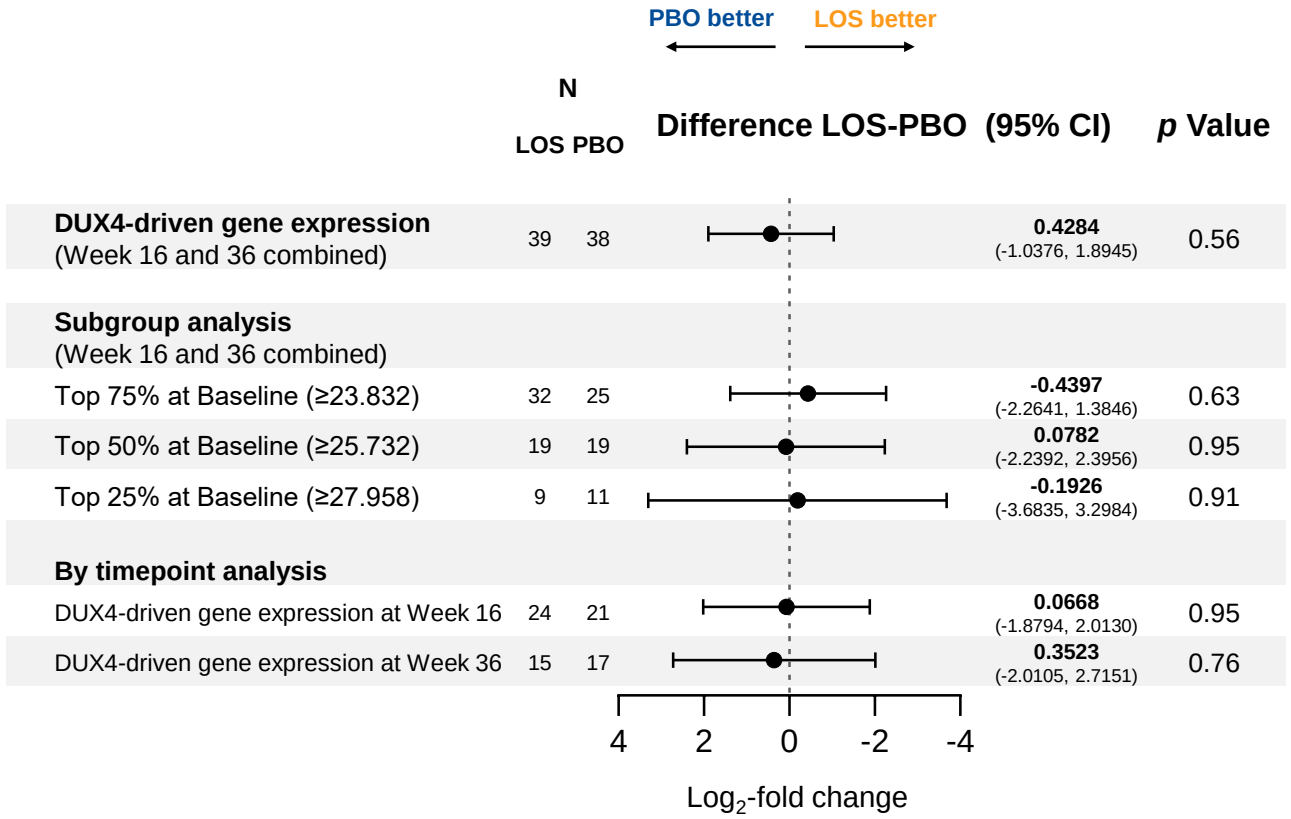


Primary Endpoint: Reduction of DUX4-Driven Gene Expression in Muscle Biopsies

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

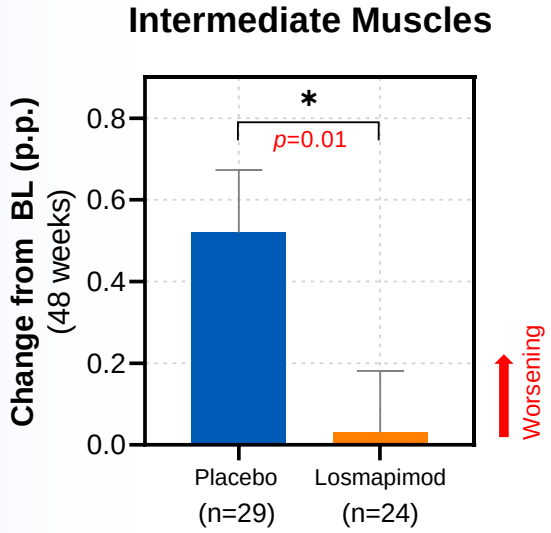




*Primary analysis at 16 or 36 weeks. †Y-axis in log2 scale. Lines represent mean.

