

Annualized Rates of Change from A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 48-Week Study of Losmapimod in Subjects with FSHD: ReDUX4

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Fulcrum
Therapeutics



Disclosures

Consultant for Fulcrum Therapeutics, Arrowhead pharma, Ipsen Pharma, miRecule, MT Pharma and Roche Pharma; Advisory board: Fulcrum Therapeutics, Avidity Bio and Dyne Therapeutics

FSHD is a Relentlessly Progressive Disease Leading to Significant Disability that Impacts Quality of Life

Symptoms and Progression



Facial weakness



Scapular winging



Impaired ability to raise arms caused by scapular elevation



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

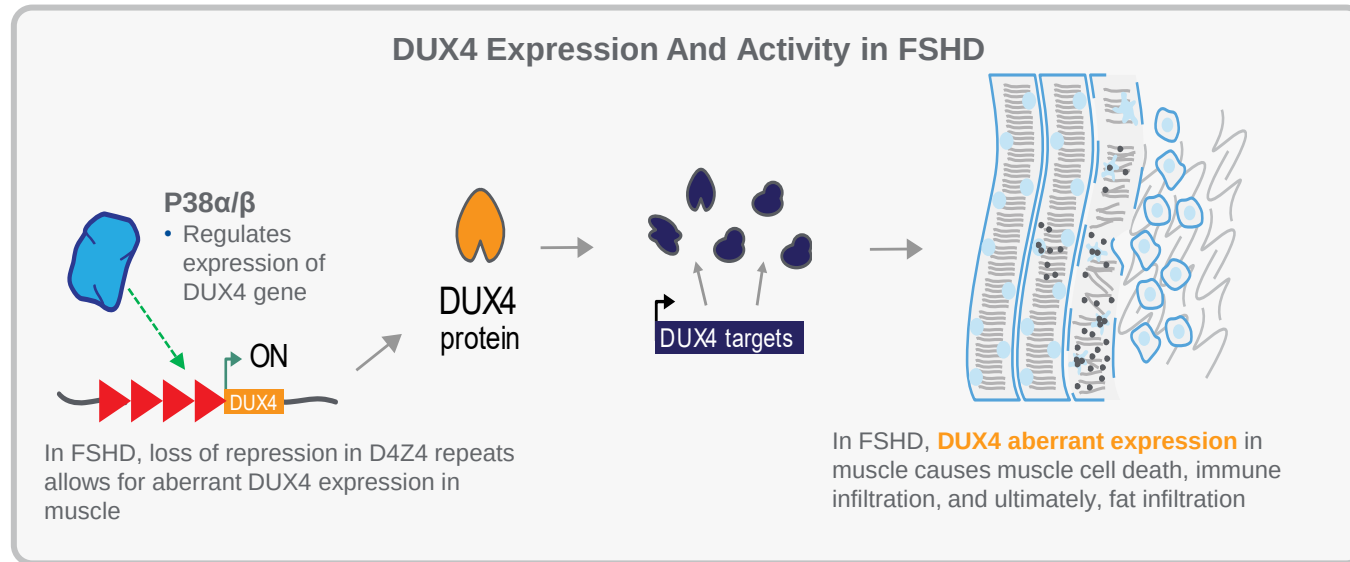


Wheelchair dependence

- FSHD initially affects facial and scapular muscles, eventually progressing to the arms, trunk and legs
- **MUSCLE PATHOLOGY** leads to accumulation of disability
- Progression ultimately leads to significant **impairment of upper extremity function** and mobility, and many patients are unable to work or live independently

