Fulcrum Therapeutics

An Open-Label Study of Losmapimod to Evaluate the Safety, Tolerability, and Biomarker and Clinical Outcome Assessment Changes in Subjects with FSHD1

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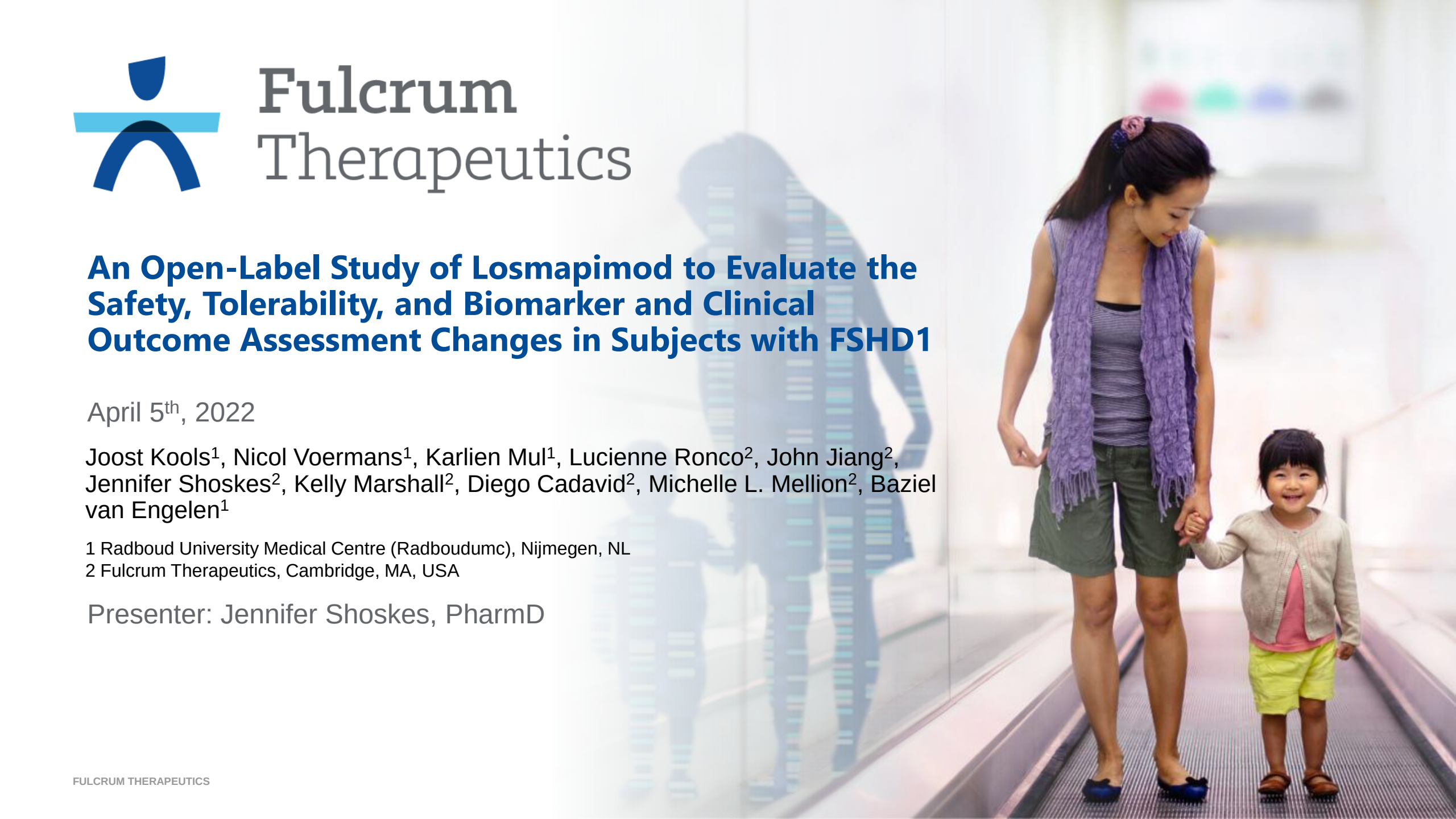
Joost Kools[1], Nicol Voermans[1], Karlien Mul[1], Lucienne Ronco[2], John Jiang[2], Jennifer Shoskes[2], Kelly Marshall[2], Diego Cadavid[2], Michelle L. Mellion[2], Baziel van Engelen[1]

1 Radboud University Medical Centre (Radboudumc), Nijmegen, NL
2 Fulcrum Therapeutics, Cambridge, MA, USA

Presenter: Jennifer Shoskes, PharmD



Disclosures

- Jennifer Shoskes is an 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

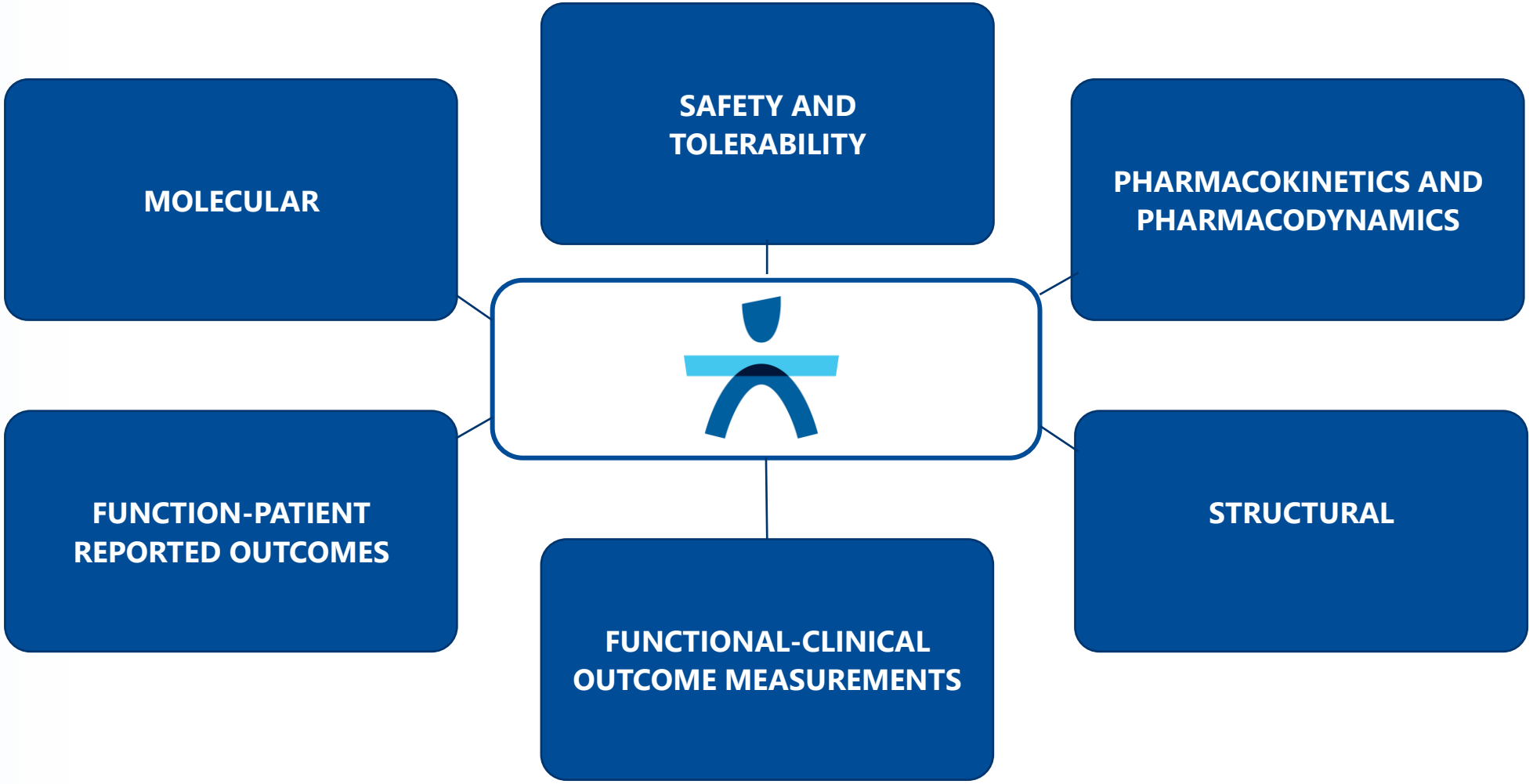
PATHOLOGICAL ACTIVITY AND MALADAPTIVE REMODELING lead to muscle fiber death and immune and fat infiltration