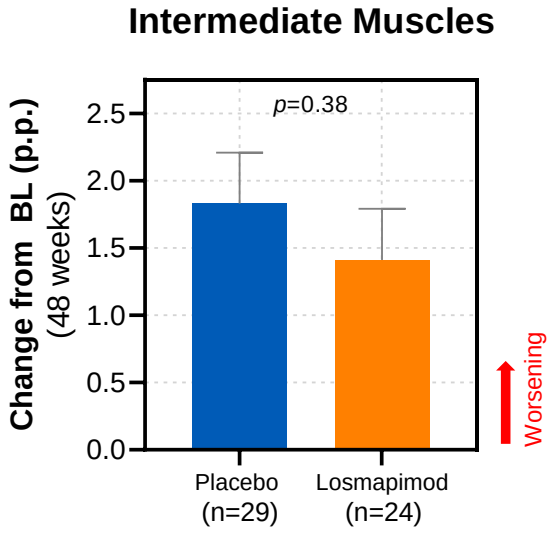
Losmapimod Treated Participants Showed Significantly Less Muscle Fat Infiltration (MFI) vs Placebo in Intermediate Muscles*

Muscle Fat Infiltration (MFI)



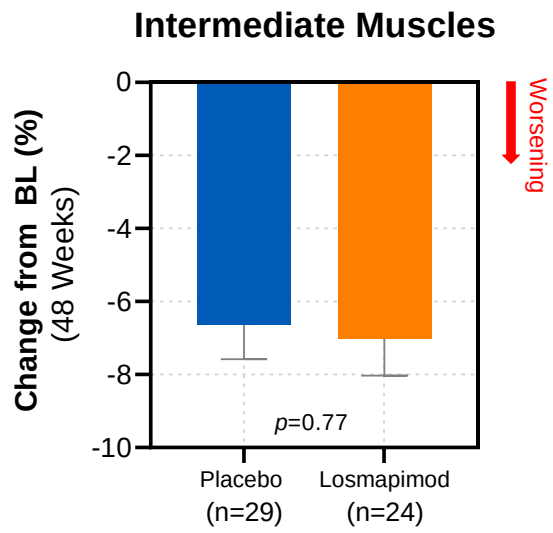
LS means + SE

Muscle Fat Fraction (MFF)



LS means + SE

Lean Muscle Volume (LMV)



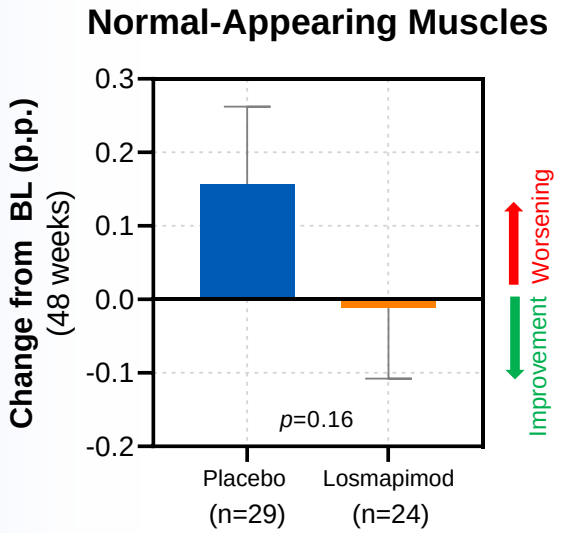
LS means + SE

*Please see poster:
Widholm P, et al. "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.

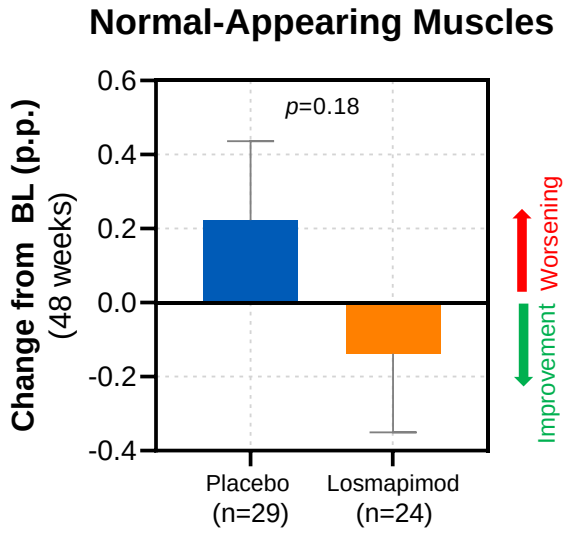
Normal-Appearing Muscles Appear Preserved With Losmapimod vs Placebo*

Muscle Fat Infiltration (MFI)



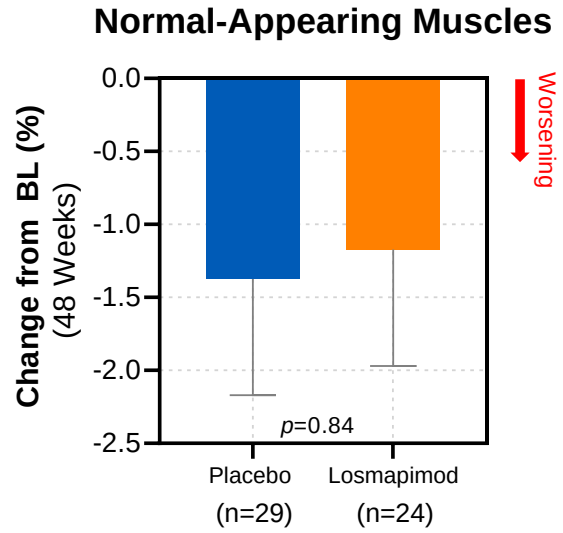
LS means + SE

Muscle Fat Fraction (MFF)



LS means + SE

Lean Muscle Volume (LMV)