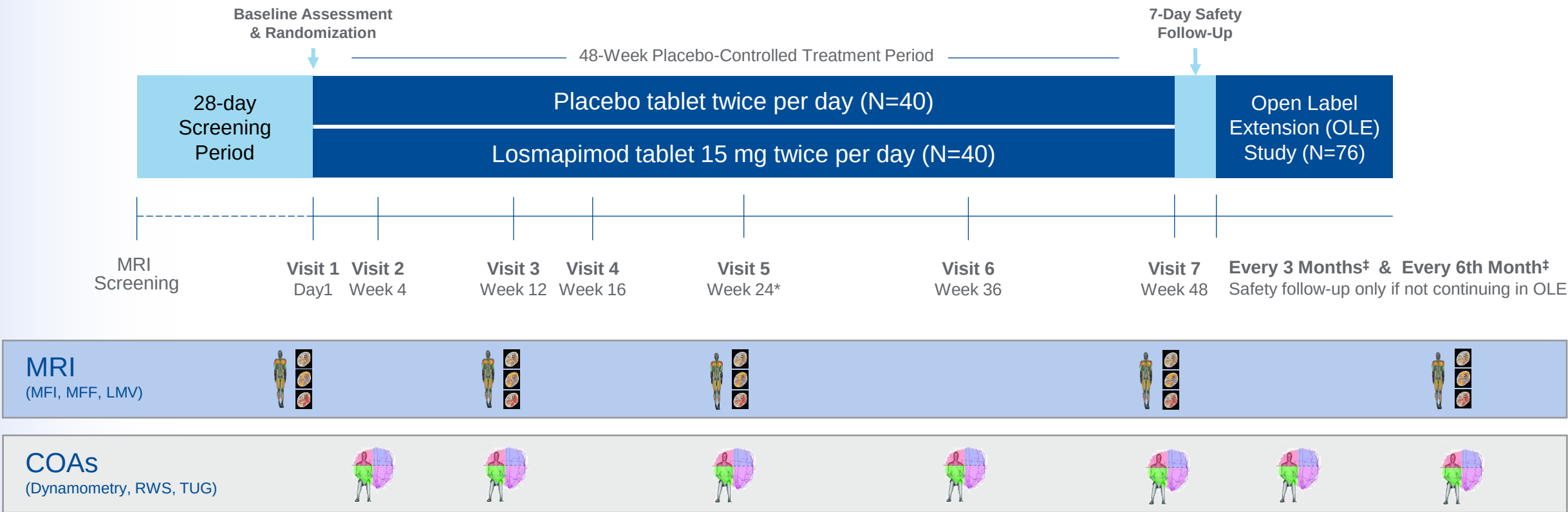
Currently, there are no treatment options for people living with FSHD that prevent and/or slow muscle wasting and weakness