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

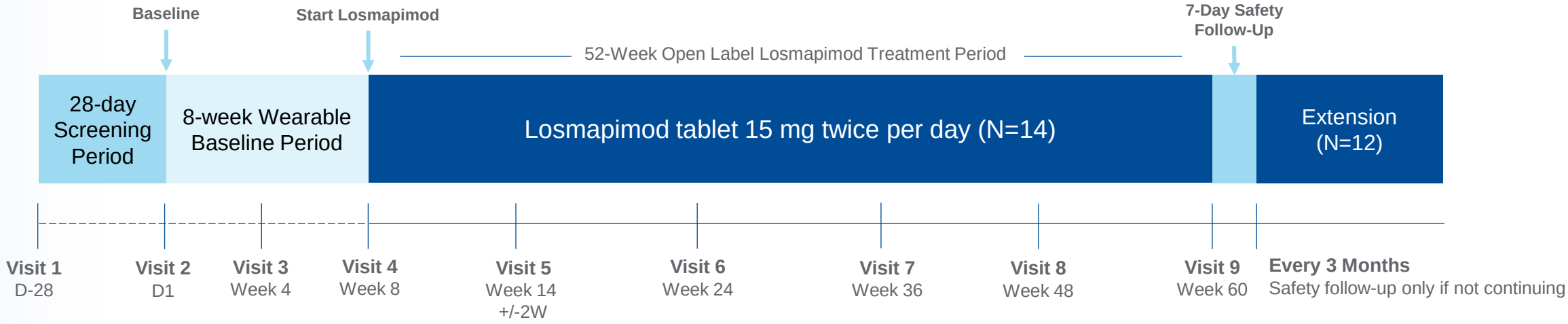
Currently, there are no treatment options for people living with FSHD that prevent and/or slow muscle wasting and weakness

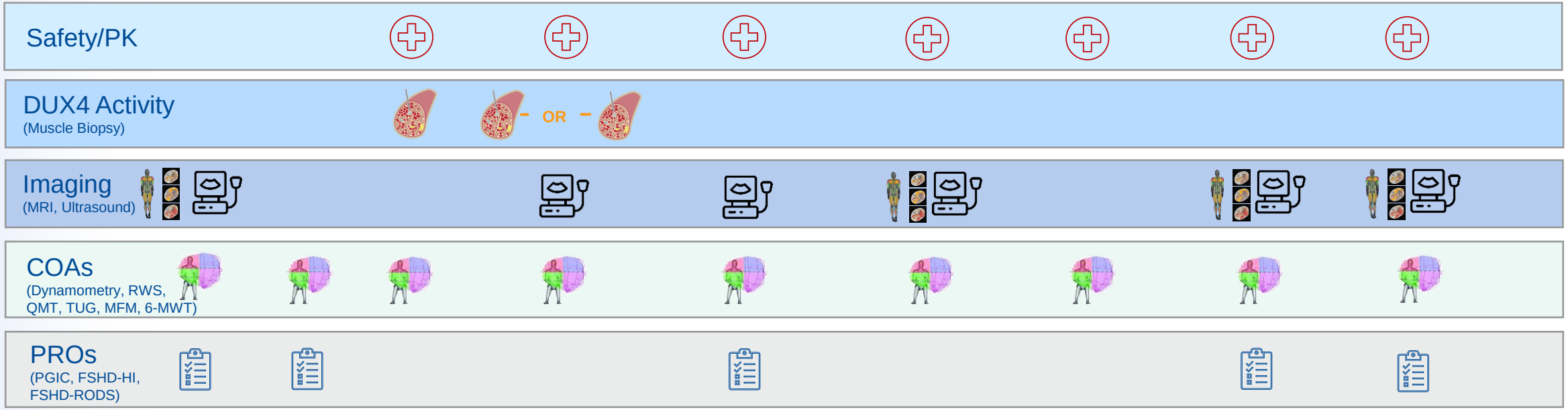
Phase 2 Studies were Designed To Capture a Wide Range of FSHD Disease Progression



OLS Design

Single Site Open Label Study





Baseline and Demographic Characteristics

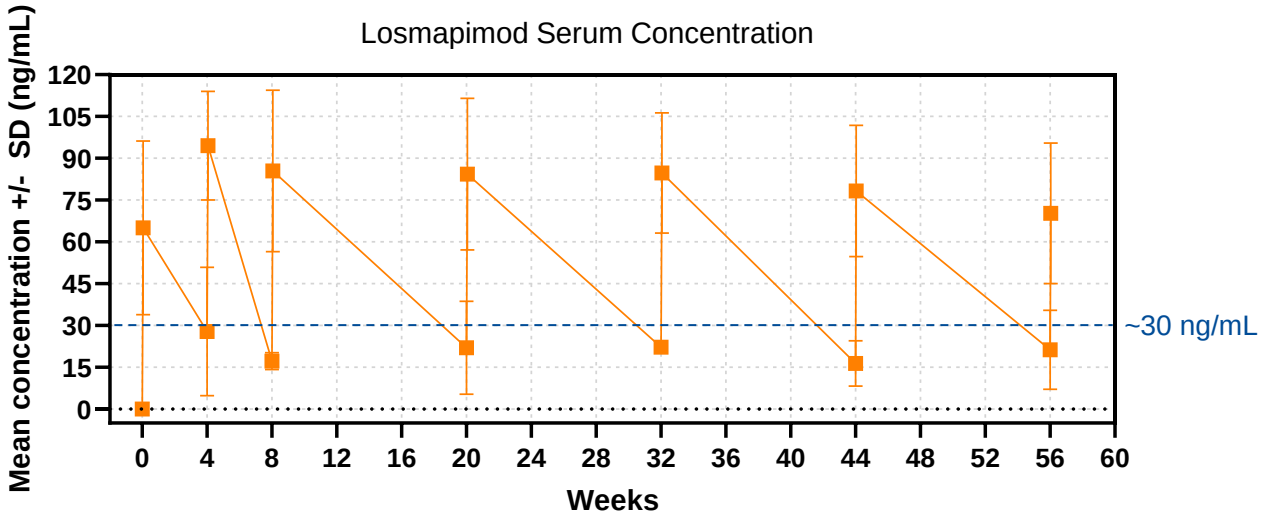
		Open-Label Study Losmapimod 15 mg BID (N=14)
Completed		14 (100%)
Discontinued*		0
DEMOGRAPHICS		
Age (years)	N	14
	Mean (SD)	45.7 (+/- 11.61)
Race n (%)	White	13 (92.9)
	Asian	0
	Other	1 (7.1)
	Not Applicable	0
Ethnicity n (%)	Hispanic or Latino	0
	Not Hispanic or Latino	14 (100)
	Not Applicable	0
Body Mass Index (BMI) (kg/m^2)	N	14
	Mean (SD)	24.04 (+/- 2.939)
D4Z4 Repeat Category n (%)	1-3 Repeats	3 (21.4)
	4-9 Repeats	11 (78.6)
Ricci Score n (%)	2	0
	2.5	1 (7.1)
	3	5 (35.7)
	3.5	2 (14.3)
	4	**6 (42.9)**

