Fulcrum Therapeutics

Key Opinion Leader Event: Losmapimod in FSHD

March 24, 2022

Disclaimer and Notice

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the development status of the Company’s product candidates, the potential advantages and therapeutic potential of the Company’s product candidates planned meetings with regulatory agencies and availability of clinical trial data. All statements, other than statements of historical facts, contained in this press release, including statements regarding the Company’s strategy, future operations, future financial position, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, risks associated with Fulcrum’s ability to obtain and maintain necessary approvals from the FDA and other regulatory authorities; continue to advance its product candidates in clinical trials; initiate and enroll clinical trials on the timeline expected or at all; correctly estimate the potential patient population and/or market for the Company’s product candidates; replicate in clinical trials positive results found in preclinical studies and/or earlier-stage clinical trials of losmapimod and its other product candidates; obtain, maintain or protect intellectual property rights related to its product candidates; manage expenses; and raise the substantial additional capital needed to achieve its business objectives. For a discussion of other risks and uncertainties, and other important factors, any of which could cause the Company’s actual results to differ from those contained in the forward-looking statements, see the “Risk Factors” section, as well as discussions of potential risks, uncertainties and other important factors, in the Company’s most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent the Company’s views as of the date hereof and should not be relied upon as representing the Company’s views as of any date subsequent to the date hereof. The Company anticipates that subsequent events and developments will cause the Company’s views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so.

Today's Agenda

Opening remarks and corporate overview

Bryan Stuart, President and Chief Executive Officer, Fulcrum Therapeutics

FSHD disease overview and unmet need

Nicholas E. Johnson, M.D., M.Sci., FAAN, Associate Professor of Neurology and Human and Molecular Genetics and Vice Chair of Research in Neurology at Virginia Commonwealth University

Losmapimod overview and Phase 3 trial design

Judith Dunn, Ph.D., President, Head of R&D, Fulcrum Therapeutics

Reachable Workspace (RWS) as functional primary endpoint

Jay J. Han, M.D., Professor and Acting Chair, Physical Medicine & Rehabilitation; Medical Director, Acute Rehabilitation Unit (ARU), Physical Medicine & Rehabilitation; Residency Program Director, Physical Medicine & Rehabilitation, UCI School of Medicine

Losmapimod: First-to-market opportunity

Mel Hayes, Chief Commercial Officer

Q&A

Here's What You Will Take Away from Today

- Losmapimod is positioned to be first-to-market therapy for FSHD
- FSHD represents an area of high unmet need
  - Severe, progressive and debilitating disease
  - Large and addressable patient population
  - No approved therapies for FSHD and nothing else in clinical development
- Phase 3 REACH trial optimally designed to demonstrate efficacy
  - Aligned with regulators on Reachable Workspace (RWS) as primary endpoint
  - Leverages insights gained from ReDUX4
- FSHD represents meaningful commercial opportunity

Corporate Overview

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 program; positioned to be first-to-market with a disease-modifying therapy

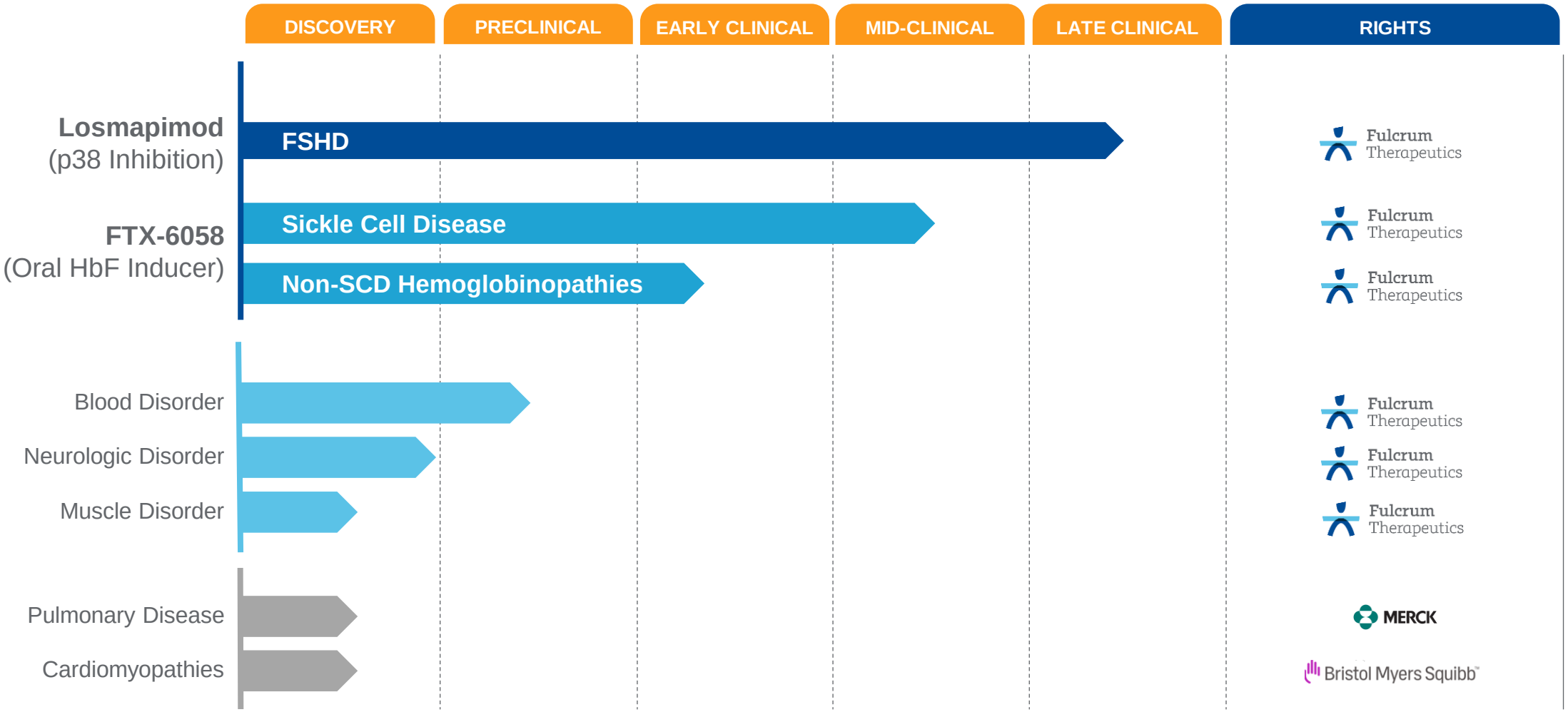
Sickle cell disease: Phase 1b patient study; potential first oral functional cure

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

Pipeline of Potentially Disease-modifying Therapies



Next IND by end of 1Q 2023

Poised for Substantial Growth in 2022 and Beyond

FSHD Disease Overview and Unmet Need

Nicholas Johnson, MD, MSCI, FAAN
Vice Chair of Research
Associate Professor of Neurology, Human and Molecular Genetics
Virginia Commonwealth University

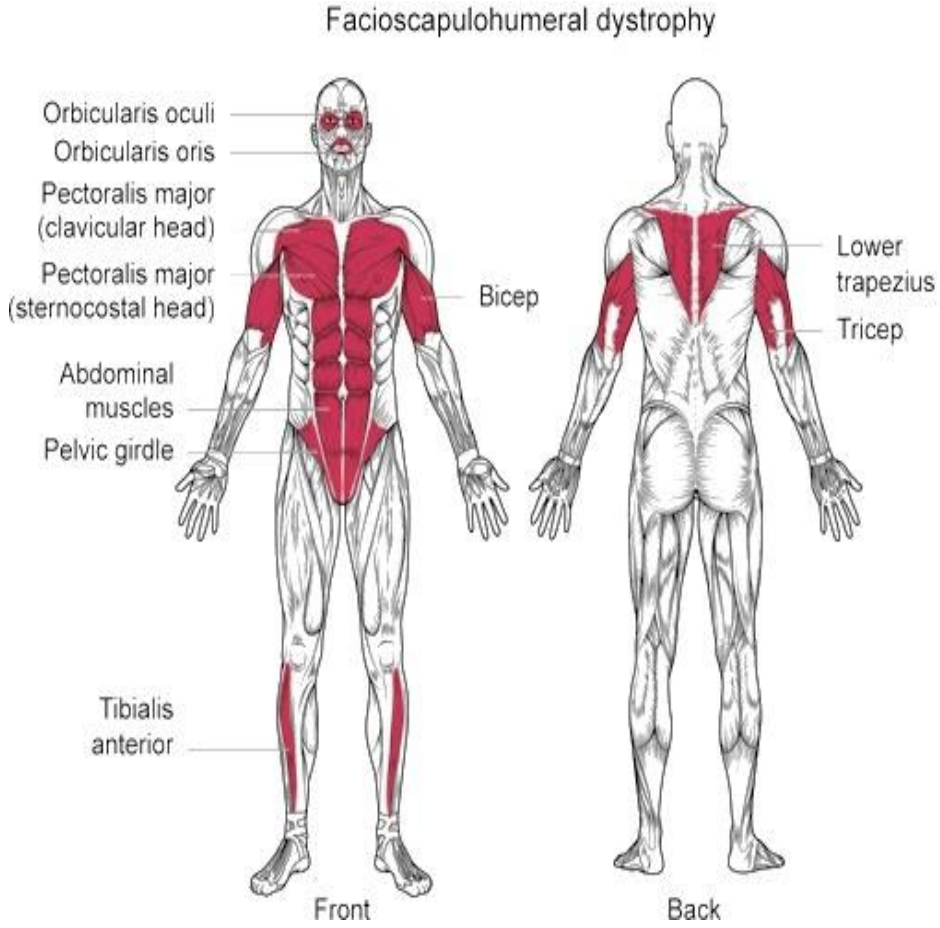
VCU Health

Disclosures

- **Grant/Research support**: NINDS (1K23NS091511-05; R01NS104010-01), FDA (R01FD006071-02), Myotonic Dystrophy Foundation, Muscular Dystrophy Association, Coalition to Cure Calpainopathies, AveXis, Fulcrum, AMO Pharma, Sarepta, Dyne, ML Bio
- **Consultant/Advisory Board**: ML Bio, AskBio, Fulcrum, Vertex, Dyne, AveXis, AMO Pharma, Avidity, Acceleron
- **Royalties** from CMTHI, CCMDHI