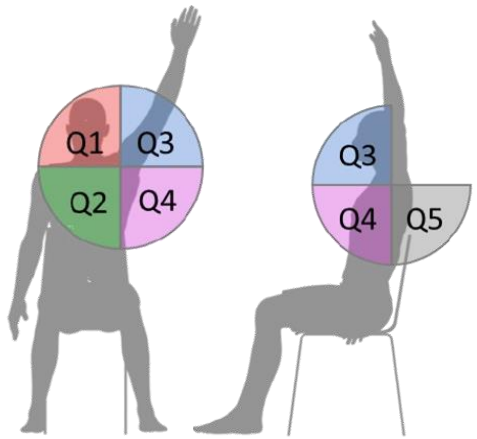


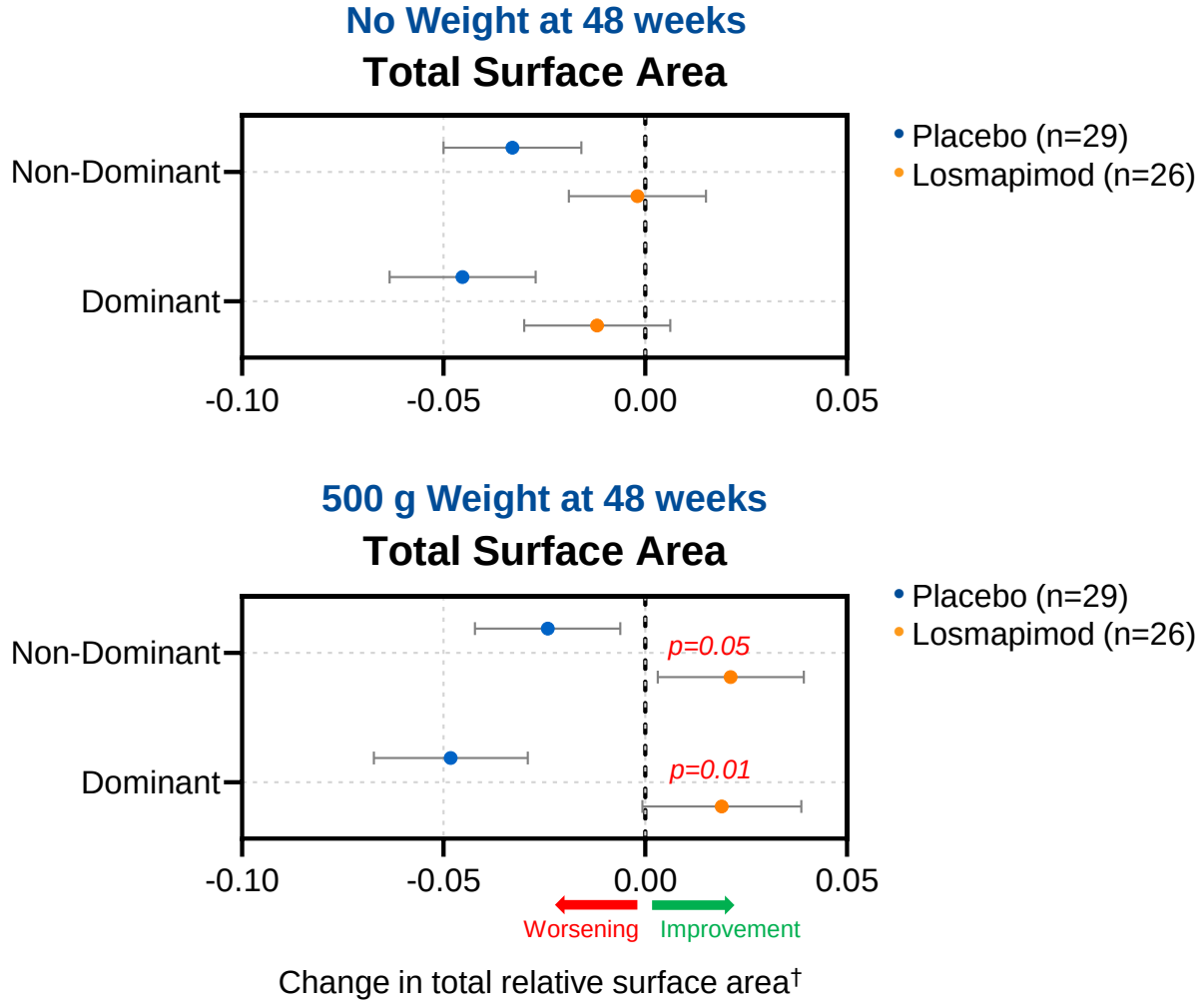
LS means + SE

*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%

Losmapimod Showed Significant Improvement 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*