All 14 subjects completed the study

- 2 subjects declined participation in the extension study - Unrelated to study drug/adverse events

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

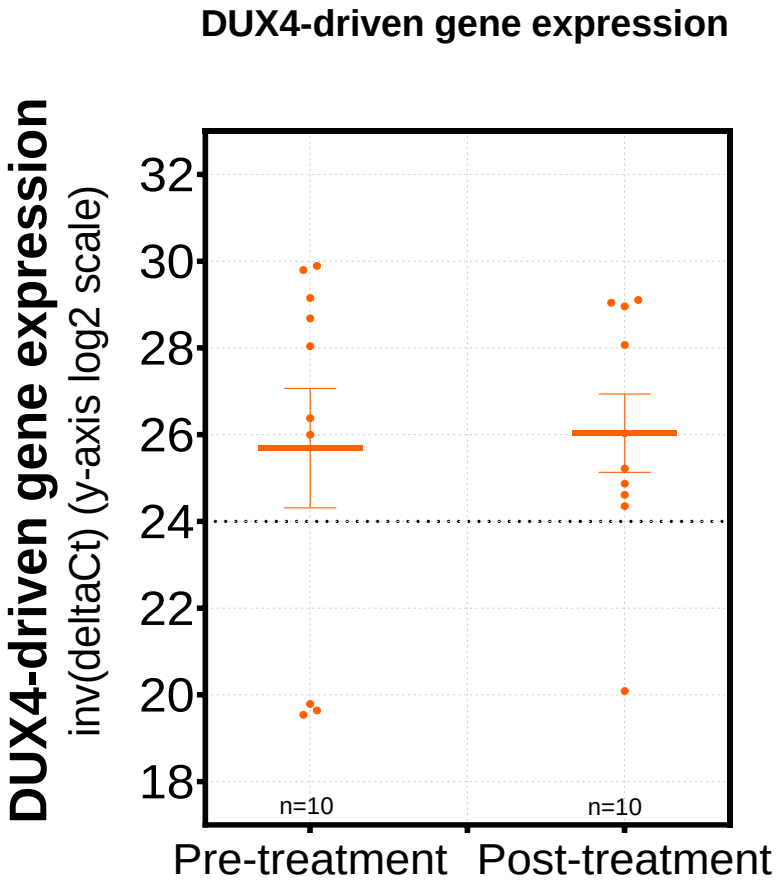
- Compliance was ~98.5% based on pill count
- Blood and muscle concentrations were within the expected range based on pre-clinical data
- Target engagement in blood was within the expected range (~40% to 55% change from baseline at C_{max})

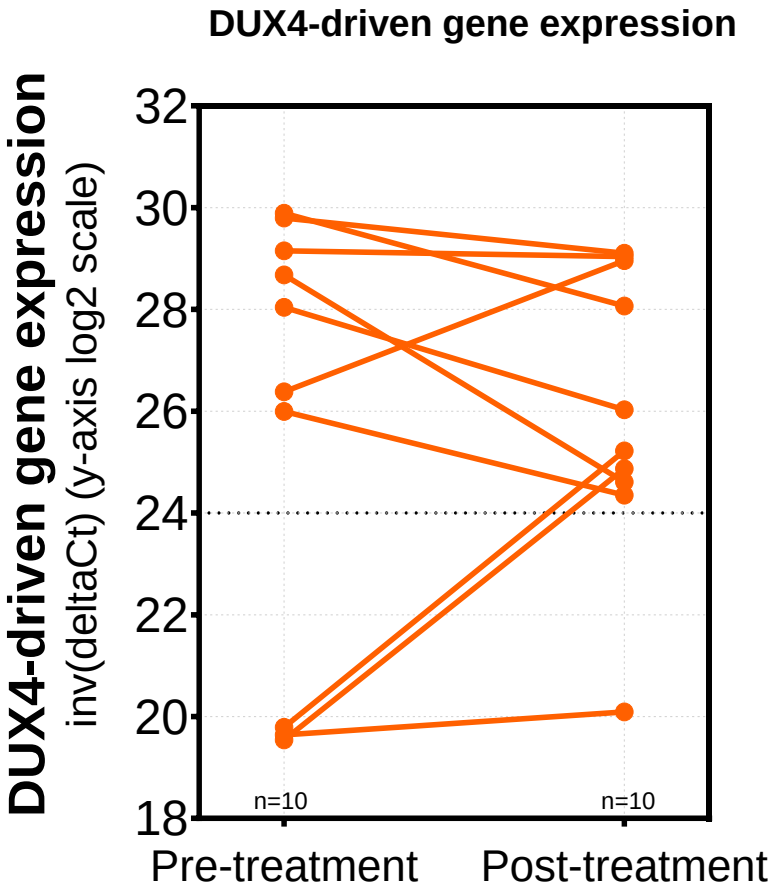


DUX4-Driven Gene Expression in Muscle Biopsies

Changes from baseline were not observed in the treatment period

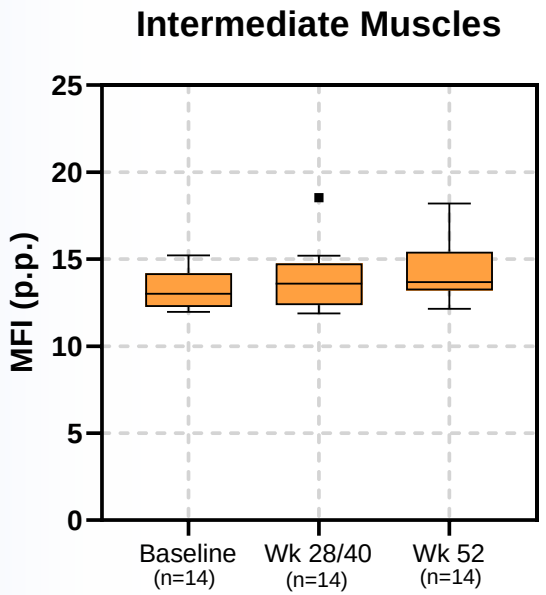
- DUX4-driven gene expression was highly variable in OLS study group