Facioscapulohumeral muscular dystrophy

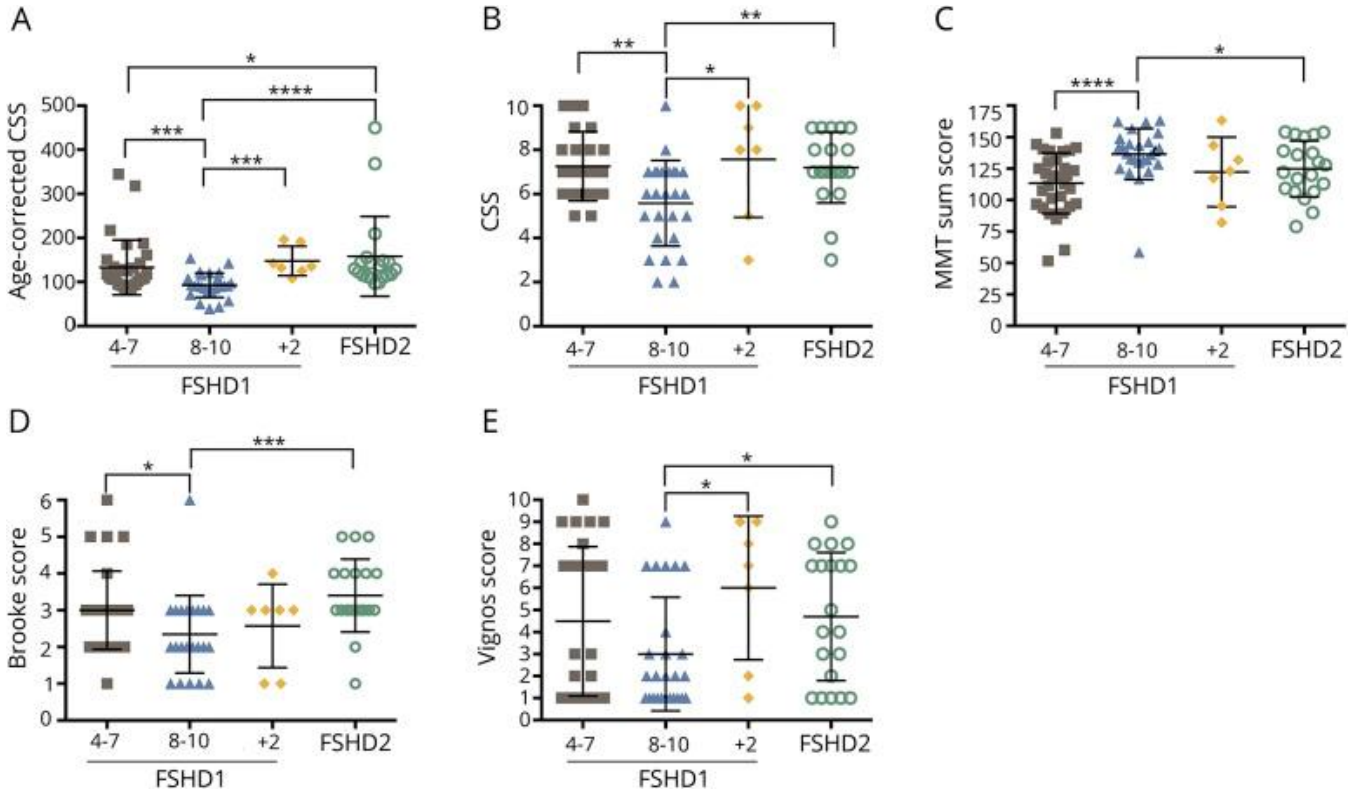
- Rare, genetic disorder in which skeletal muscle is replaced by fat
- Caused by aberrant expression of DUX4 gene
  - Autosomal dominant
- Onset and severity vary widely
  - Most develop symptoms as teens or young adults
  - Ranges from infantile onset to non-manifesting carriers
  - Variable progression, often with periods of progression and plateaus



Lek et al. Trends Mol Med 2015; 21 (5): 295-306

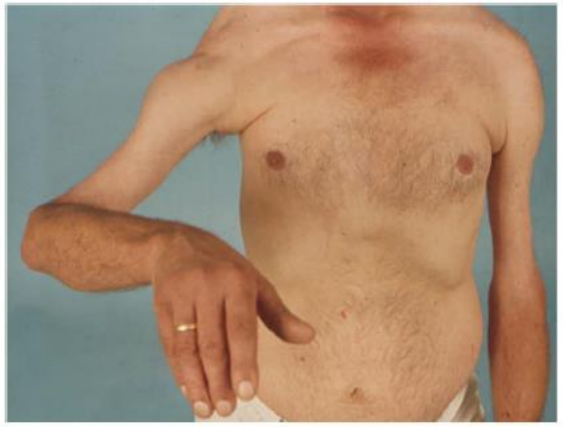
FSHD1 and 2 are clinically the same

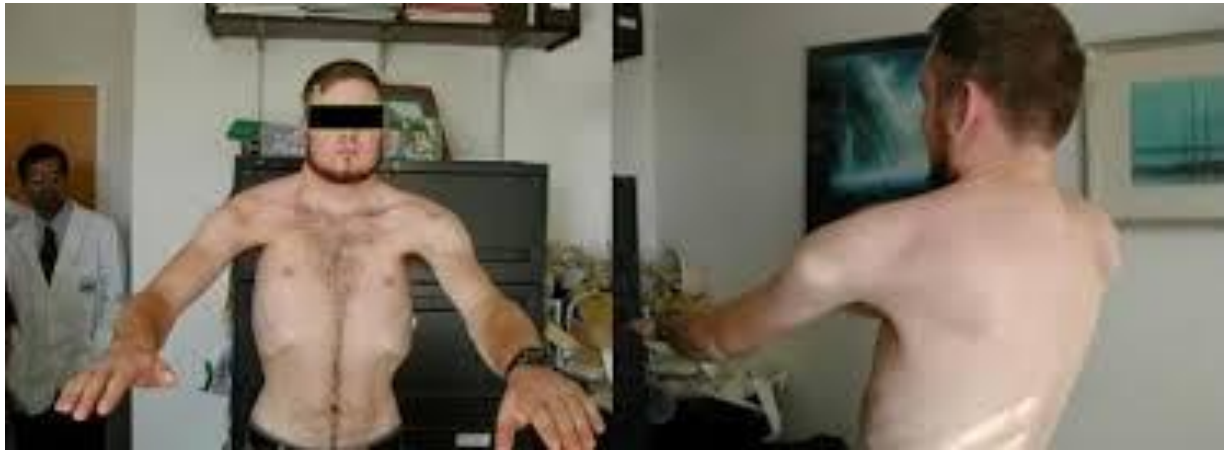
- Two forms of FSHD:
  - FSHD1 = ~95% of cases
  - FSHD2 = ~5% of cases
- Genetically distinct but both result in aberrant expression of DUX4
- Clinical manifestation is the same

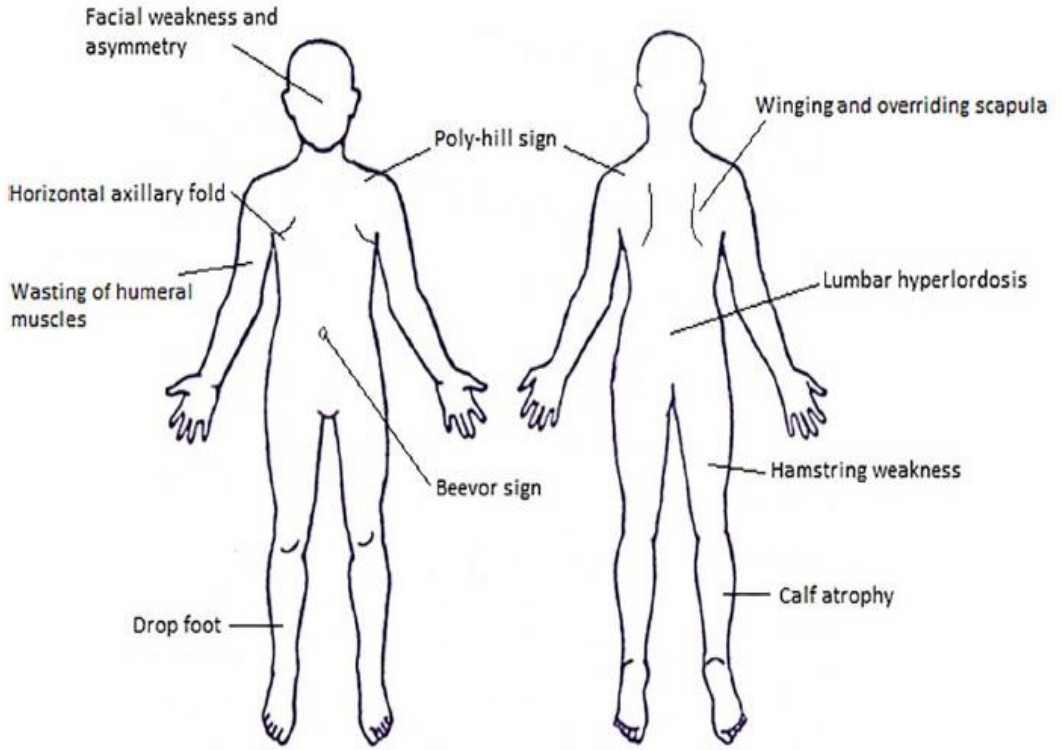


Sacconi, et al., 2019

Clinical presentation is heterogeneous







Mul K, *et al. Pract Neurol* 2016;**16**:201–207. doi:10.1136/practneurol-2015-001353

Symptoms ranked by impact on quality of life

Cross-sectional survey of 328 participants with FSHD

Table 4 Population impact score of symptomatic themes

Symptomatic themes	Population impact score[a]
Problems with shoulders or arms	2.59
Limitations with mobility or walking	2.49
Inability to do activities	2.36
Back, chest, or abdomen weakness	2.22
Changed body image due to disease	2.04
Fatigue	2.00
Pain	1.57
Problems with physical health	1.47
Decreased performance in social situations	1.29
Problems with hands or fingers	1.14
Decreased satisfaction in social situation	1.11
Emotional issues	0.97
Problems eating	0.48
Difficulty thinking	0.36
Communication difficulties	0.33

[a] Percentage of participants in whom an issue was experienced multiplied by the average life impact score of the issue.

Hamel J, et al., 2019

- >95% of patients reported problems with shoulders or arms as highest disease burden

How does FSHD affect day-to-day life?

Progressive weakening of muscles leads to significantly impaired function

- Inability to communicate via facial expression
- Inability to do activities requiring upper arms, including brushing hair, putting dishes on a shelf, shampooing, leading to loss of independence
- Difficulty getting out of bed
- Tripping and falling
- Difficulty walking unassisted
- Many become dependent on wheelchairs
- Chronic pain, extreme fatigue, anxiety and depression

Common co-morbidities

- Pain and Fatigue
  - Reported by 75% of patients in back, legs, shoulders and neck
  - 60% report fatigue
- Ophthalmologic
  - Retinal vasculopathy
  - Coats Syndrome
- Auditory
  - High frequency hearing loss
  - 1-3% requires hearing aid
- Respiratory
  - Mainly restrictive due to truncal weakness

Mul K, *et al. Pract Neurol* 2016;**16**:201–207. doi:10.1136/practneurol-2015-001353

Disease burden on patients and families

- Decline in function leads to loss of ability to maintain independence
  - Physical independence
  - Reliance on family and other caregivers
- Patient and family financial burden as disease progresses
  - Cost of supportive care
  - Loss of financial opportunity
  - Inability to work
  - Disruptive to family quality of life

FSHD is readily diagnosable

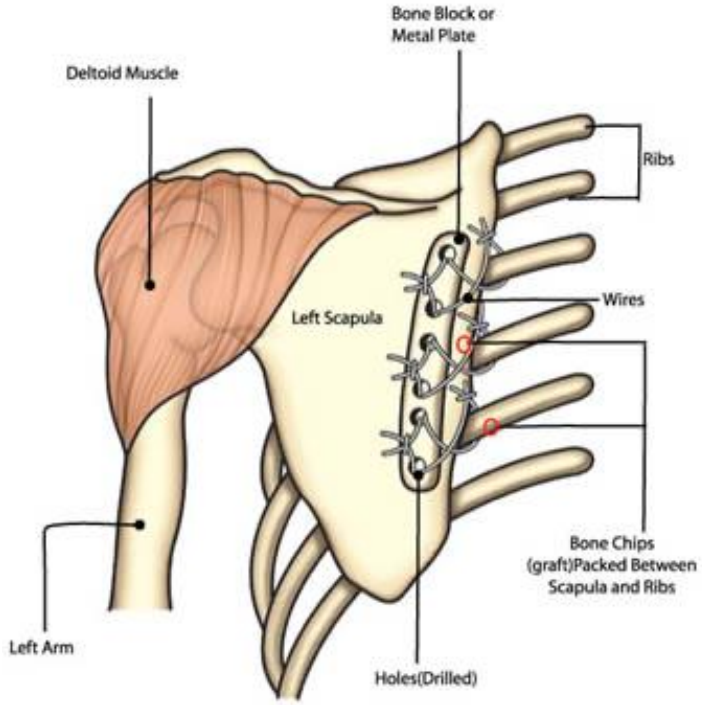
- Family members with clinical features (most common approach)
- Blood test for D4Z4 contraction (typically done in one family member due to expense)
- SMCHD1 gene test
- Methylation assay

No approved therapies for FSHD

- No therapy has been shown disease modification or clinical benefit
- Studies have denied benefit of:
  - Albuterol
  - Corticosteroids
  - Myostatin inhibitors
- No studies support supplement use
- Treatment of pain with standard therapies, avoid opioids