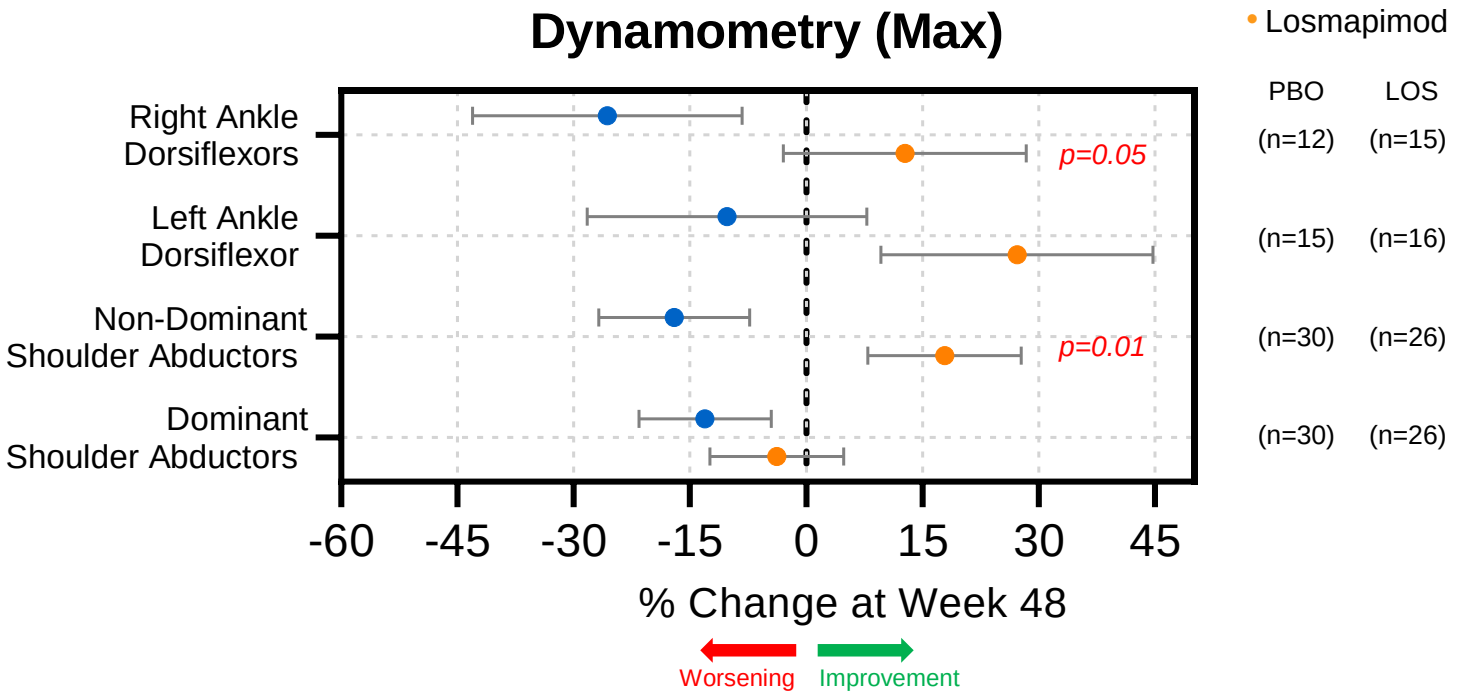




*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).
†Total relative area for the 5 quadrants used to calculate the approximate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

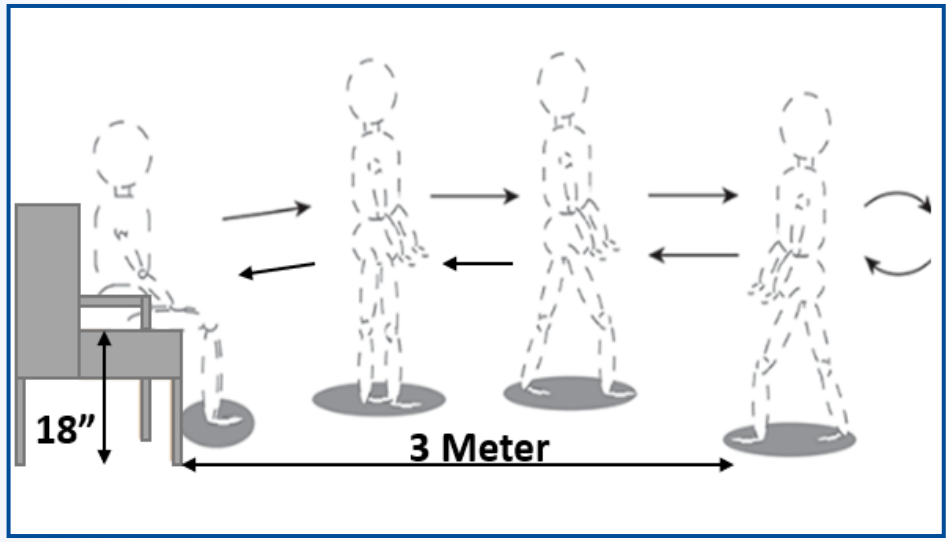
Losmapimod Showed Improved Muscle Strength vs Placebo*