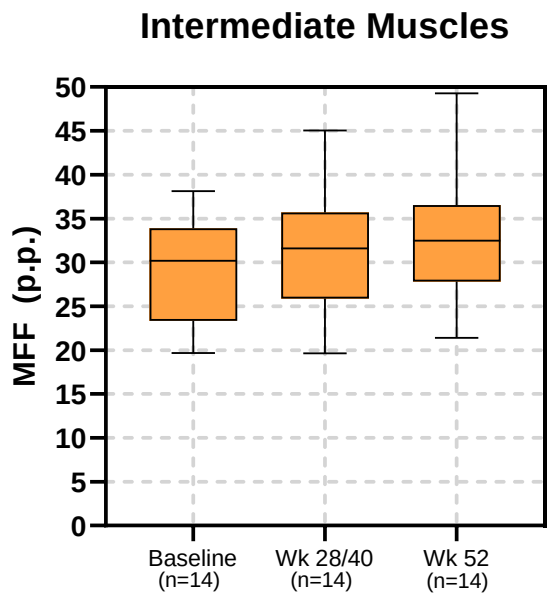


No or Minimal Changes Observed in Quantitative MRI Assessments of Intermediate Muscles

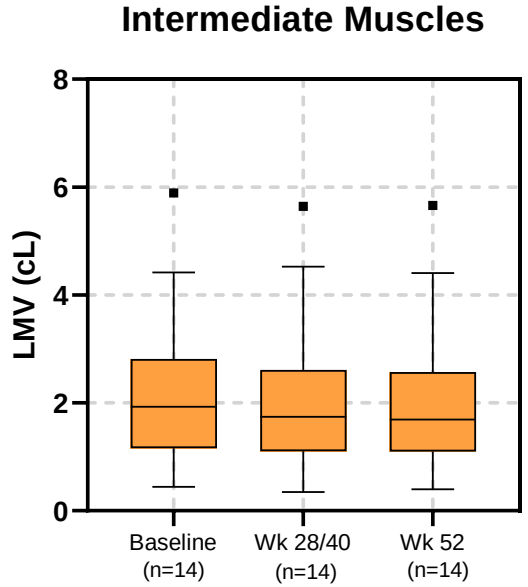
Muscle Fat Infiltration (MFI)



Muscle Fat Fraction (MFF)



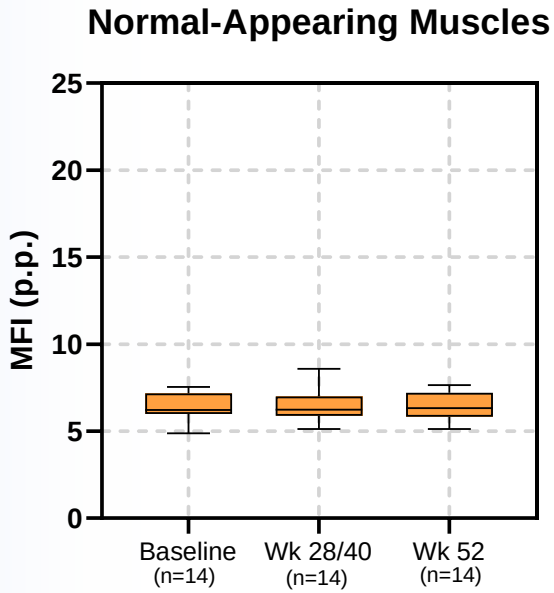
Lean Muscle Volume (LMV)



Tukey box plots display 1st quartile, 3rd quartile, and median. Values outside the whiskers are plotted as individual points

No Change Observed in Normal Appearing (A) Muscles*

Muscle Fat Infiltration (MFI)



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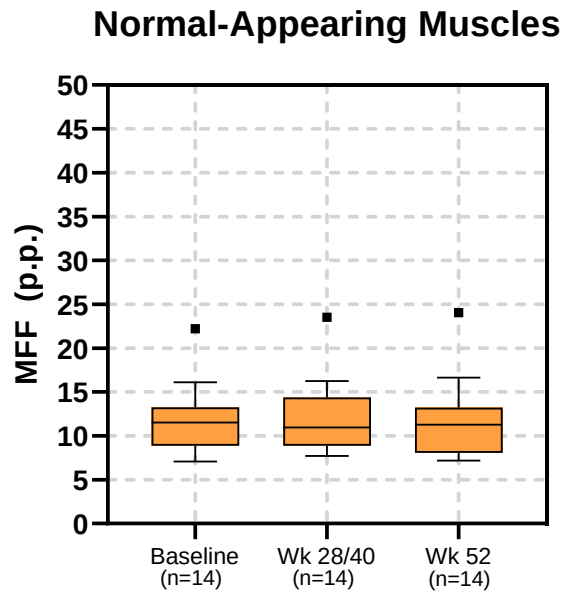

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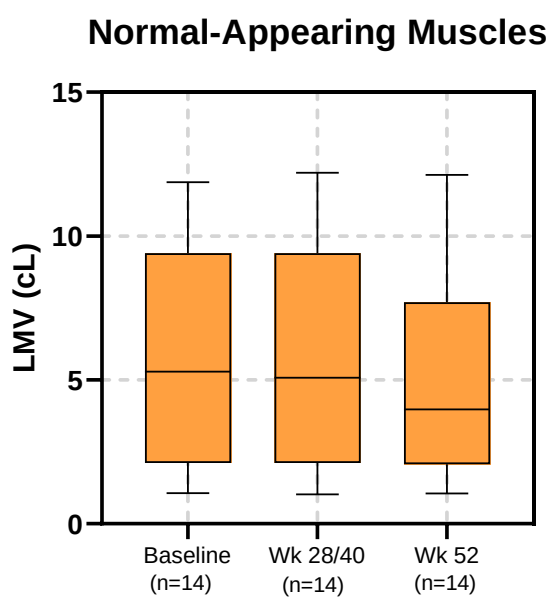


Tukey box plots display 1st quartile, 3rd quartile, and median. Values outside the whiskers are plotted as individual points

**Post-hoc analysis*

Cross-sectional Composite Values Showed Moderate to Strong Correlations to COAs at Week 52

- **Moderate and Strong Correlations Between MRI and TUG/FSHD-TUG at Week 52 (n=14)**

MRI Composite	Statistic	TUG Cross-sectional	FSHD-TUG Cross-sectional*
LMV (L)	r (p-value)	-0.89 (<0.0001)*	-0.83 (0.0002)*
MFF (%)	r (p-value)	0.86 (<0.0001)*	0.77 (0.0003)*
MFI (%)	r (p-value)	0.77 (0.0014)*	0.77 (0.0014)*