Losmapimod

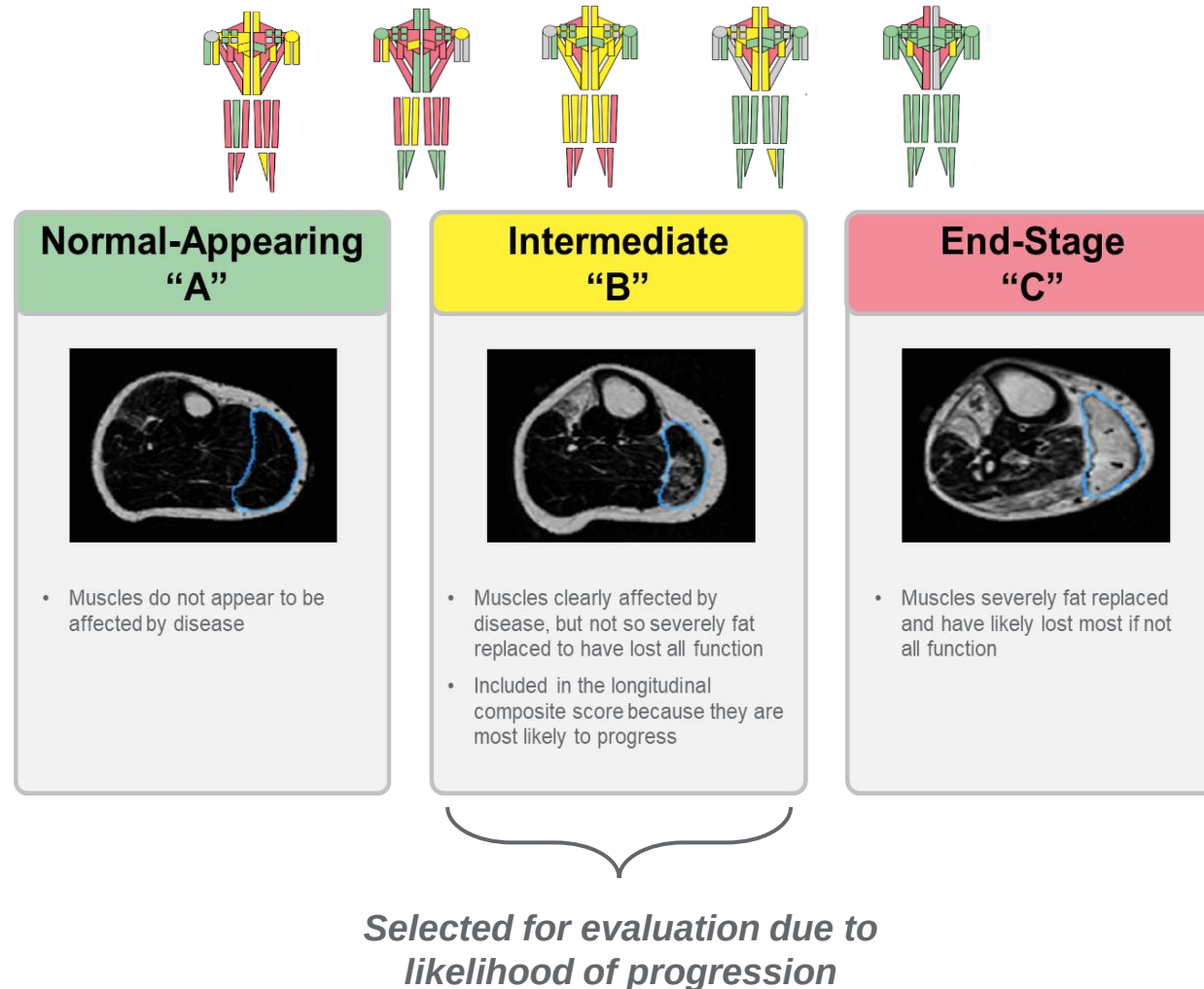


- Highly selective p38α/β MAPK inhibitor
- Generally well-tolerated, with clinical experience in >3,600 people across 11 indications
- Reduced DUX4 expression in preclinical studies
 - Aberrant expression DUX4 gene is known root cause of FSHD

ReDUX4 Trial Design



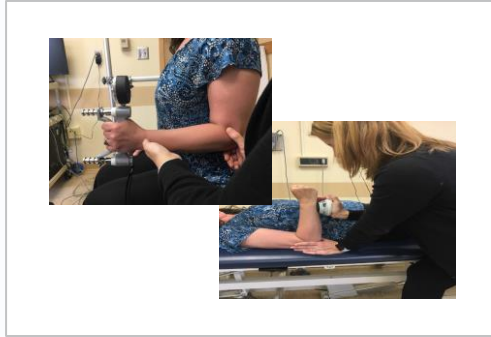
Muscle Categorization Captures FSHD Disease Heterogeneity and Progression



Function and Strength were Evaluated via Relevant Clinical Assessments

Dynamometry

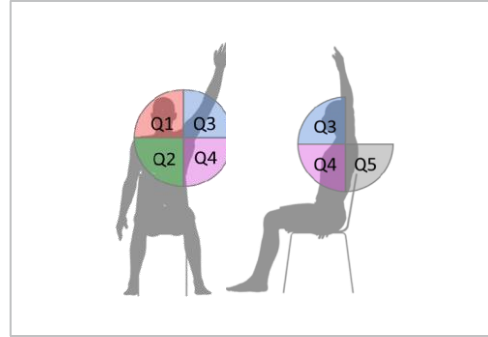
Upper and lower extremity strength



- Isometric dynamometry used to assess **muscle strength** of upper and lower limbs bilaterally

Reachable Workspace (RWS)

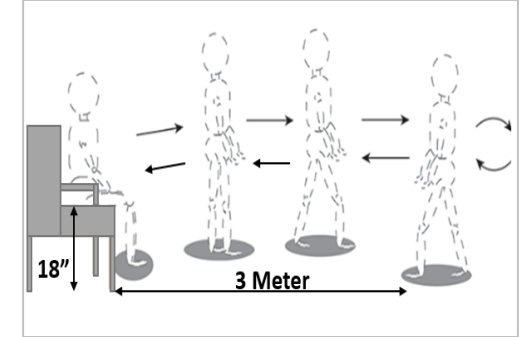
Upper arm and shoulder function



- **Reliable indicator of upper extremity function** in FSHD; quantified by relative surface area (RSA).
- Patients with larger total RSA are **more independent** and report **higher quality of life**

Timed Up and Go (TUG)