Clinical management: Surgical scapular fixation

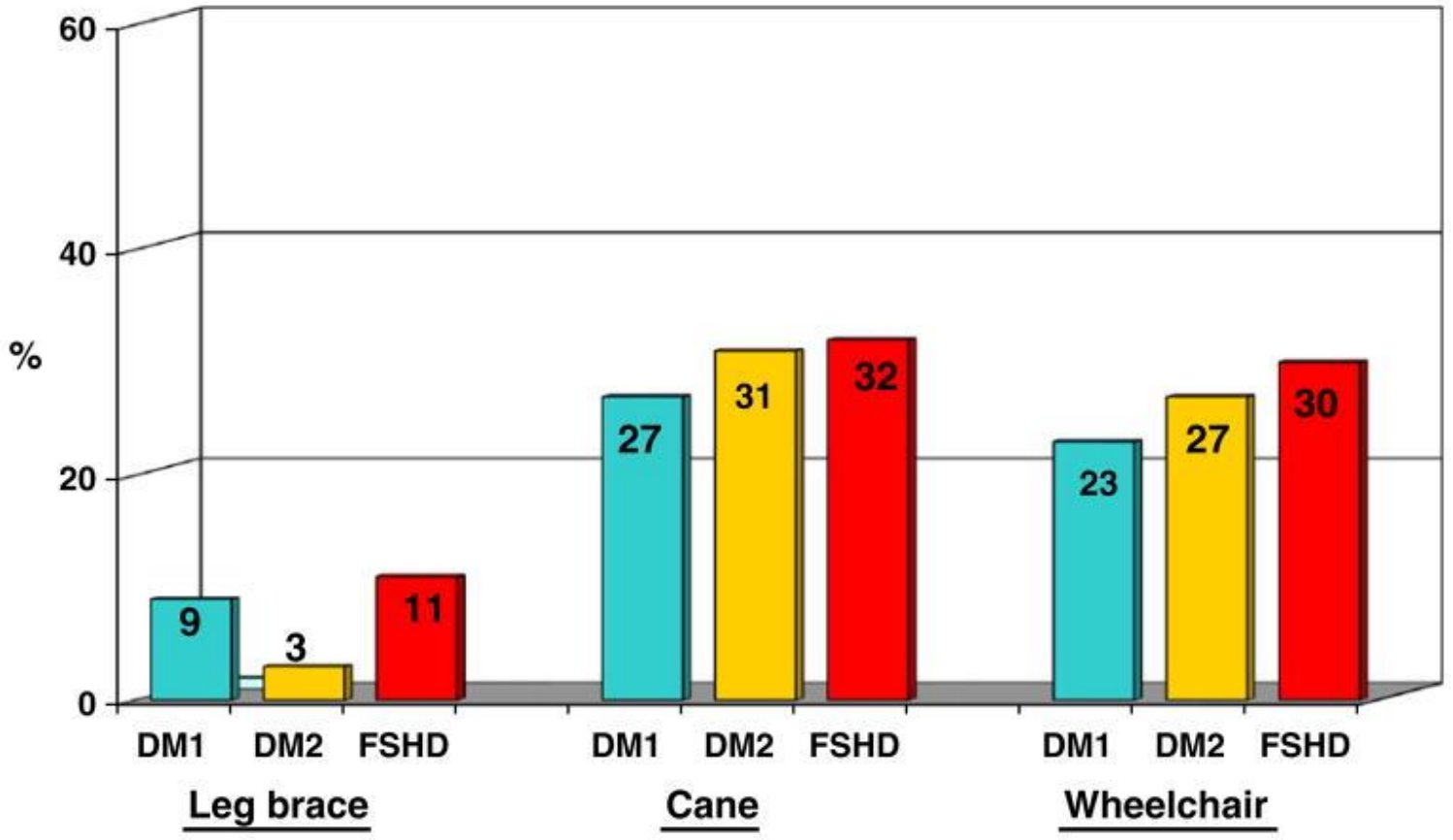
- Minority of patients benefit
- May improve shoulder range of motion in appropriate patients
- Can assess benefit with manual fixation
- Nothing else to help with shoulder and arm function



https://fsh-group.org/?page_id=273

Clinical management: assistive devices

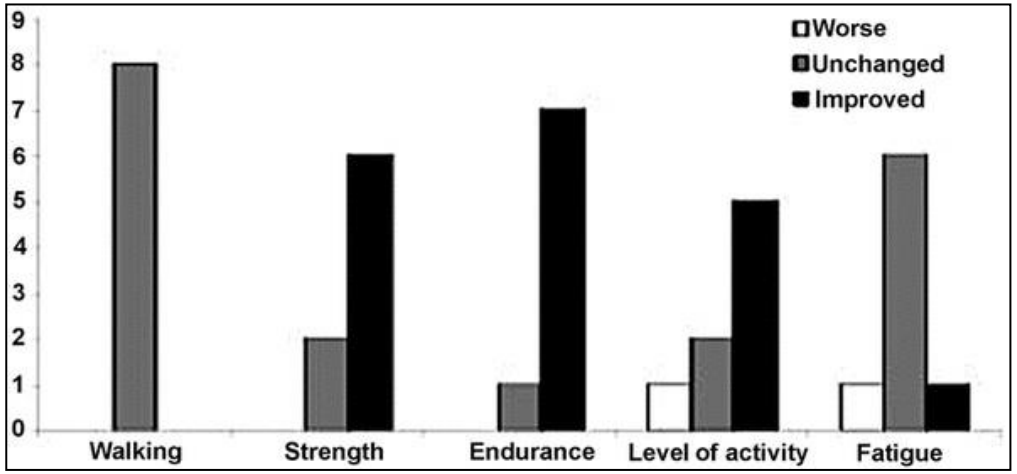
- Assistive devices
  - Leg braces
  - Canes
  - Wheelchairs



Hilbert, et al., 2012

Clinical management: Exercise

- Aerobic exercise has been shown to:
  - Improve endurance
  - Reduce fatigue
- Benefit diminishes as disease progresses and function declines
- Caution advised with weight bearing exercises



Aerobic training improves exercise performance in facioscapulohumeral muscular dystrophy.
Olsen, David; Orngreen, Mette; Vissing, John; MD, PhD

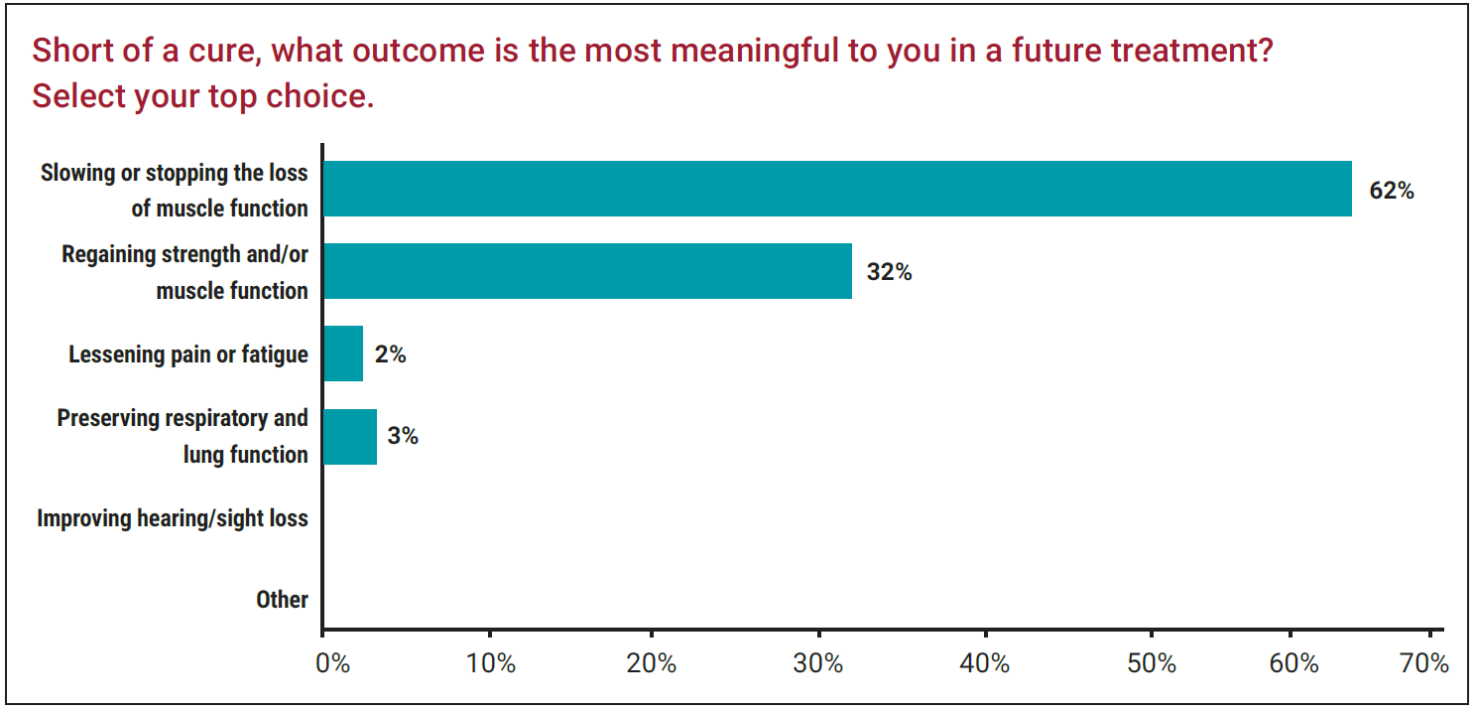
Neurology. 64(6):1064-1066, March 22, 2005.
DOI: 10.1212/01.WNL.0000150584.45055.27

Functional decline requires annual monitoring

- Pulmonary function at baseline and with symptoms
- Retinal monitoring in appropriate patients
- Pain screen
- Hearing screen

Patients Want a Disease-Modifying Therapy

FSHD Voice of Patient Report Underscores Need for Therapy to Slow or Stop Disease Progression



"I would like to see something that would **stop progression** of the disease."
– 26-year-old woman

"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

"Losing my **independence** is probably the most frightening and helpless feeling I have ever had".
– 50-year-old man

Arjomand J, et al. Facioscapulohumeral muscular dystrophy (FSHD) voice of the patient report. Published November 5, 2020. Accessed March 1, 2021. https://www.fshdsociety.org/wp-content/uploads/2020/11/Voice-of-the-Patient-Report-FINAL.pdf.

What would an ideal therapy look like?