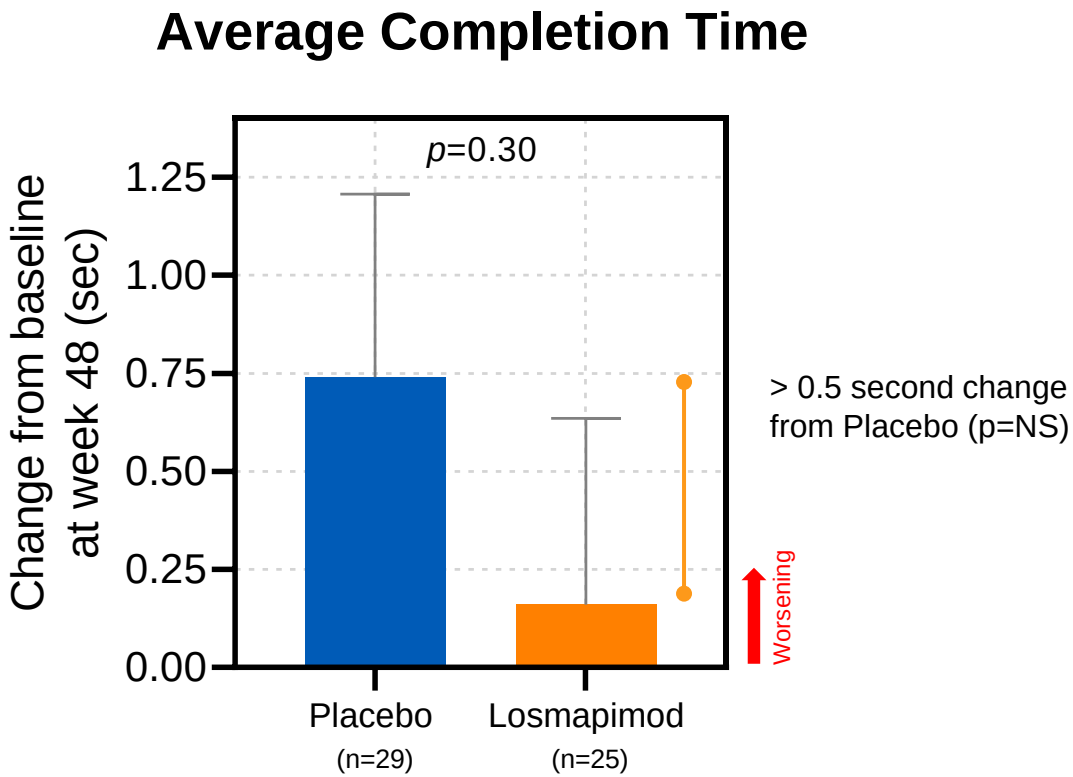
- Placebo group lost about 15% of shoulder and ankle dorsiflexors strength after 48 weeks
- Losmapimod group
  - Showed trends of slower progression (< 4% decline)
  - Improvements (12% to 27%) in the strength of non-dominant shoulder abductors and right ankle dorsiflexors compared to the placebo group



*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*



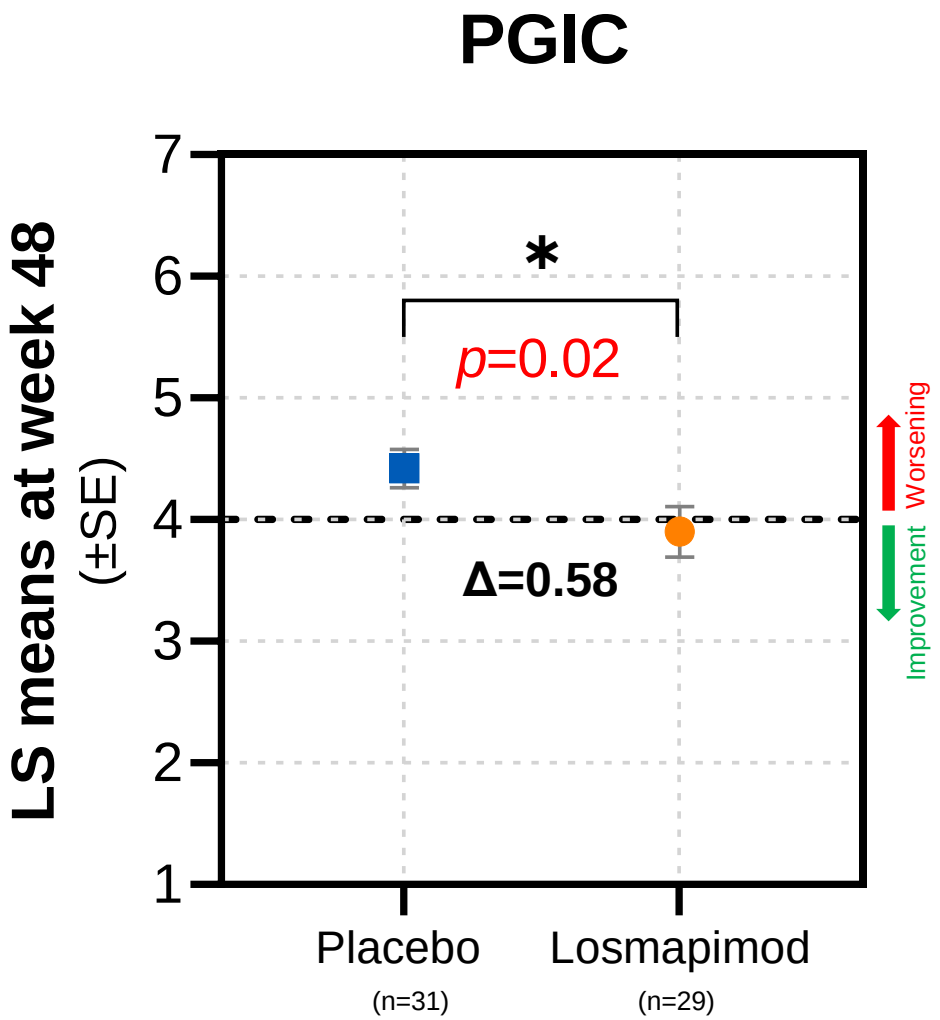


*Nominally statistically significant values (p (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint). LS means ± SE.