Patient mobility



- Assessment of mobility that requires both **static and dynamic balance**

ReDUX4 Study Participant Randomization Was Well Balanced

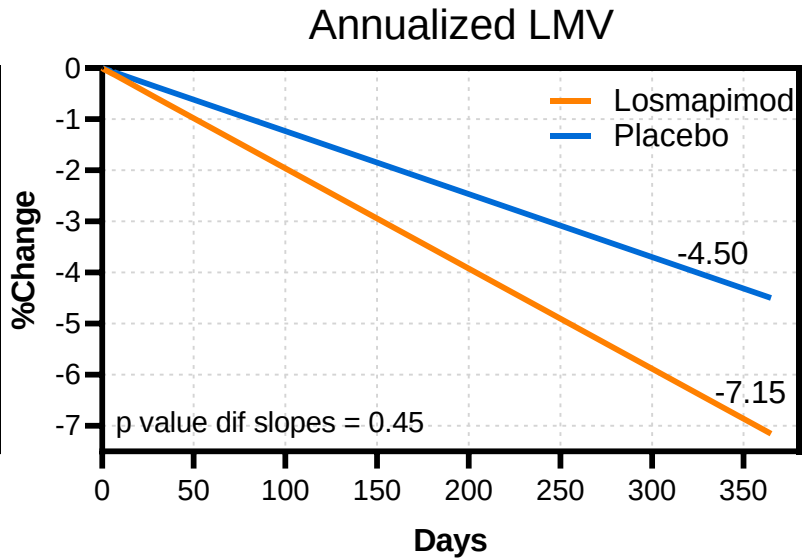
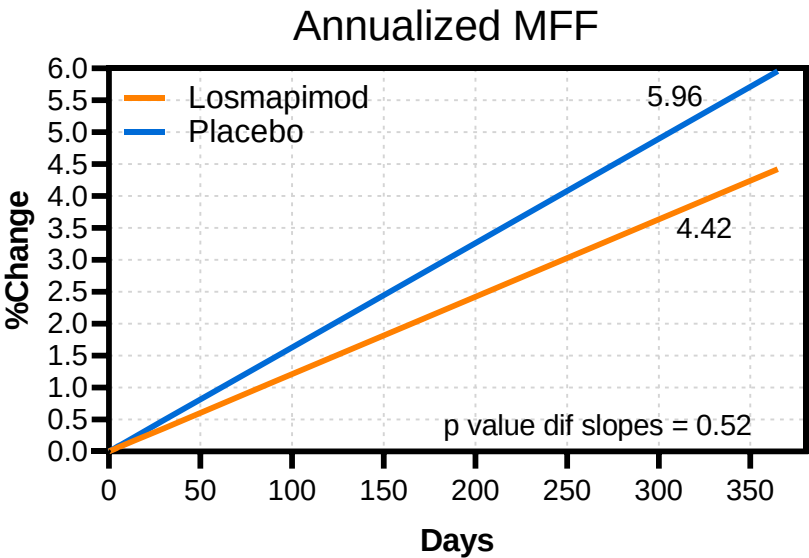
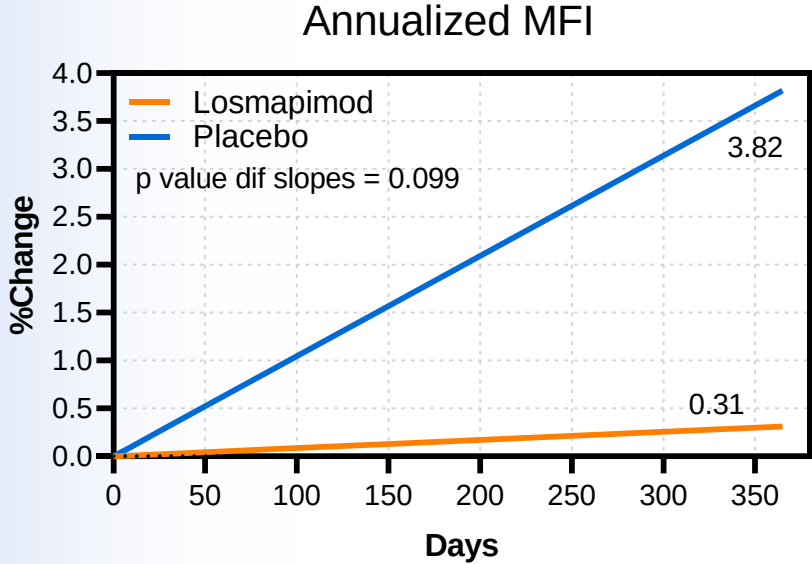
		Placebo BID (N=40)	Losmapimod 15 mg BID (N=40)
Completed		38 (95%)	39 (97.5%)
Discontinued*		2 (5.0%)	1 (2.5%)
DEMOGRAPHICS			
Age (years)	N	40	40
	Mean (SD)	45.7 (+/- 12.69)	45.7 (+/- 12.44)
Race n (%)	White	39 (97.5)	31 (77.5)
	Asian	0	5 (12.5)
	Other	0	1 (2.5)
	Not Applicable	1 (2.5)	3 (7.5)
Ethnicity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