*p<0.05

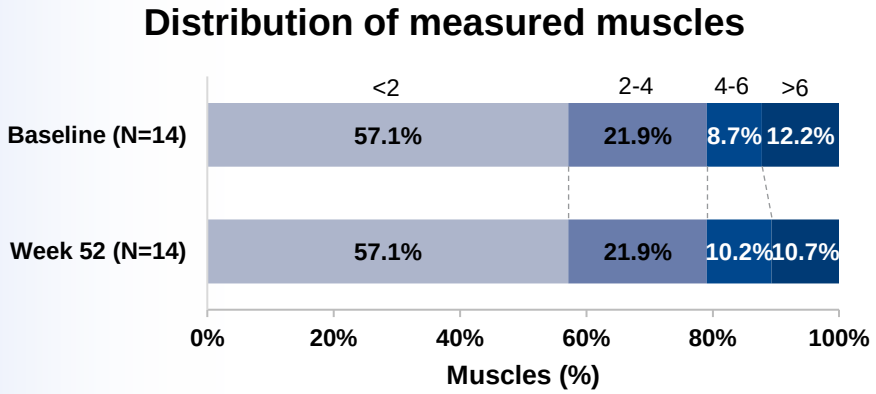
- **Moderate Correlations to Total RWS for LMV and MFF at Week 52 (n=14)**

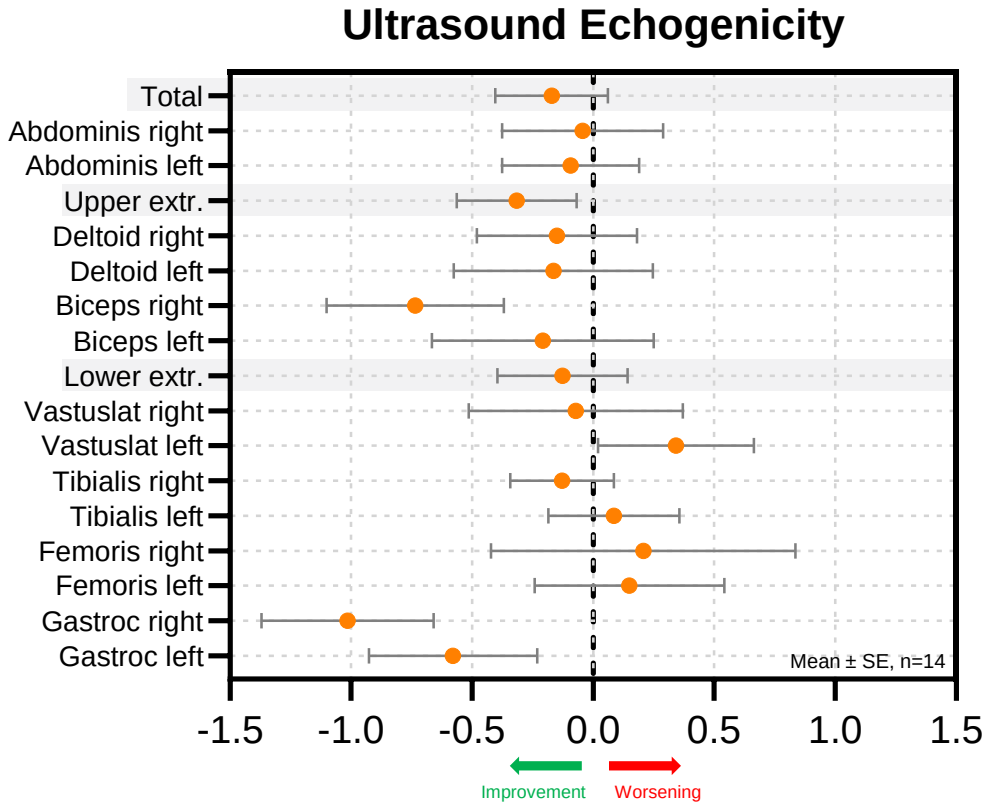
MRI Composite	Statistic	Dom Total RSA Weighted	Non-Dom Total RSA weighted
LMV (L)	r (p-value)	0.55 (0.0666)	0.43 (0.1591)
MFF (%)	r (p-value)	-0.66 (0.0199)*	-0.52 (0.0800)
MFI (%)	r (p-value)	-0.24 (0.4568)	-0.09 (0.7787)

*p<0.05

Improvement or No Change Observed in Ultrasound Assessment

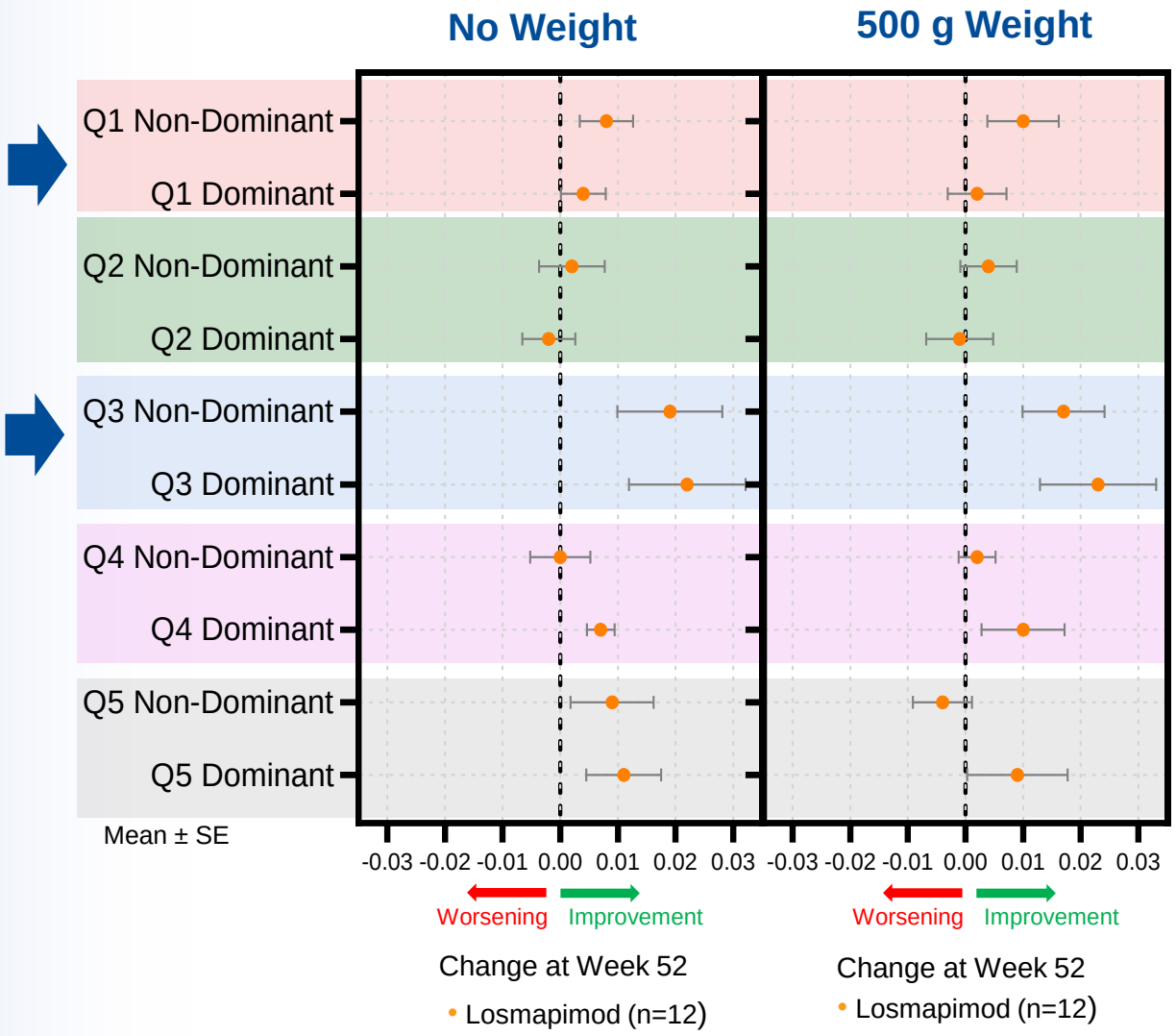
- Most muscles demonstrated stability or improvement over 52 weeks
- Natural history studies have shown most muscles increase in echogenicity in FSHD patients over 1 year[1]