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":*

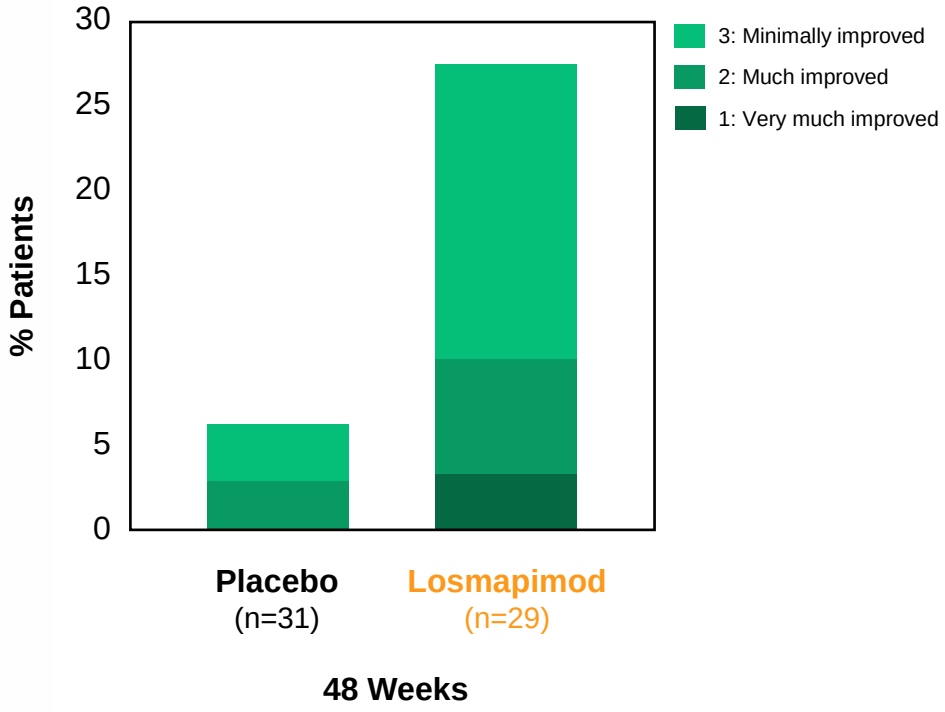
Scores	PGIC
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Worse
6	Much worse
7	Very much worse



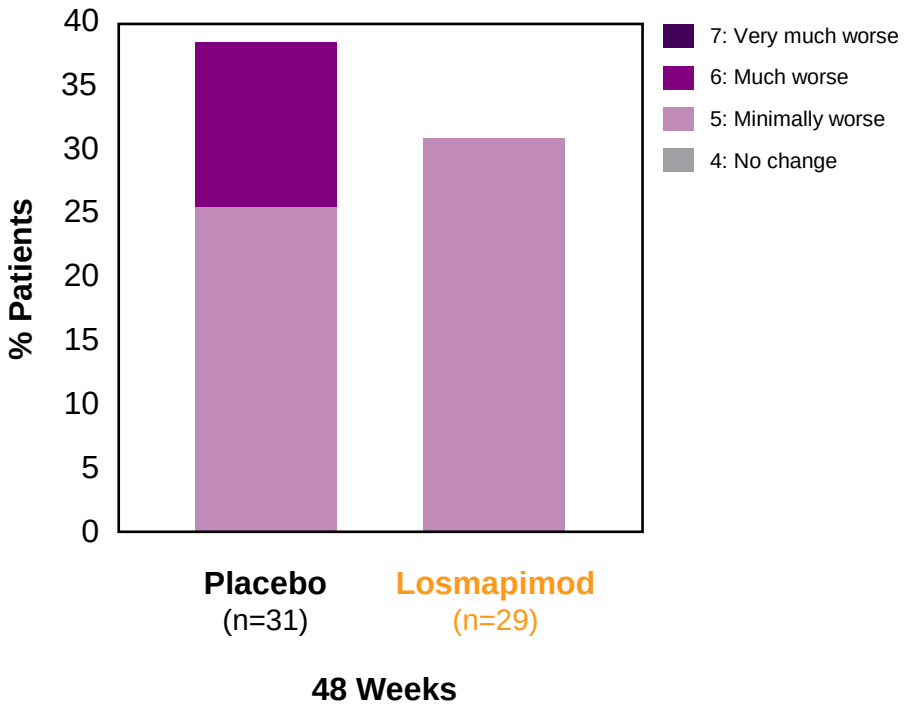
*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint).

Losmapimod-treated Patients Reported Feeling Better

Four times as many losmapimod-treated patients felt better vs placebo



20% fewer losmapimod-treated patients felt worse vs placebo



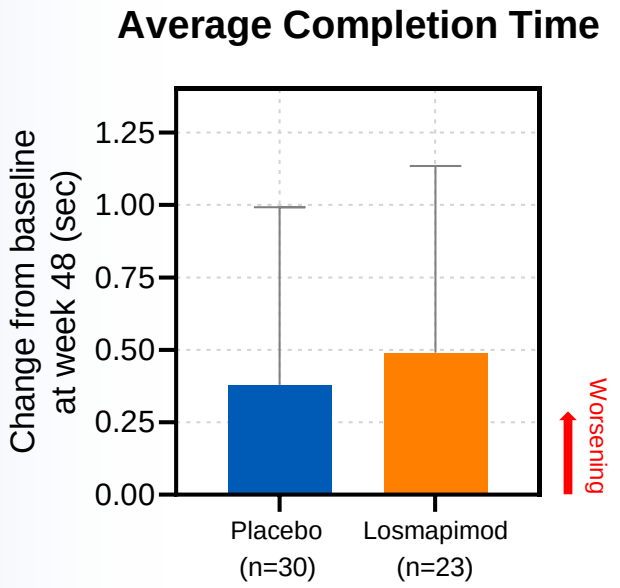
Patients' Global Impression of Change (PGIC)