Annualized Analysis

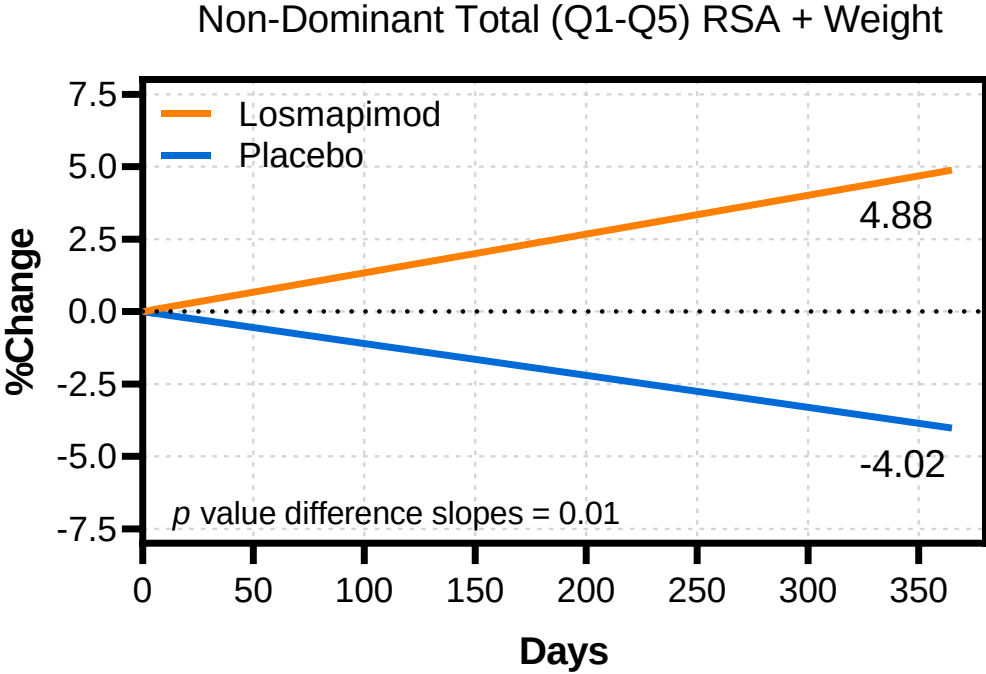
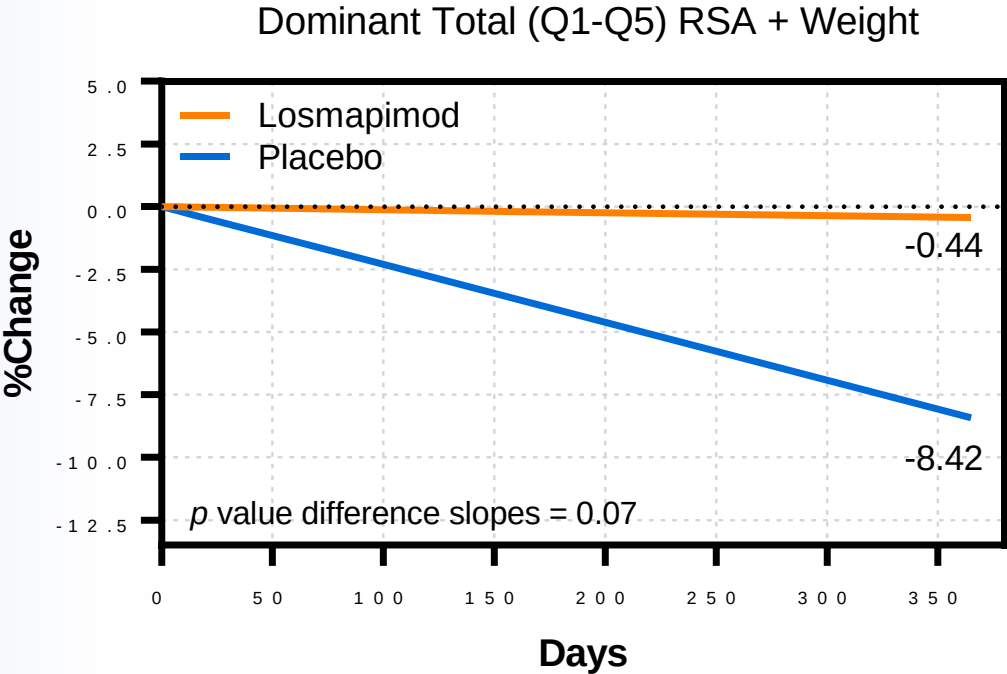
- Analyzes the slope of disease progression (placebo) and the impact of intervention (losmapimod) on progression
- Calculated using a linear mixed-effects model which estimates
 - Slope
 - Percent change per year
- Model was adjusted for repeat number category and region (EU, USA, and Canada)
- Annualized analysis of RWS (measured in Relative Surface Area, RSA) was prespecified; all other analyses are post-hoc