- Oral
- Safe and well-tolerated
- Disease-modifying – slows or stops disease progression

Therapy with this profile would be used immediately after diagnosis

- Unclear the extent of muscle recovery with long standing damage, so early treatment is essential

Summary

- Progressive and debilitating disease
- No approved therapies
- Readily diagnosable by family history and genetic testing
- Current management limited to symptomatic treatments, assistive devices, exercise and surgery
  - Benefit diminishes as disease progresses and function declines
- Safe, well-tolerated, disease-modifying therapy would be life-changing for patients

Losmapimod Overview and REACH Phase 3 Trial Design

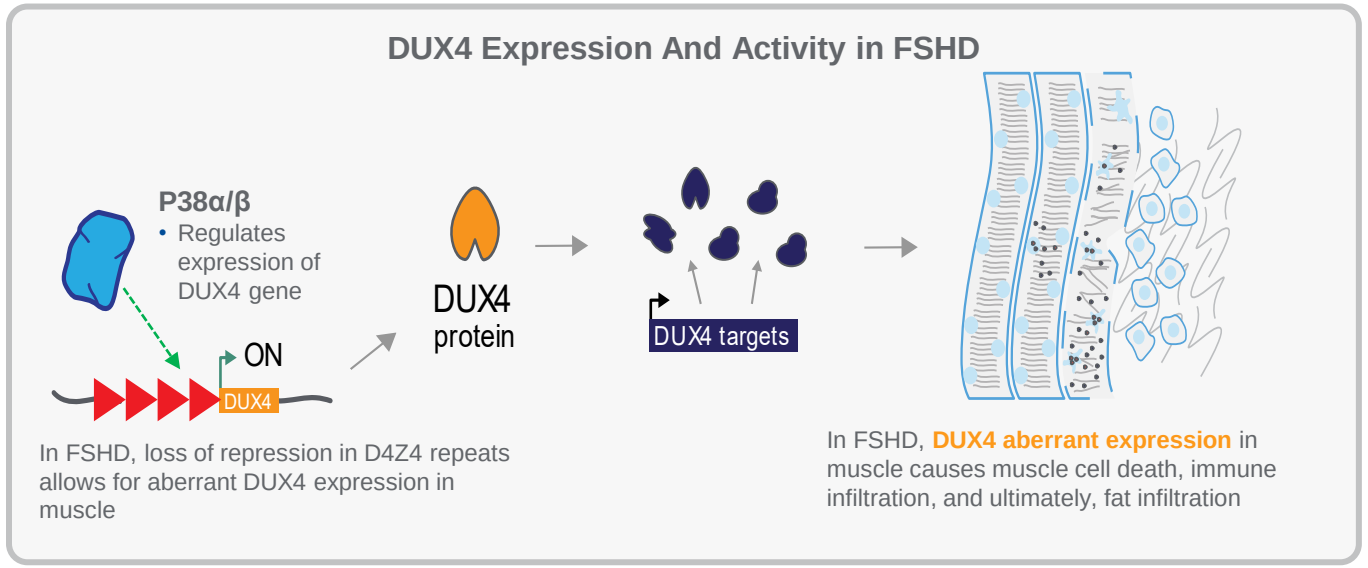
Judith Dunn, Ph.D.
President, Research & Development

Fulcrum Therapeutics

Losmapimod: Potential First-to-Market Therapy for FSHD

FulcrumSeek™ identified losmapimod as optimal 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 Demonstrated Treatment Benefit and Characterized Safety of Losmapimod

Function

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

Muscle Health

Decreased **MFI** as measured by MRI

Quality of Life

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

Safety and Tolerability

Clinical experience in ~3,600 people

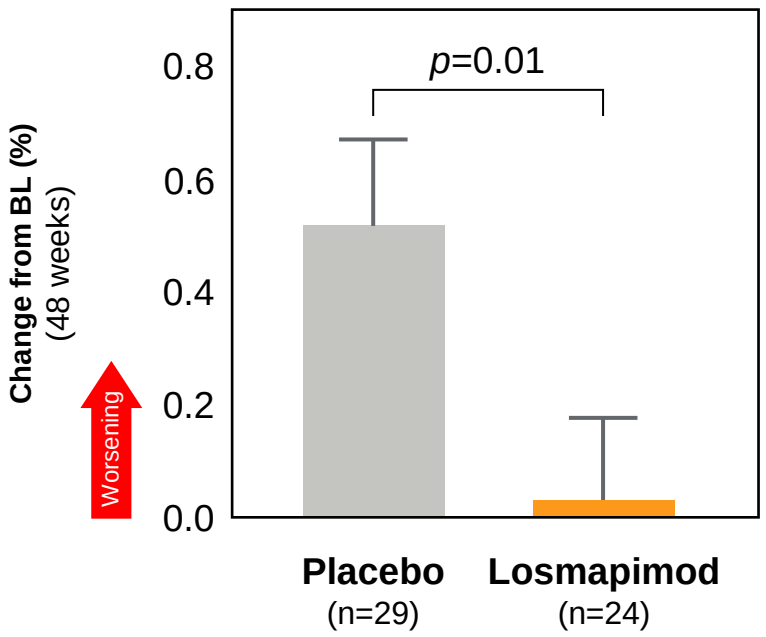
ReDUX4 enrolled 80 people with FSHD in a randomized, double-blind, placebo-controlled Phase 2b trial with a 48-week treatment period

REACH Trial Design Leverages Learnings from ReDUX4

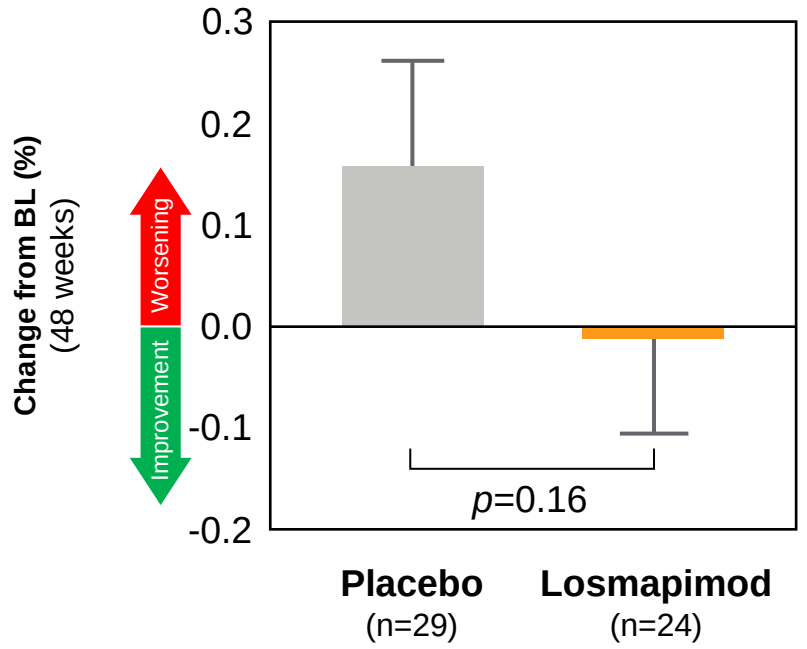
What we know from ReDUX4	REACH Phase 3 Trial Design
Losmapimod demonstrated measurable impact on disease progression at 48 weeks of treatment	48-week treatment duration
Reachable Workspace (RWS) is a reliable and quantifiable measure of function and disease progression	RWS is primary endpoint
Muscle 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

Losmapimod Decreased Muscle Fat Infiltration (MFI)

Losmapimod slowed fat infiltration in muscles already affected by disease

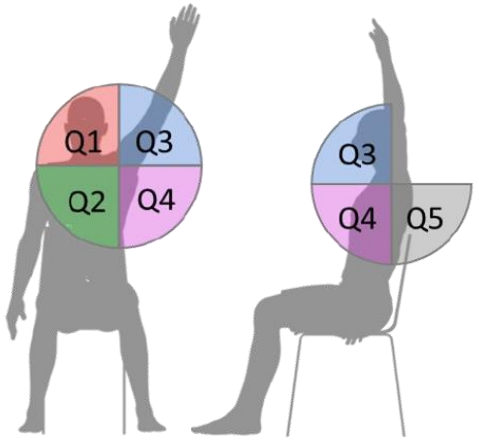


Losmapimod preserved health of normal-appearing muscles



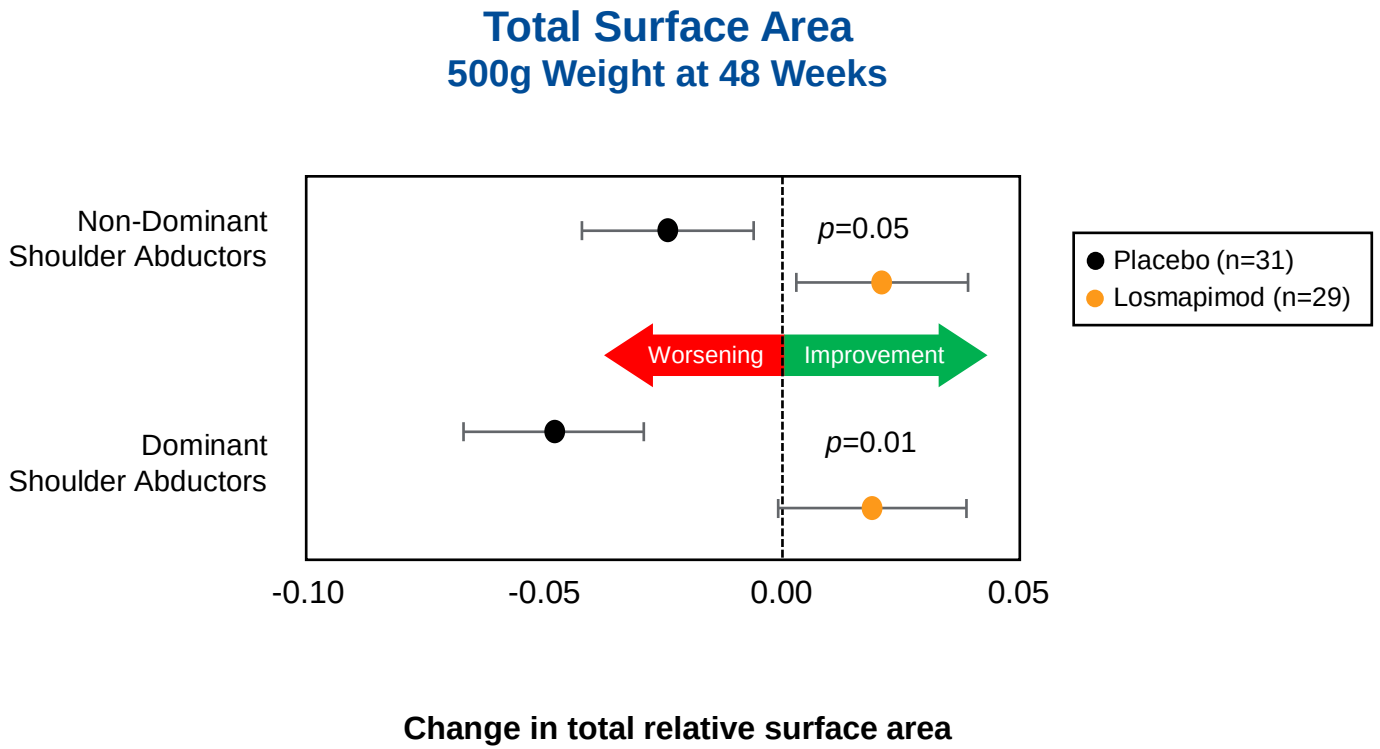
Data from ReDUX4 trial

Losmapimod Showed Significant Improvement in RWS



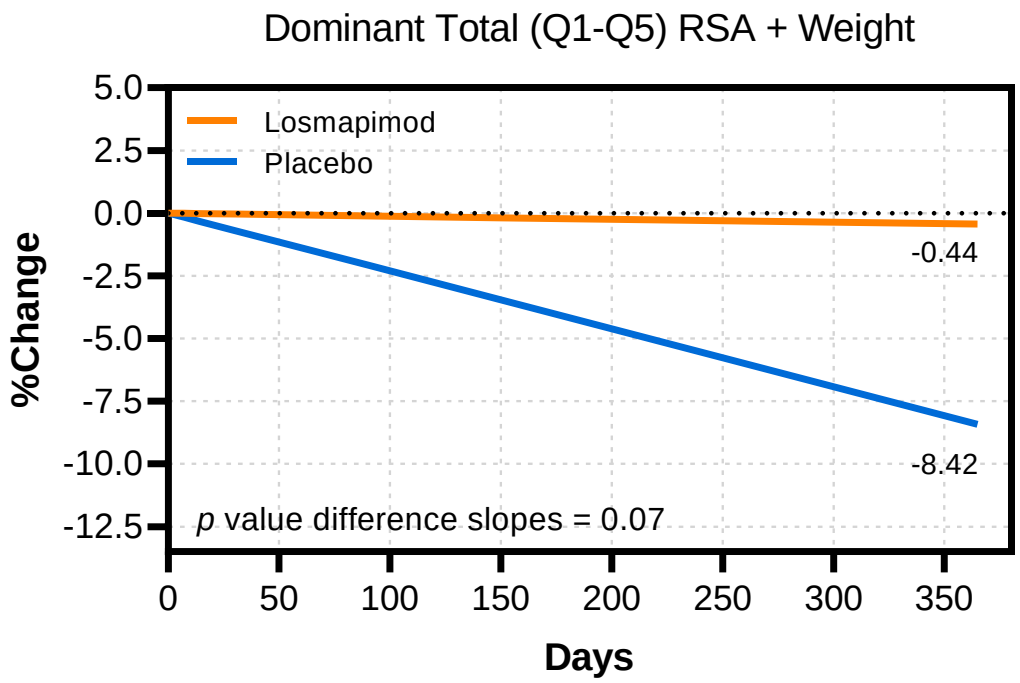
Reachable Workspace (RWS) is:

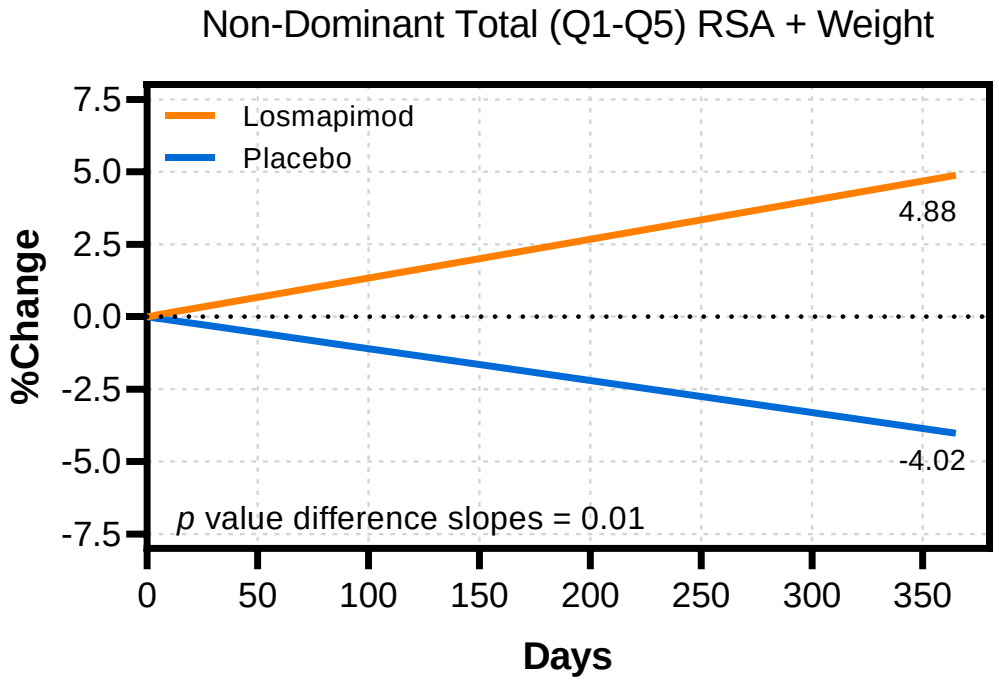
- Quantitative measure of upper extremity range of motion and function
- Objectively measured
- Highly correlated with ability to perform activities of daily living and maintain independence



Data from ReDUX4 trial

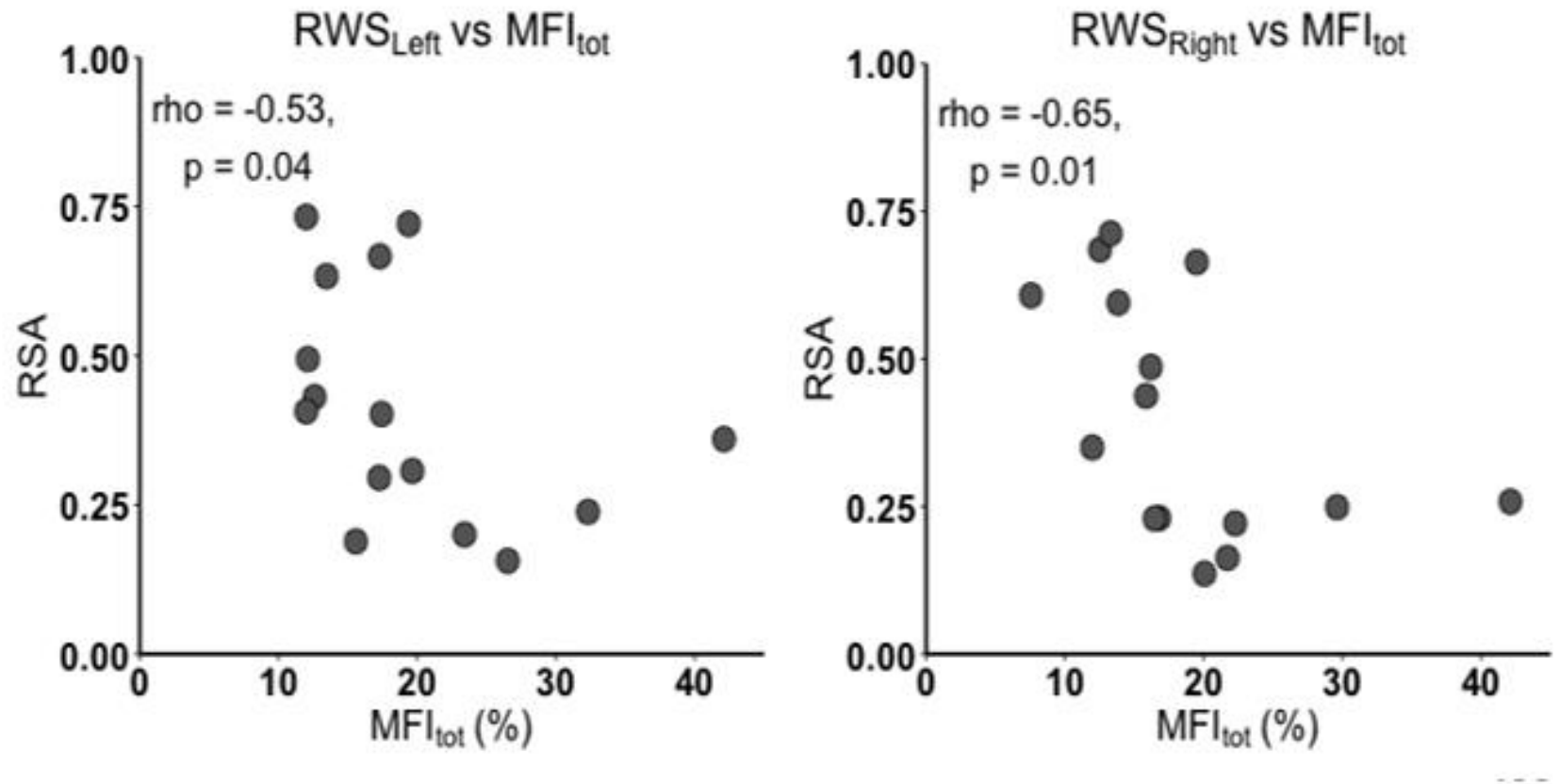
Annualized Rate of Change Shows that Losmapimod Slows Disease Progression





Data from ReDUX4 trial. 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

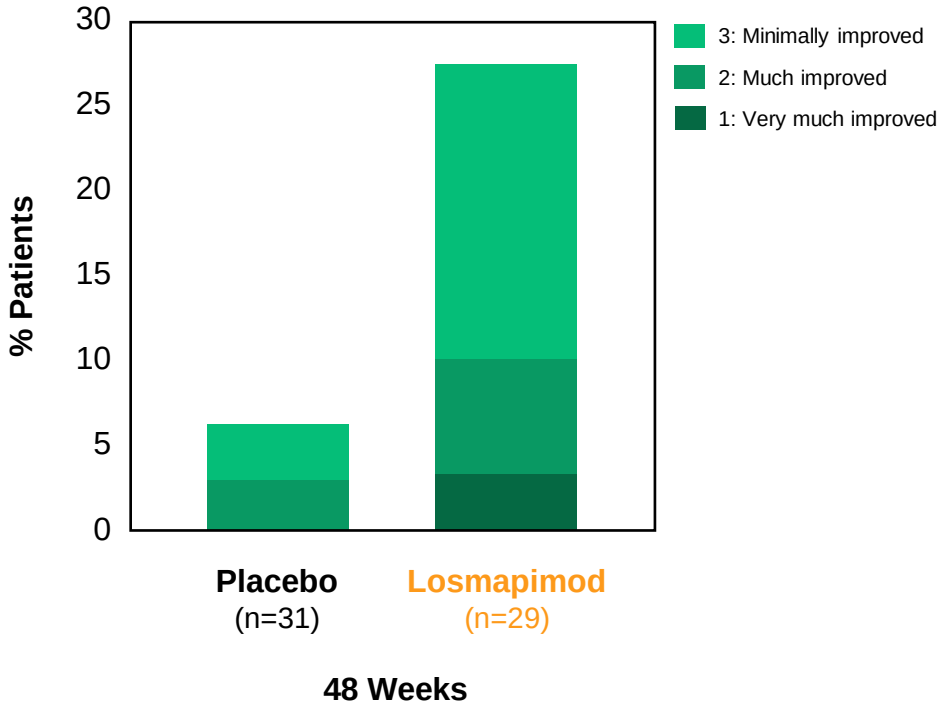
Function (RWS) Correlates with Muscle Health (MFI)