Data from ReDUX4 trial

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

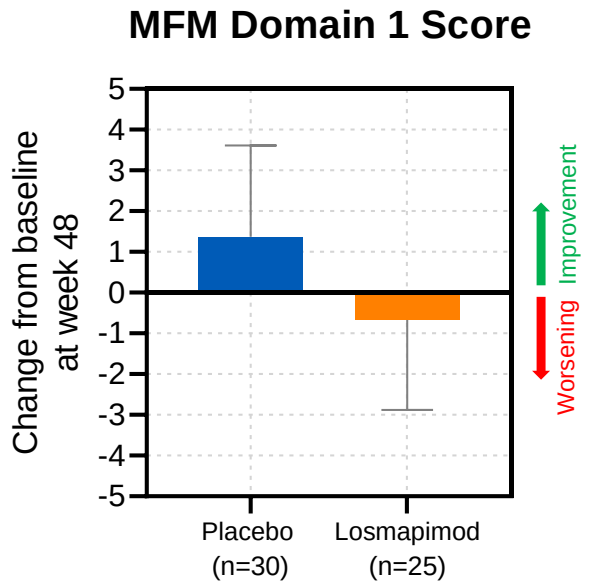
The placebo results suggest that these measures did not detect progression

FSHD-TUG



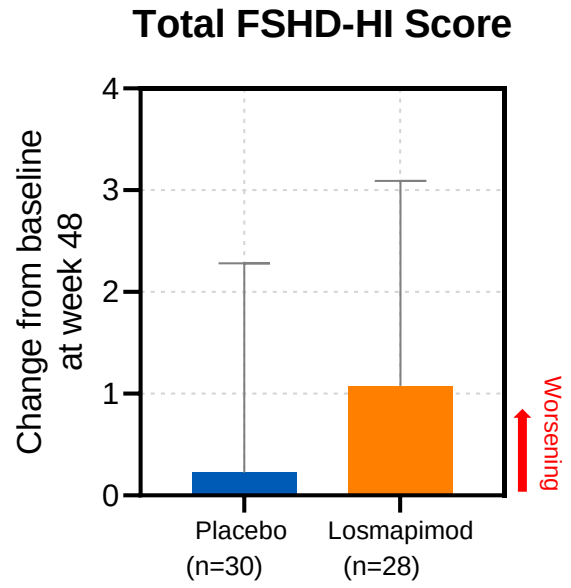
LS means + SE

Motor Function Measure



LS means + SE

FSHD Health Index (FSHD-HI)



LS means + SE

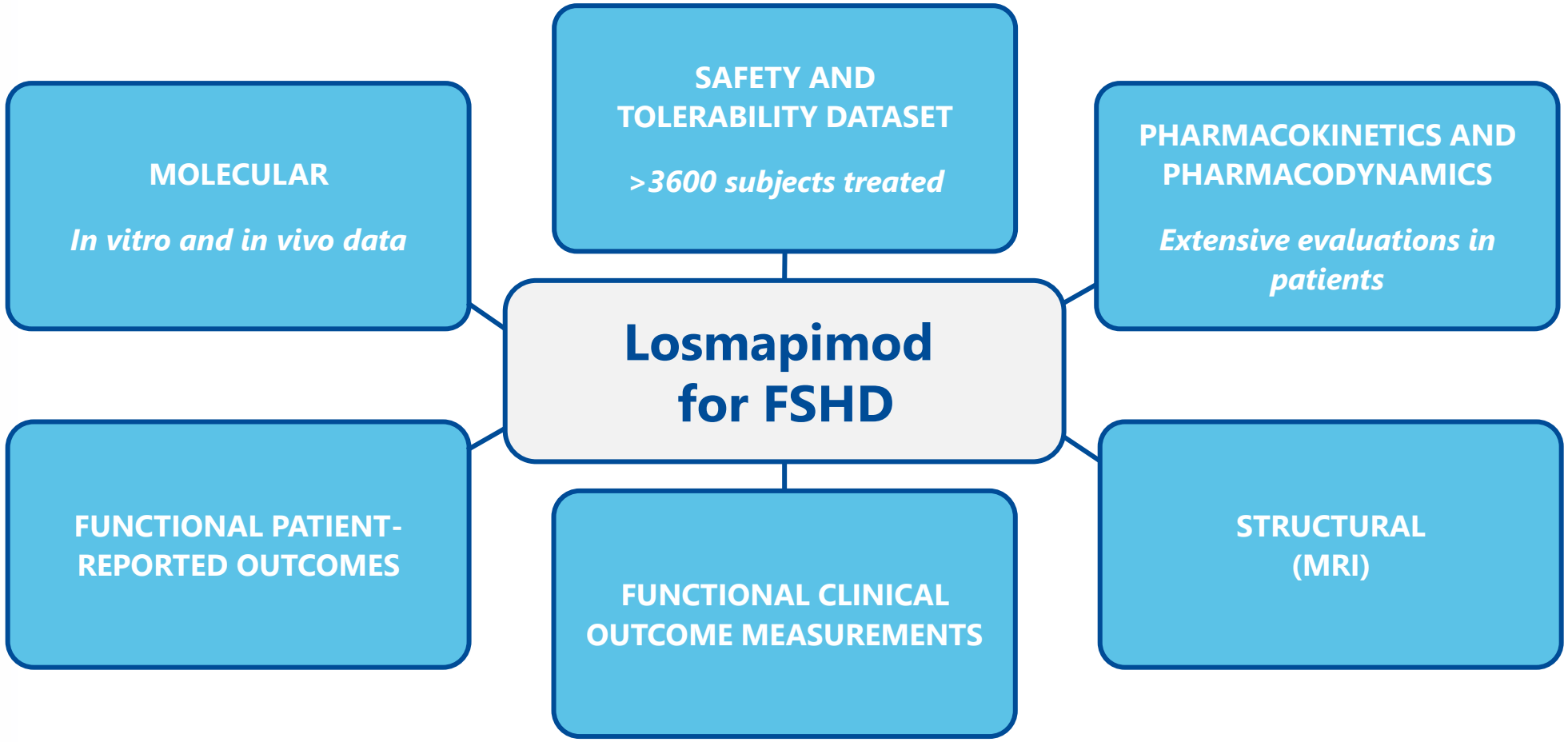
*Nominally statistically significant values (p≤0.05) are reported for secondary and exploratory endpoints. ReDUX4 was only powered to detect a hypothesized difference in the expression of DUX4-driven gene transcripts (primary endpoint). Mixed-Effects Model for Repeated Measures (MMRM) analysis. FSHD-TUG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