In the Losmapimod Group, There is Less Fat Accumulation in Muscles that are Most Likely to Progress ('B' Muscles)

Changes in Lean Muscle Volume May be Delayed



Losmapimod Shows Slowing of Disease Progression or Improvement in Function in Total RSA (Q1-Q5) with Weight



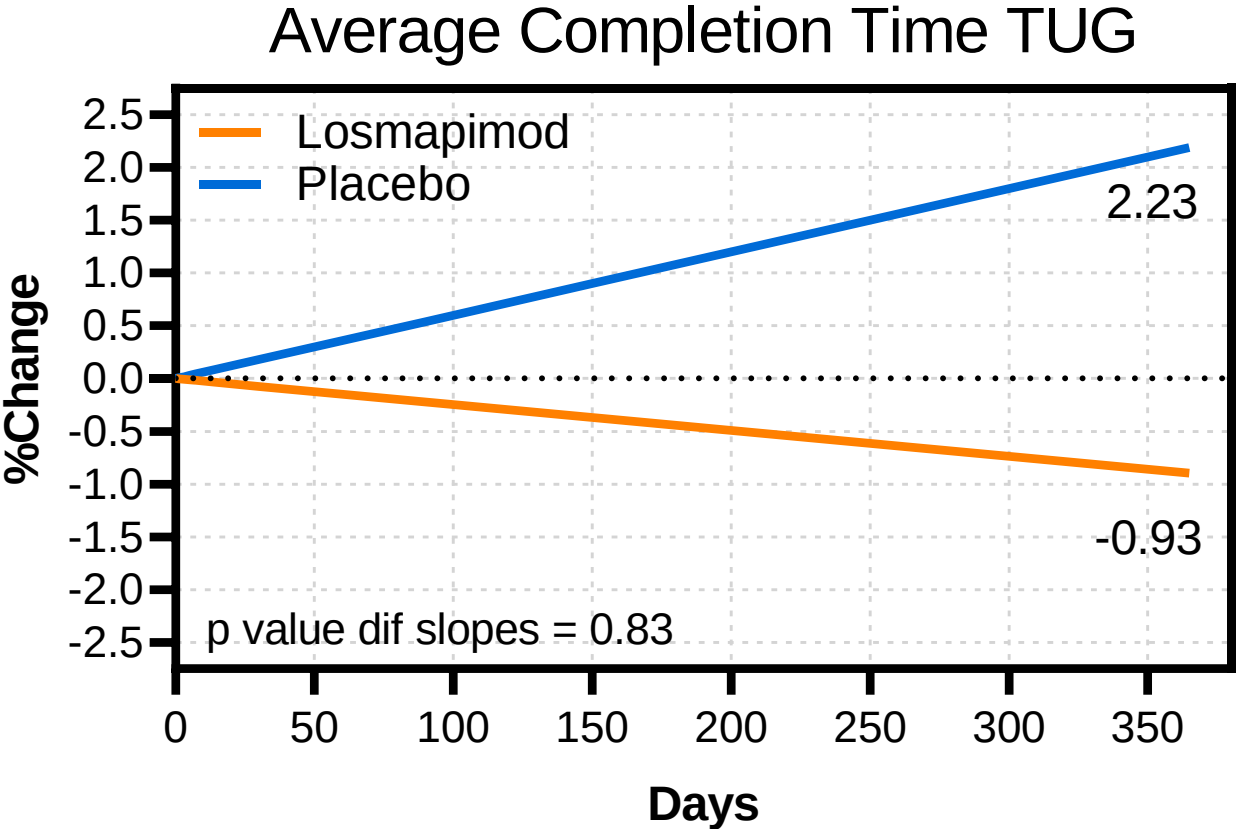
*Annualized rate of change (%) was calculated using a linear mixed-effects model to estimate percent change per year (y-axis)
RSA = relative surface area; Q = quintant