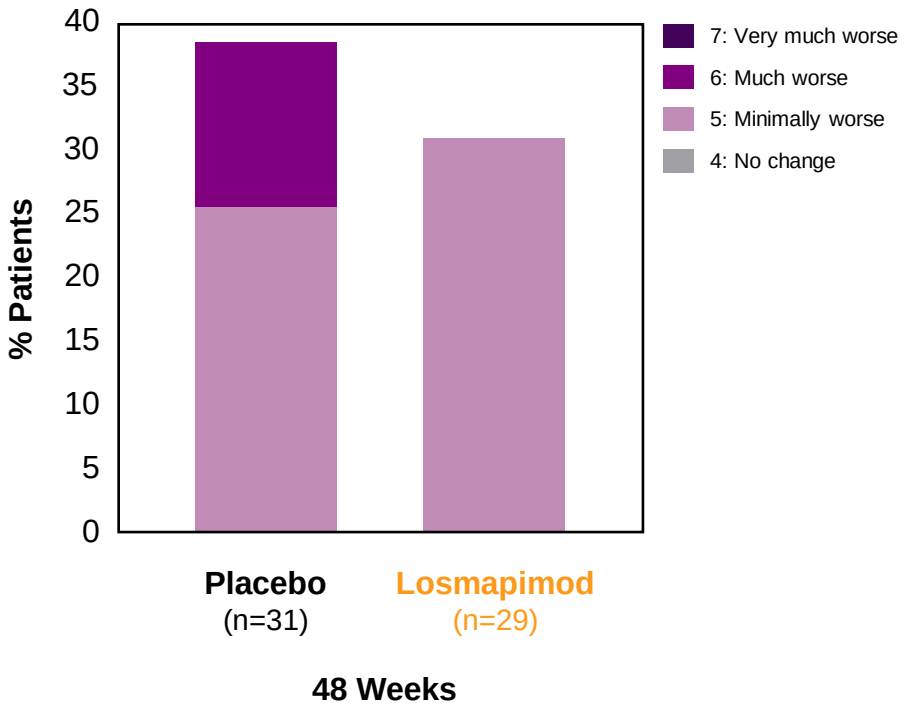
Analysis of data from ReDUX4 trial

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



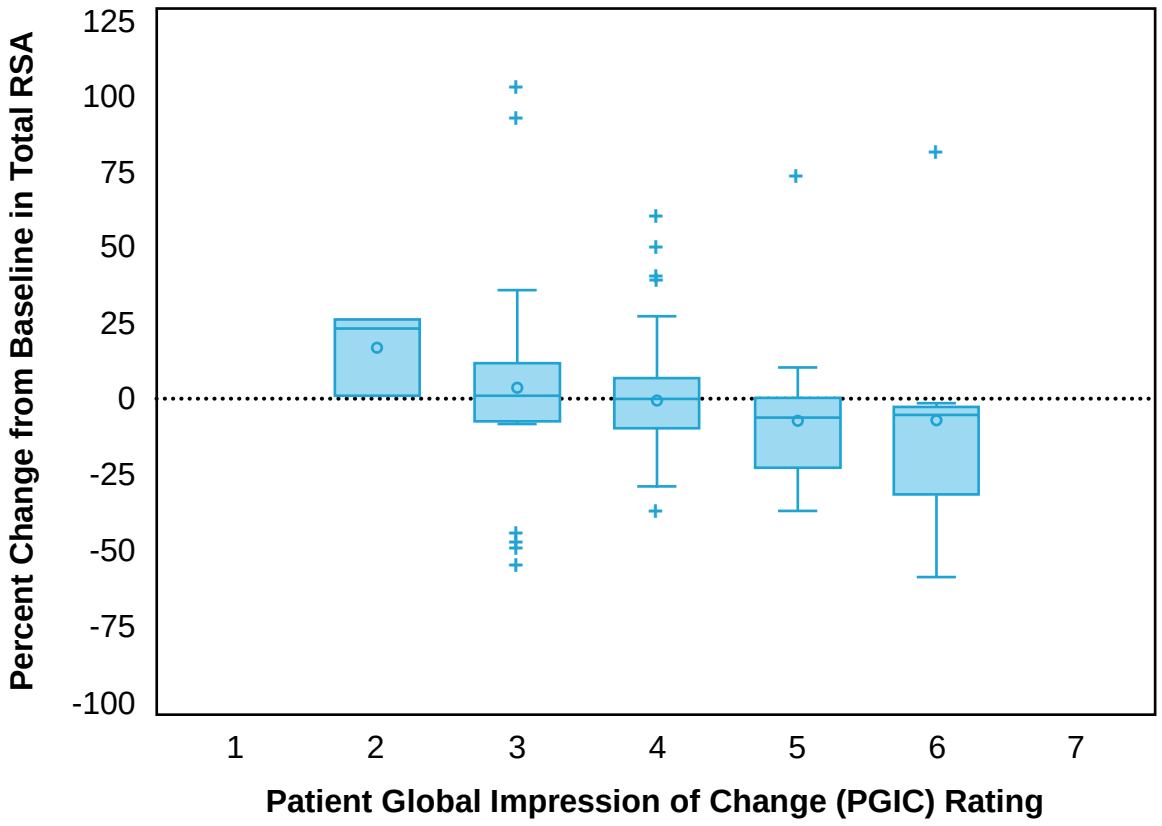
Patients' Global Impression of Change (PGIC)

Data from ReDUX4 trial

Direct Relationship Between RWS and How Patients Feel

Placebo Group

Dominant Total RSA (Q1-5) with Weight vs PGIC Score



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

Extensive Safety and Tolerability Data

- 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 **>3,600** clinical study participants

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

Data from ReDUX4 trial.

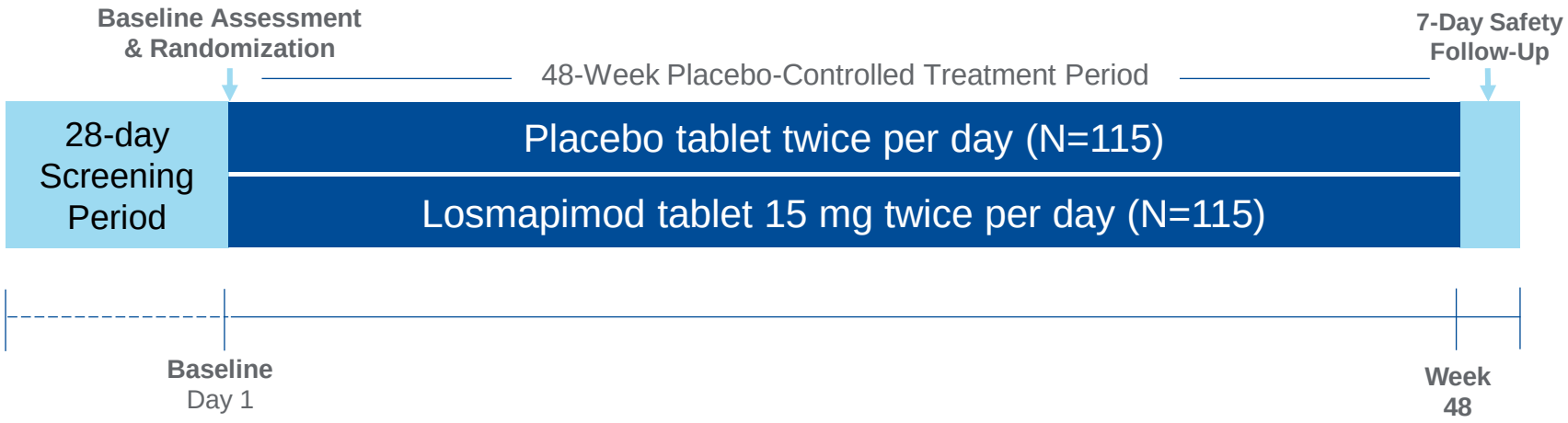
REACH: A Phase 3 Trial of Losmapimod in FSHD

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

Study Population

~230 subjects with FSHD1 and FSHD2, 18-65 years old, enriched for progression as measured by RWS

Study Design



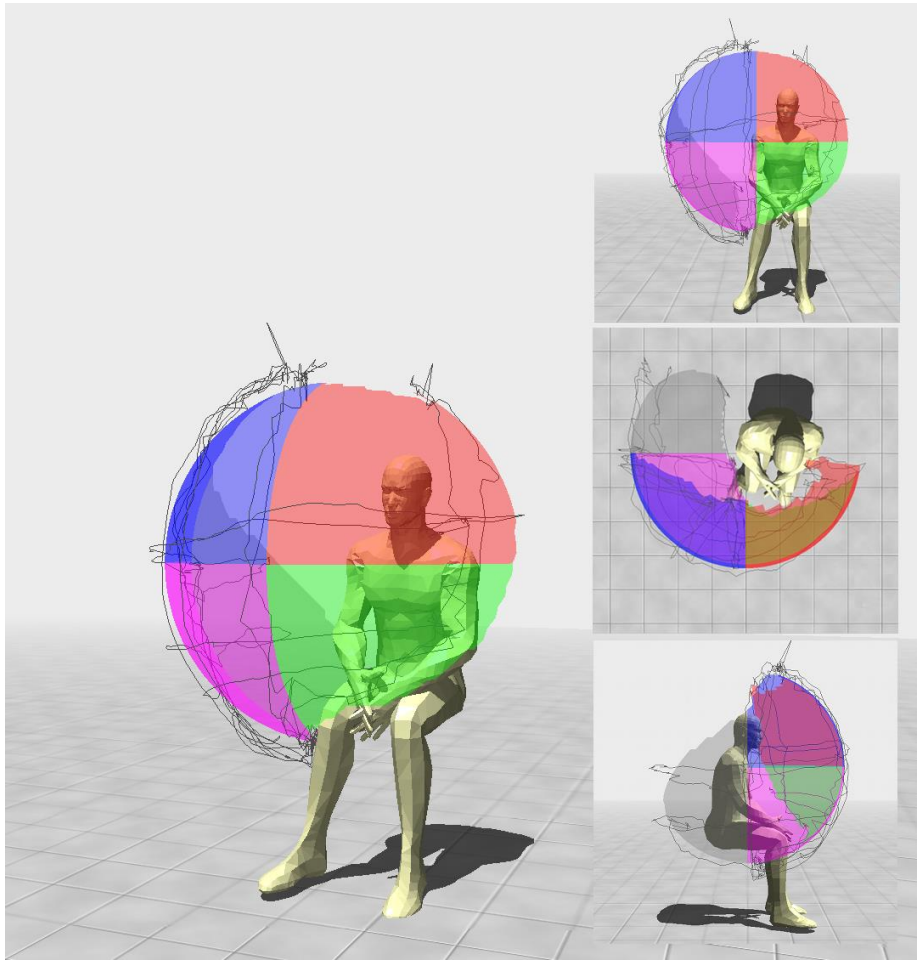
Study Endpoints

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

Summary

- Losmapimod targets root cause biology of FSHD
- ReDUX4, the most comprehensive interventional FSHD trial, demonstrated that losmapimod slows or stops disease progression
  - RWS demonstrates preservation of function
  - MRI showed decreases in muscle fat infiltration (MFI)
  - PGIC indicates that patients recognize the benefits of losmapimod
  - Generally well-tolerated with no serious treatment-related adverse events
- REACH was informed by extensive clinical program and designed with input from patients, KOLs and regulatory agencies
- REACH is optimized to show benefit on muscle health, function, and patient-reported outcomes
- REACH is intended to serve as basis for approval of losmapimod for the treatment of FSHD

Reachable Workspace (RWS) in FSHD



Jay J. Han, MD

Professor

UC Irvine School of Medicine

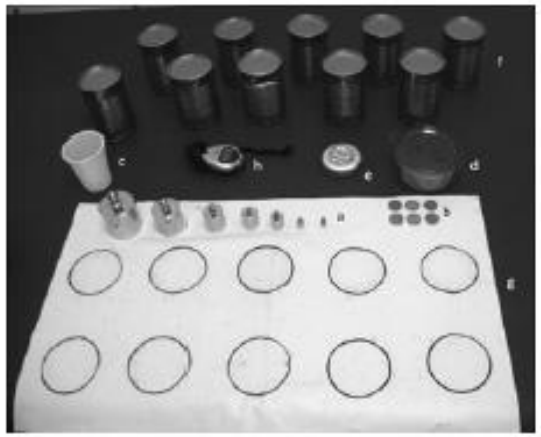
Disclosures

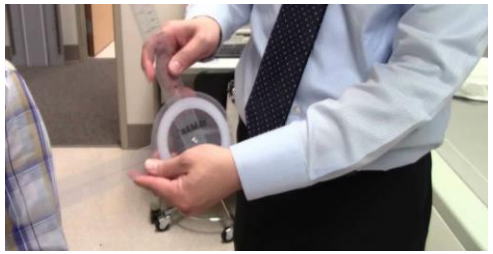
- Dr. Han is a consultant for Fulcrum and Sanofi
- Dr. Han serves as Head of Medical Affairs for Bioniks

Advances in neuromuscular research are driving need for sensitive and quantitative clinical endpoints

- Lack of sensitive, quantitative and clinically relevant endpoints
- Neuromuscular discovery research has been increasingly active
  - Small and large molecule drug candidates
  - Gene and cell therapies
  - Assistive devices and robotics
- Need for effective endpoints to:
  - Identify clinical outcome measures for planned efficacy trials
  - Improve monitoring of disease severity and progression
  - Better characterize natural history studies

Traditional tools





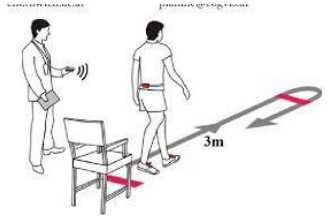
Neuro-QOL Item Bank v1.0 – Upper Extremity Function- Fine Motor, ADL

Upper Extremity Function- Fine Motor, ADL

Please respond to each question or statement by marking one box per row.