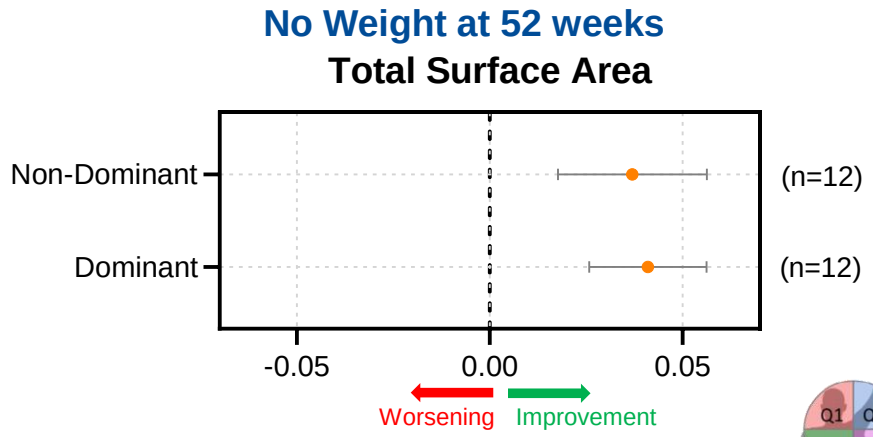


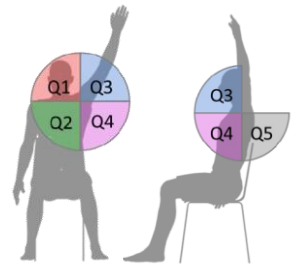


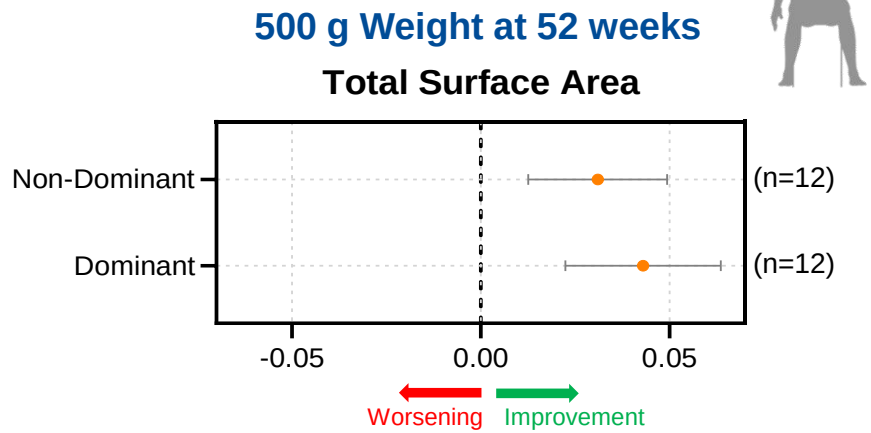
[1]Goselink et al 2020

Slowing of Disease Progression and/or Improvement was Observed on Multiple RWS Measures









Change in total relative surface area

Exploratory Annualized RWS Analysis (percent change/year)

OLS Study – Annualized RWS (% change from basline /yr)

Quadrant	With Weights		Without Weights	
	Dom	Non-Dom	Dom	Non-Dom
Q1	**9.16**	**8.60**	**11.95**	**7.73**
Q2	-0.28	1.34	-3.39	1.36
Q3	**16.66**	**10.72**	**16.05**	**9.37**
Q4	2.23	0.58	1.10	0.18
Q5	4.49	-2.11	4.44	6.25
Q1+Q3	13.92	9.79	14.53	8.58
Total RSA	5.68	3.28	4.90	4.28

UCI 5-yr longitudinal study (n=18)