Losmapimod Shows Slowing of Disease Progression or Improvement in Function on Multiple RWS Metrics

Losmapimod (N=40)					Placebo (N=40)			
	With Weights		W/o Weights		With Weights		W/o Weights	
	Dom	Non-Dom	Dom	Non-Dom	Dom	Non-Dom	Dom	Non-Dom
Q1	9.02	10.50	-4.02	0.34	-8.87	-4.77	-7.10	-0.58
Q2	-1.49	5.70	-6.44	-0.97	-7.10	-0.27	-4.36	2.24
Q3	-0.59	7.02	-1.65	1.74	-10.98	-3.79	-10.59	-4.54
Q4	-1.74	2.01	0.14	-0.43	-4.02	-2.29	-1.58	-2.99
Q5	-2.79	5.31	-3.01	0.83	-15.02	-9.33	-12.57	-9.06
Q1+Q3	3.12	8.41	-2.69	1.17	-10.34	-4.17	-9.22	-2.99
Q1 to Q4	0.03	4.81	-2.18	-0.12	-7.03	-2.87	-5.27	-2.13
Total RSA (Q1-5)	-0.44	4.88	-2.19	0.11	-8.42	-4.02	-6.48	-3.42

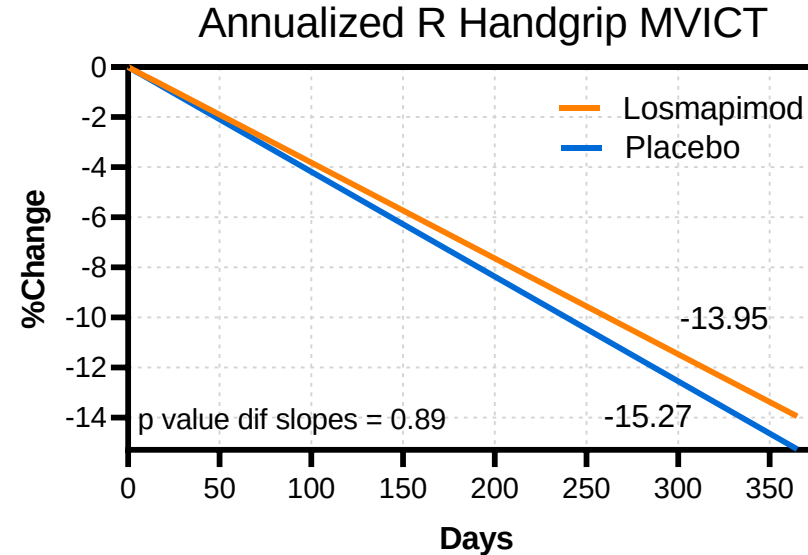
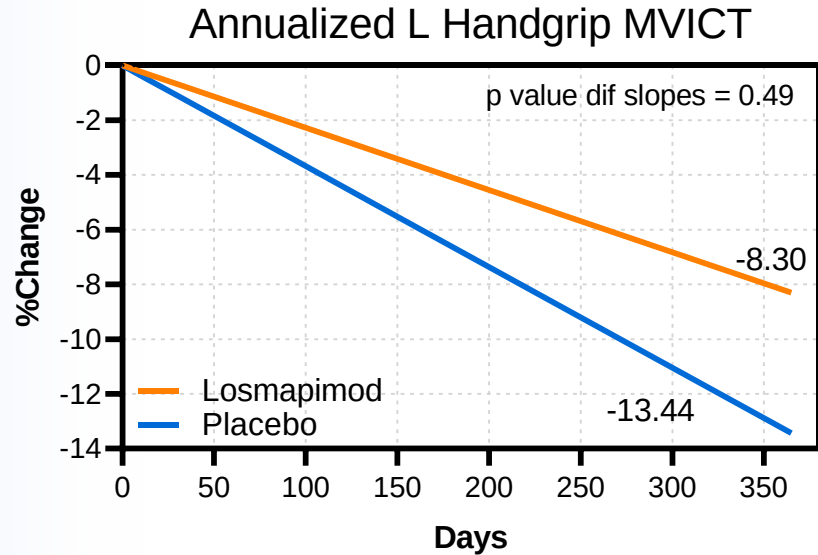
W/o = without, Q=quintant, Dom = Dominant, Non-Dom = Non-dominant