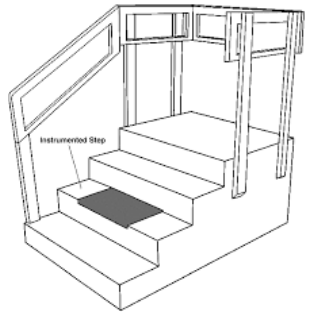
		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA40	Are you able to turn a key in a lock?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA50	Are you able to brush your teeth?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX44	Are you able to make a phone call using a touch tone key-pad?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB21	Are you able to pick up coins from a table top?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA43	Are you able to write with a pen or pencil?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA35	Are you able to open and close a zipper?...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body?..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA22	Are you able to open previously opened jars?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB22	Are you able to hold a plate full of food?..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA47	Are you able to pull on trousers?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA54	Are you able to button your shirt?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB41	Are you able to trim your fingernails?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA46	Are you able to cut your toe nails?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA9	Are you able to bend down and pick up clothing from the floor?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

English ©2010 David Cella, PhD Page 1 of 2

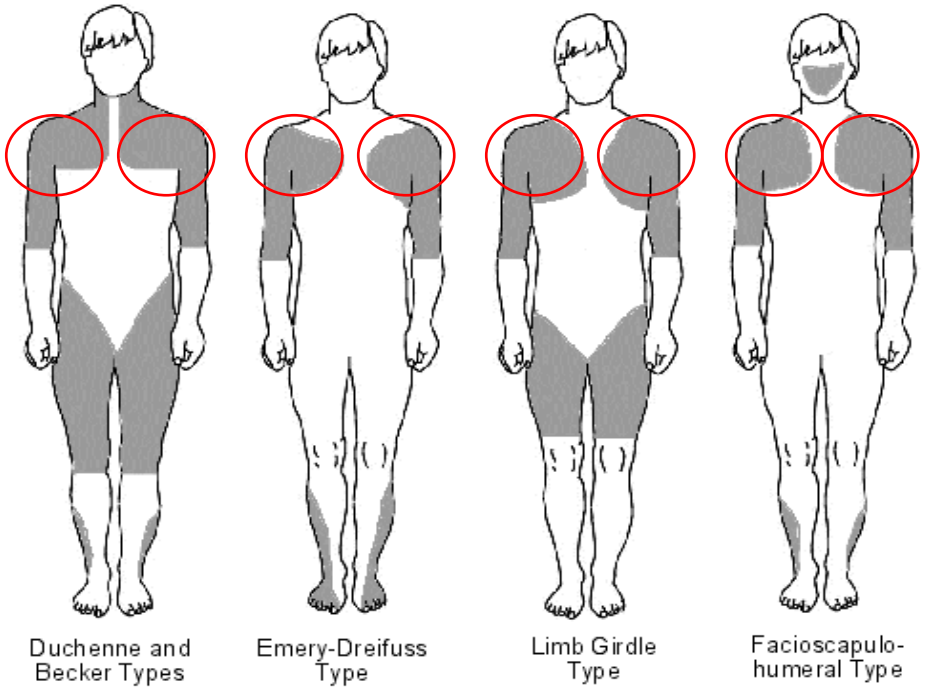


B rooke Upper Extremity Rating Scale

Grade	Description
1	Starting with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head. *
2	Can raise arms above head only by flexing the elbow (shortening the circumference of the movement) or using accessory muscles.*
3	Cannot raise hands above head, but can raise an 8-oz glass of water to the mouth.
4	Can raise hands to the mouth, but cannot raise an 8-oz glass of water to the mouth.
5	Cannot raise hands to the mouth, but can use hands to hold a pen or pick up pennies from the table.
6	Cannot raise hands to the mouth and has no useful function of hands.



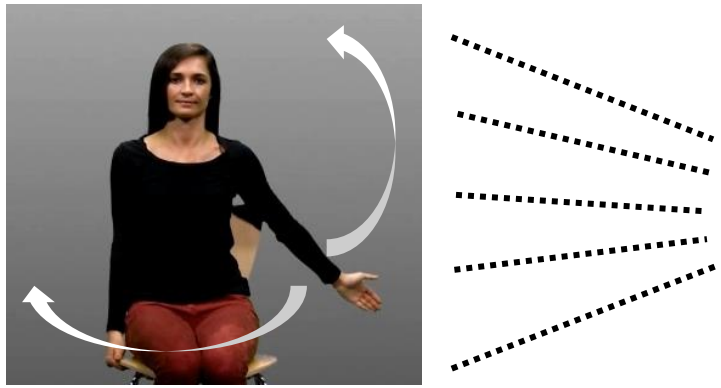
What do we measure?



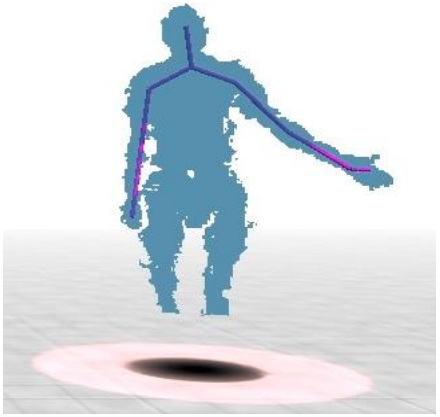
- Stereotypical pattern of muscle weakness in NMD
  - Proximal > distal weakness – limb girdle weakness pattern

RWS was developed as functional endpoint to quantify Upper Extremity impairment and measure disease progression

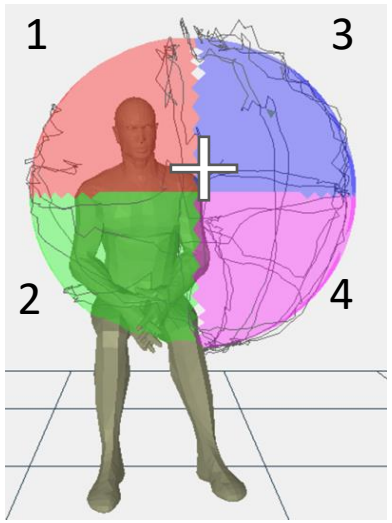
Arm movement protocol

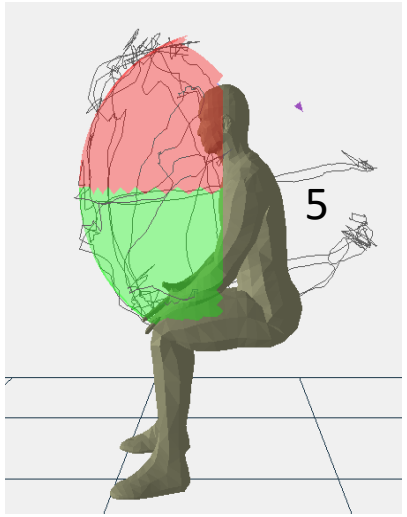


Kinect sensor detected arm motion

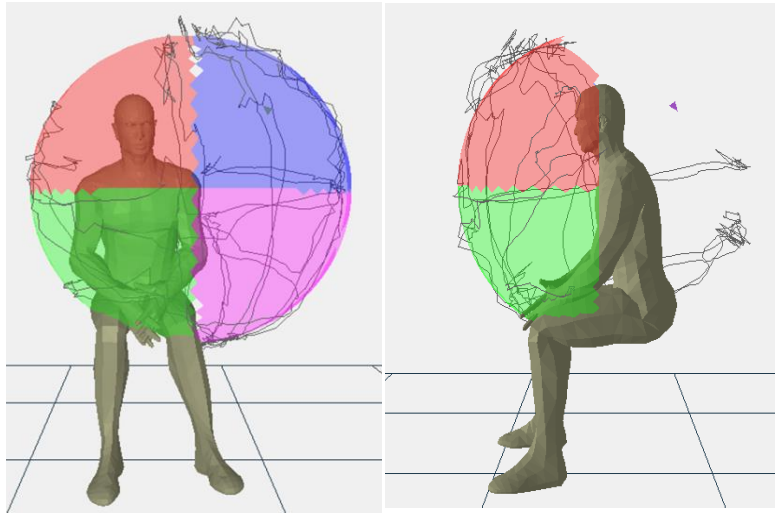


Reconstructed Reachable Workspace: Q1-Q5





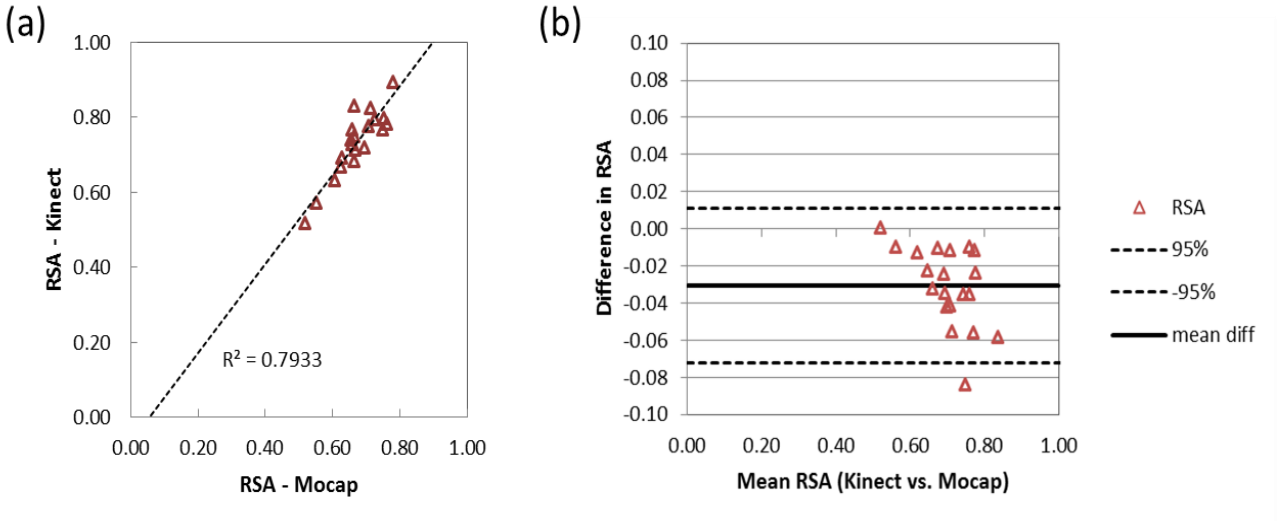
RWS is quantitative, non-invasive, and intuitive with simple patient interface



- Simple
- Quick
- Unobtrusive (no markers)
- Intuitive (visualization of reachable workspace)

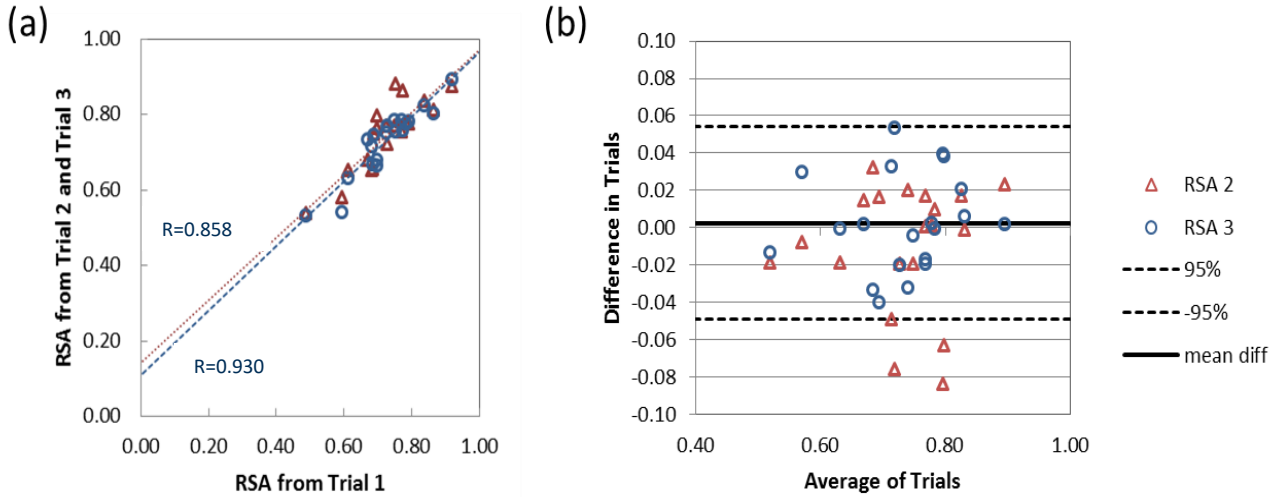
Kinect Reachable Workspace RSA - Reliability testing

Kinect vs. Motion capture



Test and retest

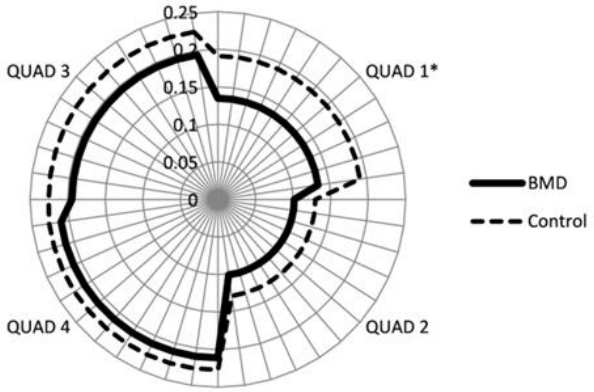
FSHD: R=0.952

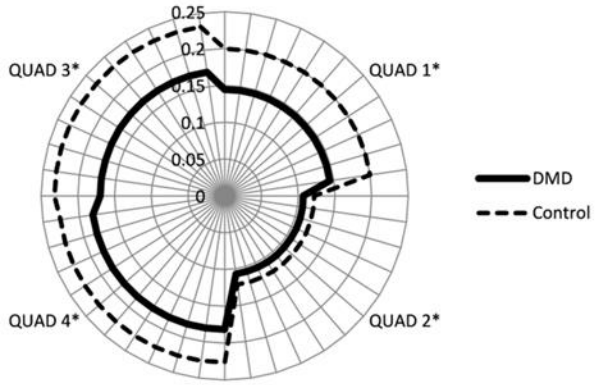


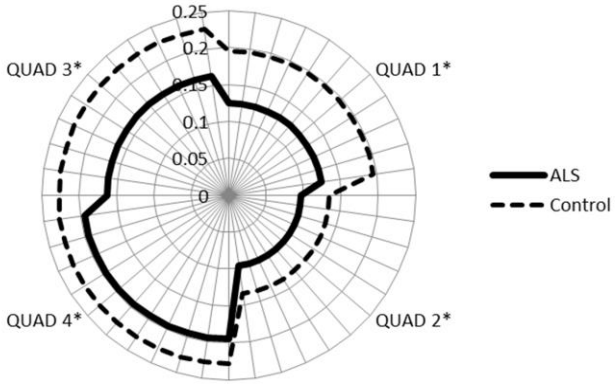
Han JJ, de Bie E, Nicorici A, Abresch RT, Bajcsy R, Kurillo G. Muscle Nerve. 2015 Dec;52(6):948-55.