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 (ECG) were observed
- Losmapimod has shown favorable safety and tolerability in > 3600 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.

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



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 in FSHD	Patient-reported outcomes (PGIC and Neuro-QoL) are secondary endpoints

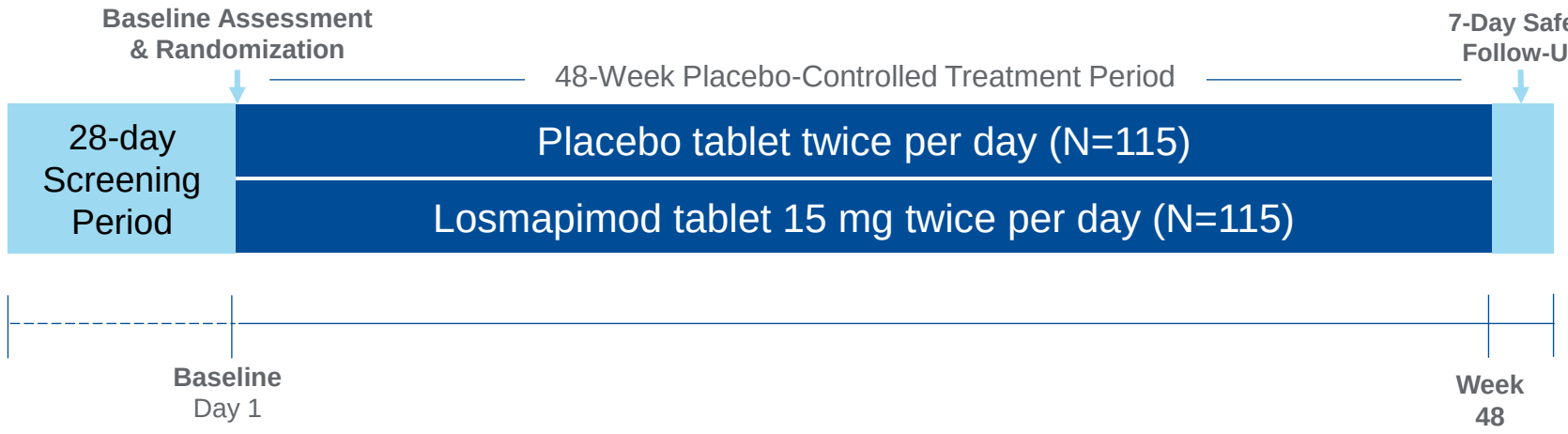
REACH: A Phase 3 Trial of Losmapimod in FSHD

Aligned with regulators on key aspects of trial design; plan to initiate REACH in Q2 2022

Study Population

Subjects with FSHD Aged 18 – 65

Study Design



Study Endpoints

Primary	Secondary	Healthcare Utilization
RWS quantification of total relative surface area with 500g wrist weight in dominant arm	▪ MFI ▪ Neuro-QoL Upper Extremity ▪ PGIC ▪ Safety and tolerability	▪ Healthcare utilization questionnaire ▪ EQ-5D questionnaire

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
- Jeffrey Statland, MD. KUMC
- 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

- Jay Han, MD, and Maya Hatch, PhD at UC Irvine

Principal Investigator

Rabi Tawil, MD. URMC

Site Investigators

- Alan Pestronk, MD. WUSTL
- Angela Genge, MD. Montreal Neurological Inst.
- David Reyes Leiva, MD. HSCSP
- Doris Leung, MD, PhD. KKI
- Hanns Lochmüller, MD, PhD. CHEO
- Jeffrey Statland, MD. KUMC
- Johanna Hamel, MD. URMC
- Jordi Diaz Manera, MD, PhD. HSCSP
- Jorge Alonso-Perez, MD. HSCSP
- Lawrence Hayward, MD, PhD. UMMS
- Leo Wang, MD, PhD. UW Medicine
- Namita Goyal, MD. UCI
- 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 GIVING THE WORLD A HELPING HAND
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

ReDUX4
Assessing losmapimod in FSHD

Fulcrum Therapeutics, Inc.
26 Landsdowne Street
Cambridge, MA, USA 02139
info@fulcrumtx.com

Thank you!