Treatment with Losmapimod Results in a Trend of Annualized Reduction of TUG Times as Compared with Placebo

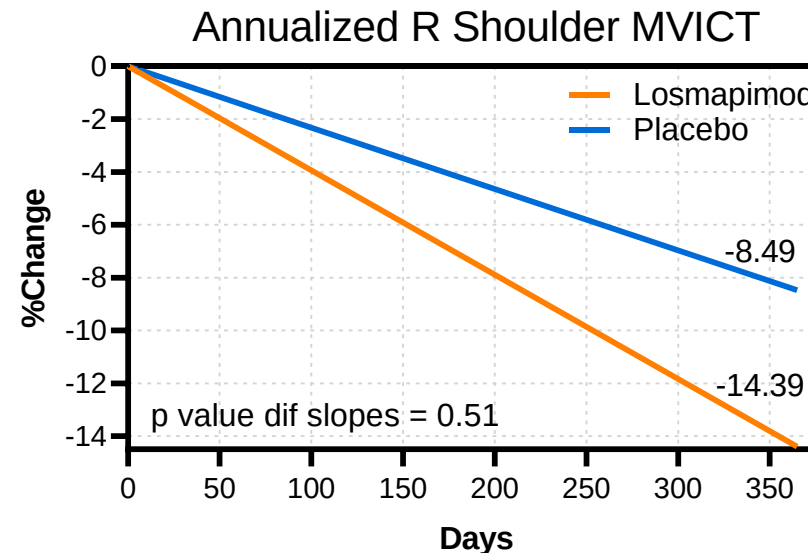
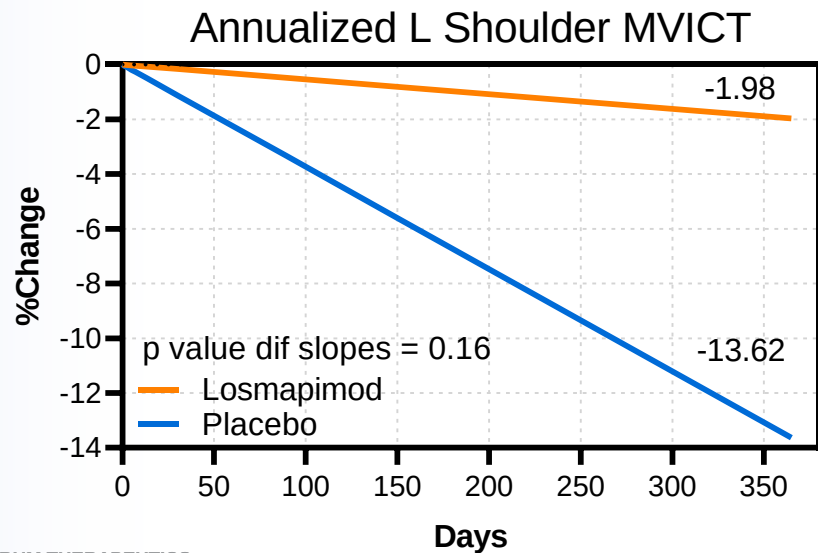


	LOS	PBO
Slope (SE)	-0.09 (1.1)	0.22 (1.0)

Losmapimod Treatment Results in a Trend of Slowing of Progression in Strength in Multiple Muscle Groups



Slope (SE)	LOS	PBO
L Handgrip	-2.82 (1.79)	-4.58 (1.76)
R Handgrip	-4.34 (2.04)	-4.75 (2.03)



Slope (SE)	LOS	PBO
L Shoulder	-0.12 (0.34)	-0.80 (0.33)
R Shoulder	-0.69 (0.31)	-0.41 (0.30)

Limitations

- Limited data for 1 year; ideally would have observations over several years
- Small dataset
- Sensitive to outliers throughout the study duration
- All p-values are nominal as the study did not meet the primary endpoint

Conclusions

- Annualized rates of change in clinical outcomes support disease slowing or improvement in losmapimod treated participants compared to placebo
- These data provide additional evidence supporting the effectiveness of losmapimod as a disease modifying treatment for FSHD
- Data support continued development with a Phase 3 study planned to start recruiting later this year



Acknowledgements



People Living With FSHD Participating in This Study

ReDUX4 Study Sites

ReDUX4 Physical Therapists

ReDUX4 Study Coordinators

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Collaborating Organizations



Patient Groups