Quadrant	With	W/o
	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

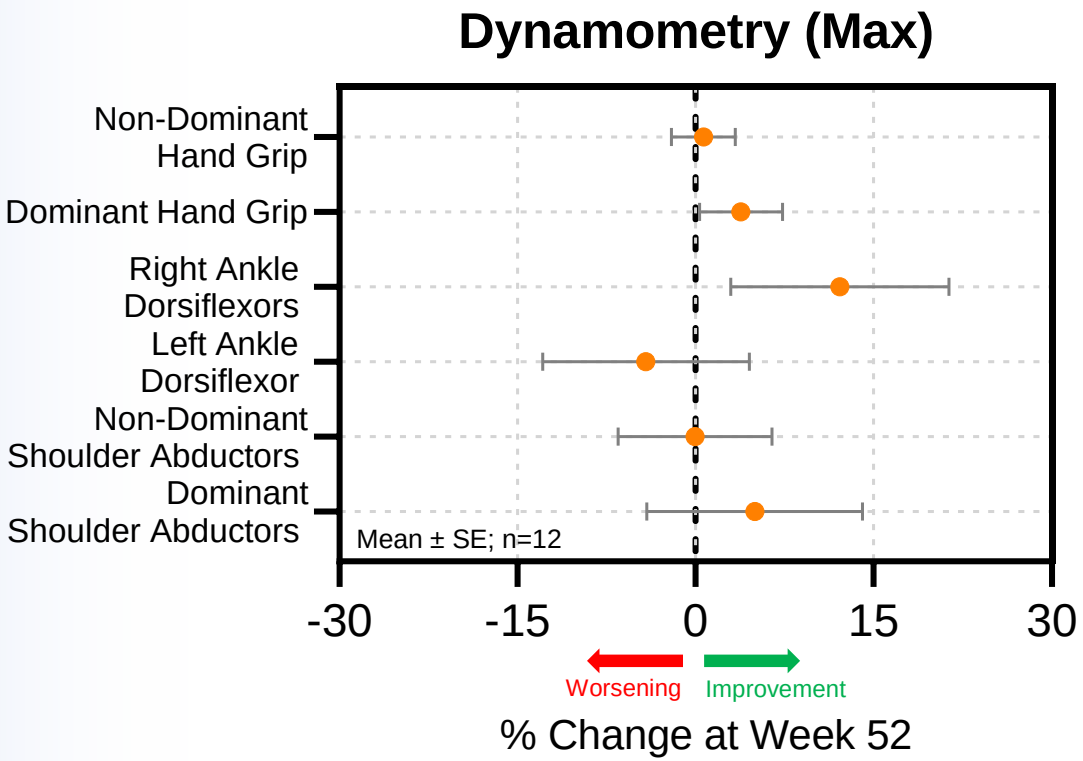
*not including Q5

Han J. et al 2019

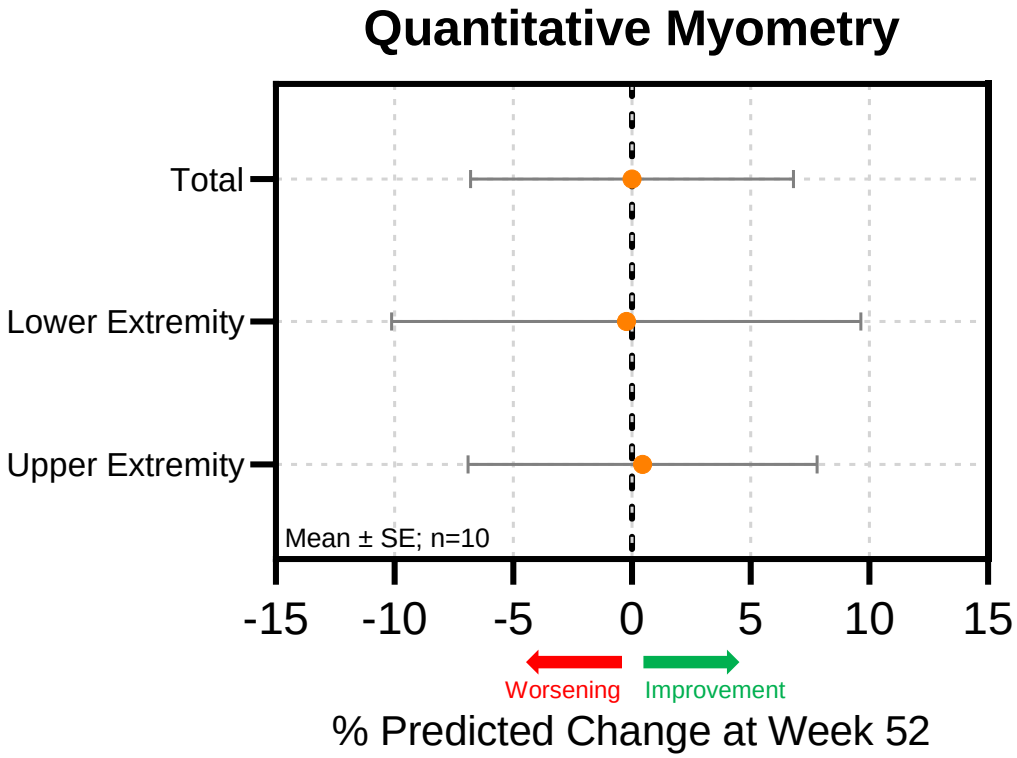
Annualized RWS increased for all quadrants in the OLS, with the largest increases in Q1 and Q3 of 7-17%. In a 5-yr observational study, Q1 and 3 decreased by 7-9% annually

Stability or Improved Muscle Strength in Hand-Held Dynamometry and Quantitative Myometry

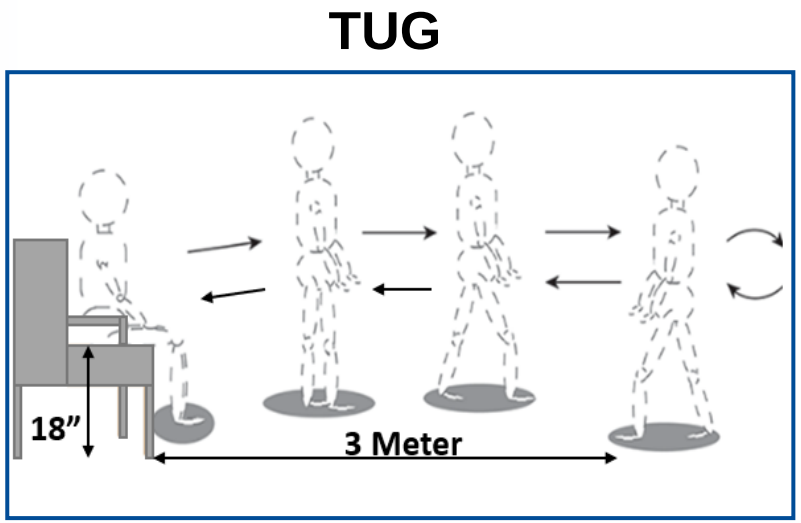
- Stability or improvements from baseline, in the bilateral strength of shoulder abductors, ankle dorsiflexors, and hand grip

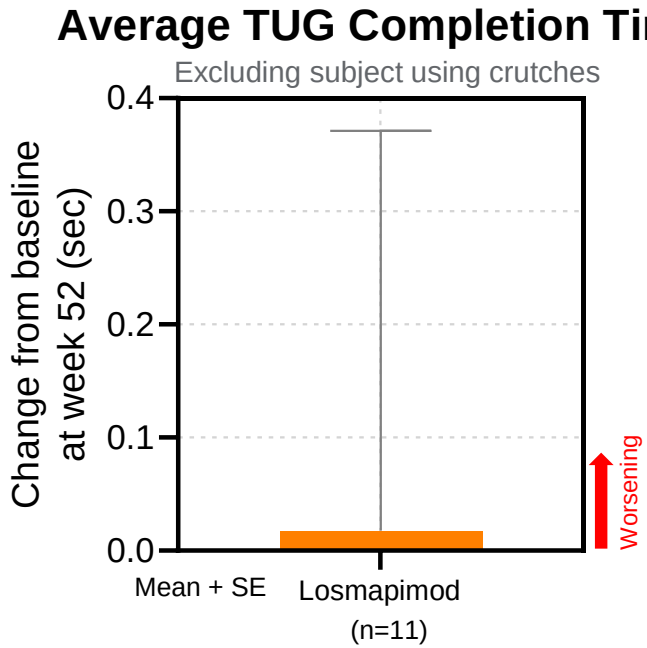


- Stability of muscle strength via quantitative bedframe myometry at 52 weeks



Minimal Change Observed in Other Clinical Outcome Assessments Over 52 Weeks





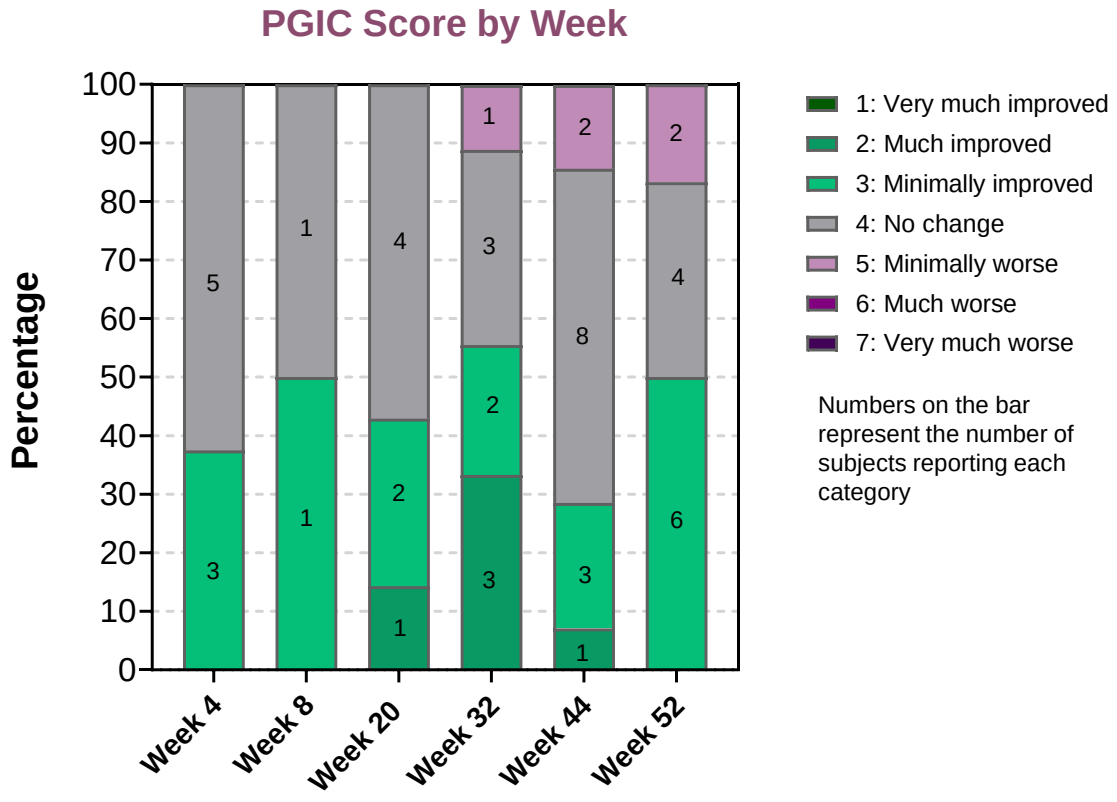
Minimal or No Change in FSHD-TUG, FSHD-RODS, Motor Function Measurement, FSHD-HI, and 6-MWT Over 52 Weeks of Treatment

Participants Reported Improvement with Losmapimod Treatment Over Time

- Over 80% of subjects reported improvement or no change after 52 weeks of treatment; no patients reported feeling much worse over 52 weeks

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":*

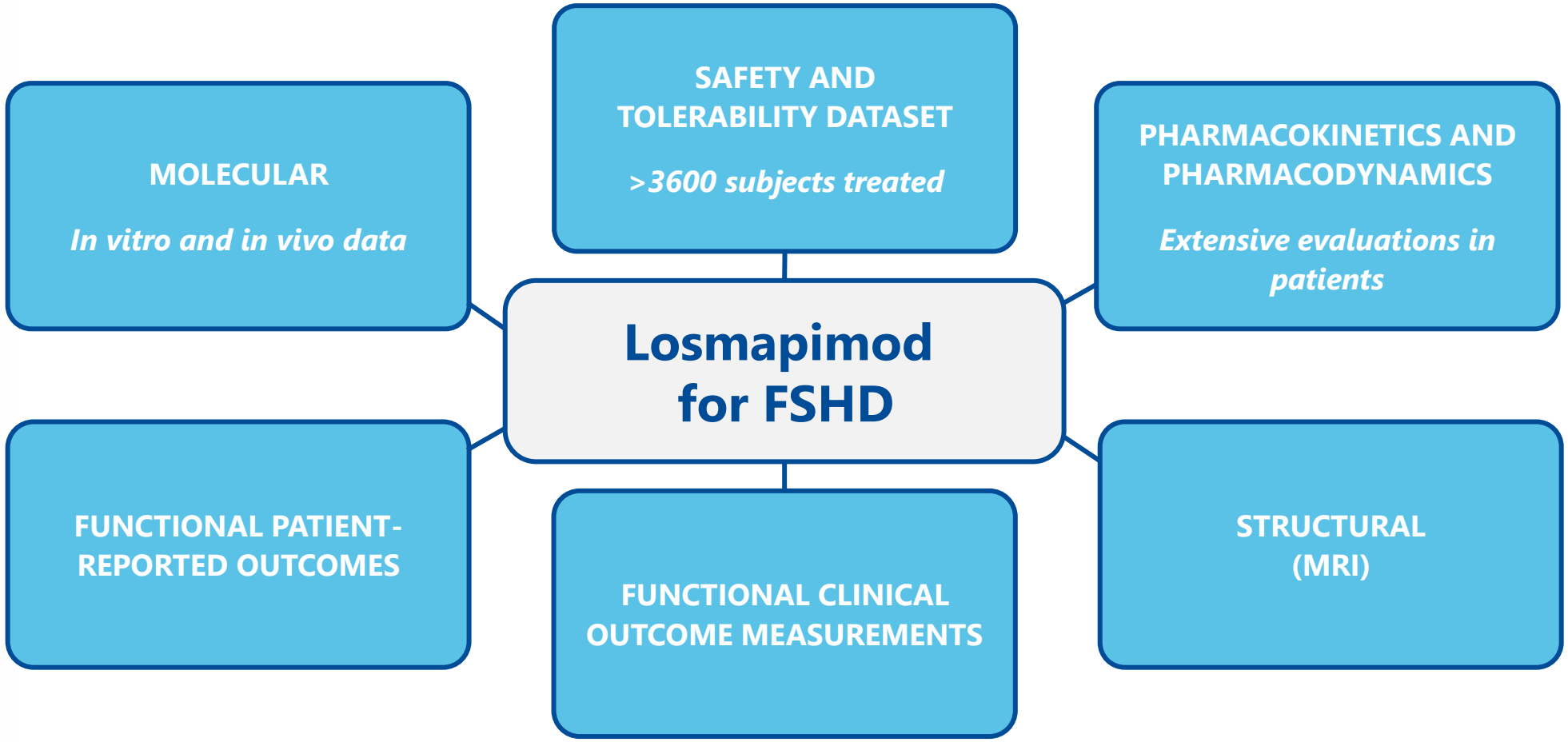
Scores	PGIC
1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Worse
6	Much worse
7	Very much worse



Losmapimod Was Generally Well Tolerated

- No SAEs or deaths were observed
- The most common AE was increased ALT (35.7%), of which all cases were mild and transient
  - All cases resolved with continued dosing, and none led to treatment discontinuation
- Nine subjects (64.3%) reported events in the SOC of Skin and Subcutaneous tissue disorders, with dry skin being the most frequently reported skin event (28.6%)
- No trends were observed in the Related AEs
- All severe AEs occurred in single subjects, except for dry skin, which occurred in 2 subjects
  - Severe AEs: hyperkeratosis, abdominal pain upper, back pain, intervertebral disc protrusion, onychomycosis, dry skin
- No significant changes in vital signs, laboratory studies or EKG were observed
- Losmapimod has shown favorable safety and tolerability in >3600 subjects exposed to at least one dose

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



Acknowledgements

People Living With FSHD Participating in This Study

OLS Site

OLS Physical Therapists

OLS Study Coordinators

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- Baziel van Engelen, MD, PhD Radboud UMC
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Other Collaborators

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Collaborating Organizations

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IMMUNOLOGIX LABORATORIES

BIONIKS GIVING THE WORLD A HELPING HAND

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Patient Groups

FSHD SOCIETY

MDA® Muscular Dystrophy Association

friends of FSH research

NORD® National Organization for Rare Disorders

Fulcrum Therapeutics

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

Thank you! Questions?