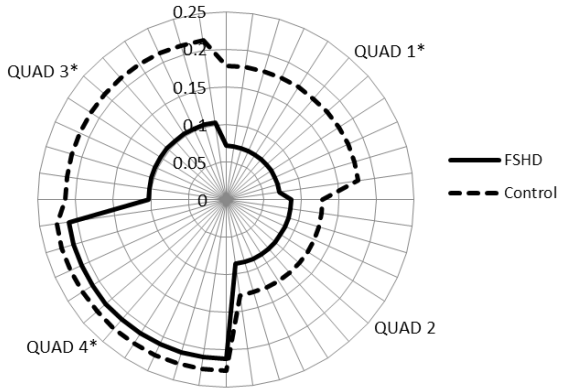
Kurillo G, Chen A, Bajcsy R, Han JJ. Evaluation of upper extremity reachable workspace using Kinect camera. Technol Health Care. 2013;21(6):641-56

Reachable Workspace Shown to be Effective in DMD, BMD, FSHD, and ALS



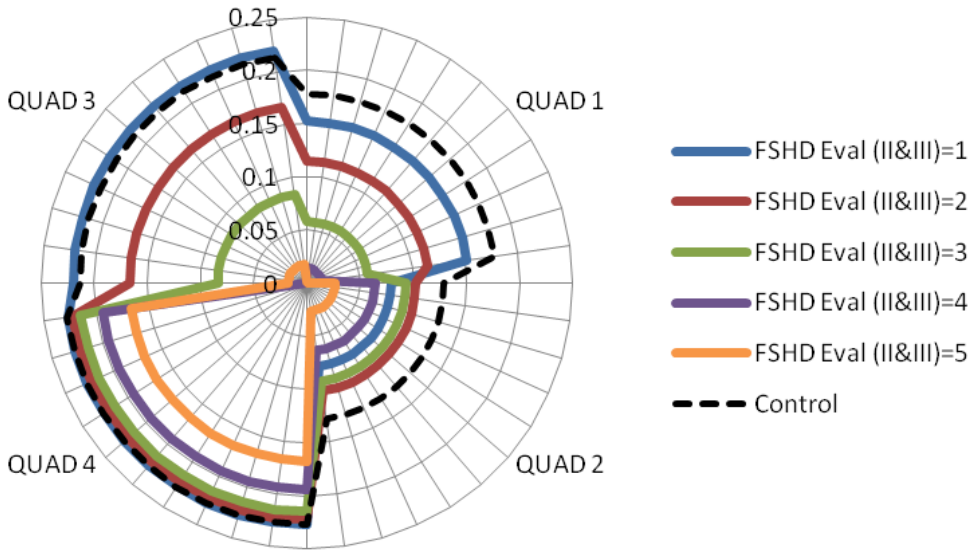






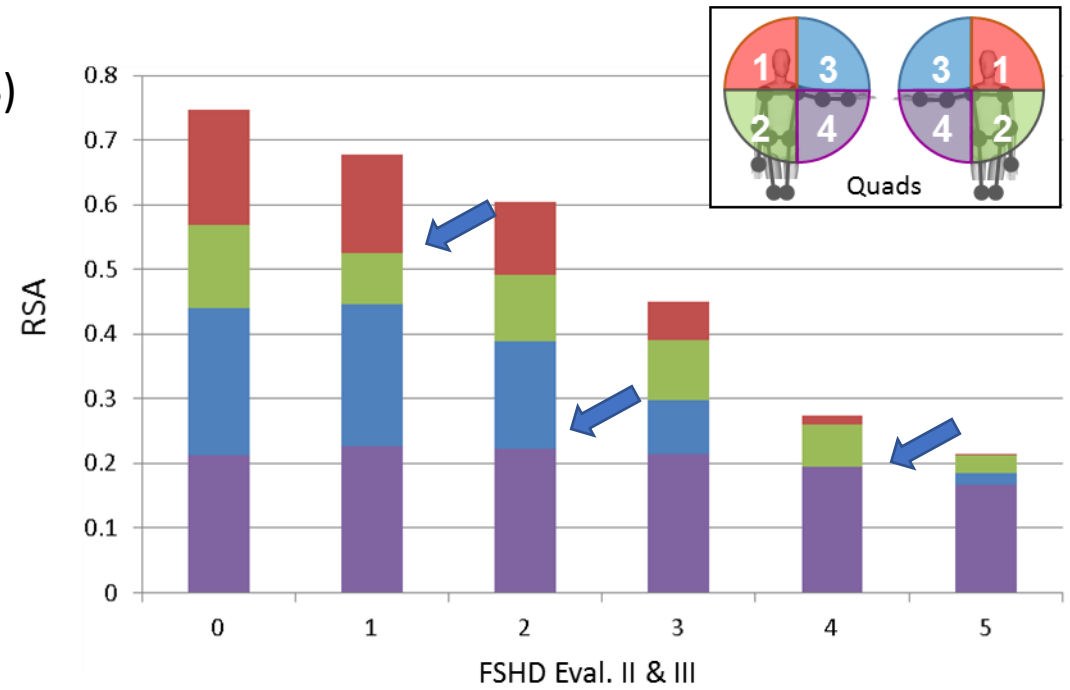
RWS correlates with disease severity

(A)



RSA vs. FSHD Eval Score (II + III)

(B)

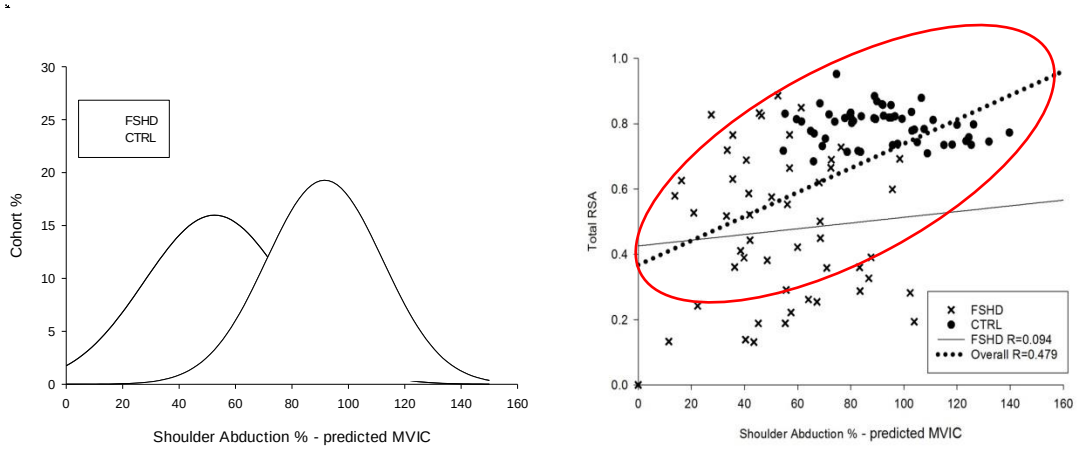


Han JJ, Kurillo G, Abresch RT, de Bie E, Nicorici A, Bajcsy R. Reachable Workspace in Facioscapulohumeral muscular dystrophy (FSHD) by Kinect. Muscle Nerve. 2015 Feb;51:168-75.

Strength is correlated with RWS

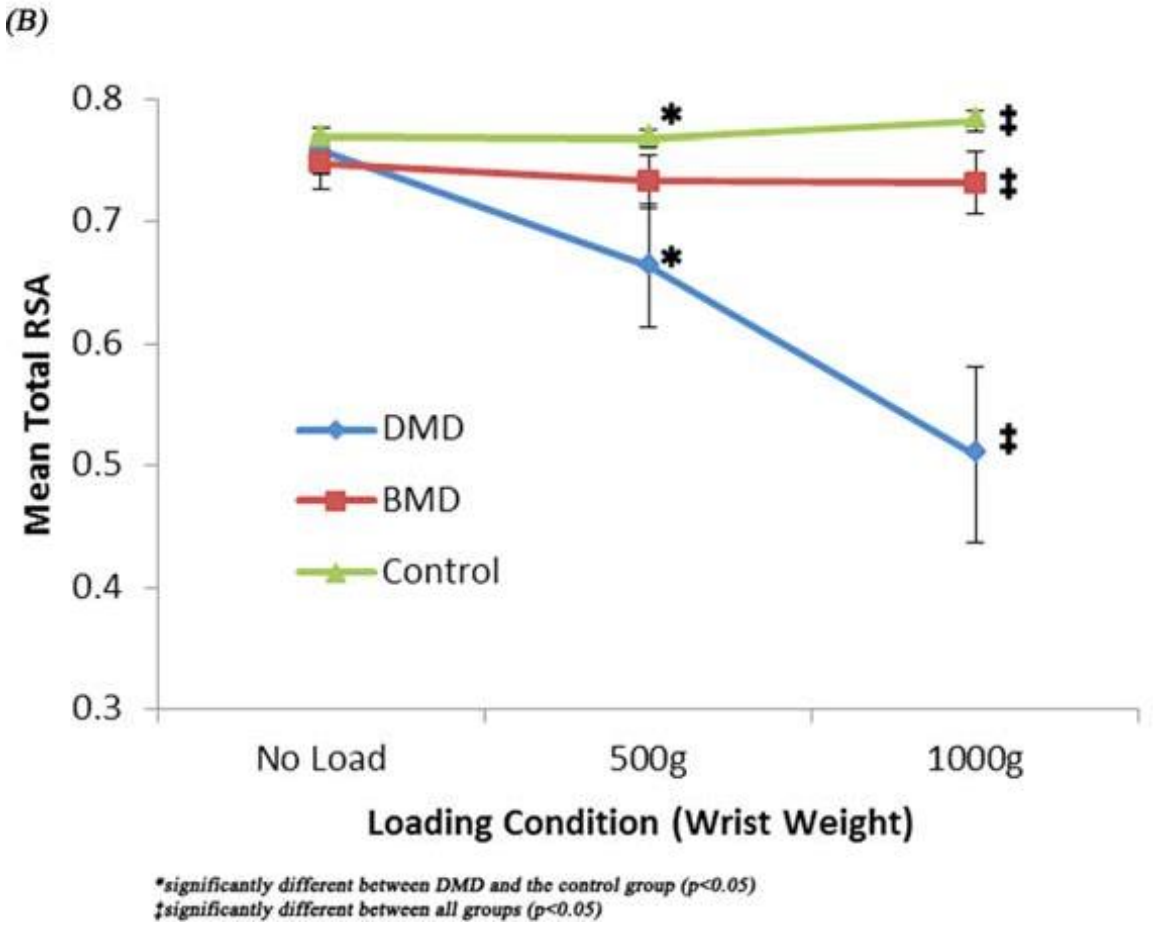
Shoulder Abduction

RSA vs. Strength (FSHD)



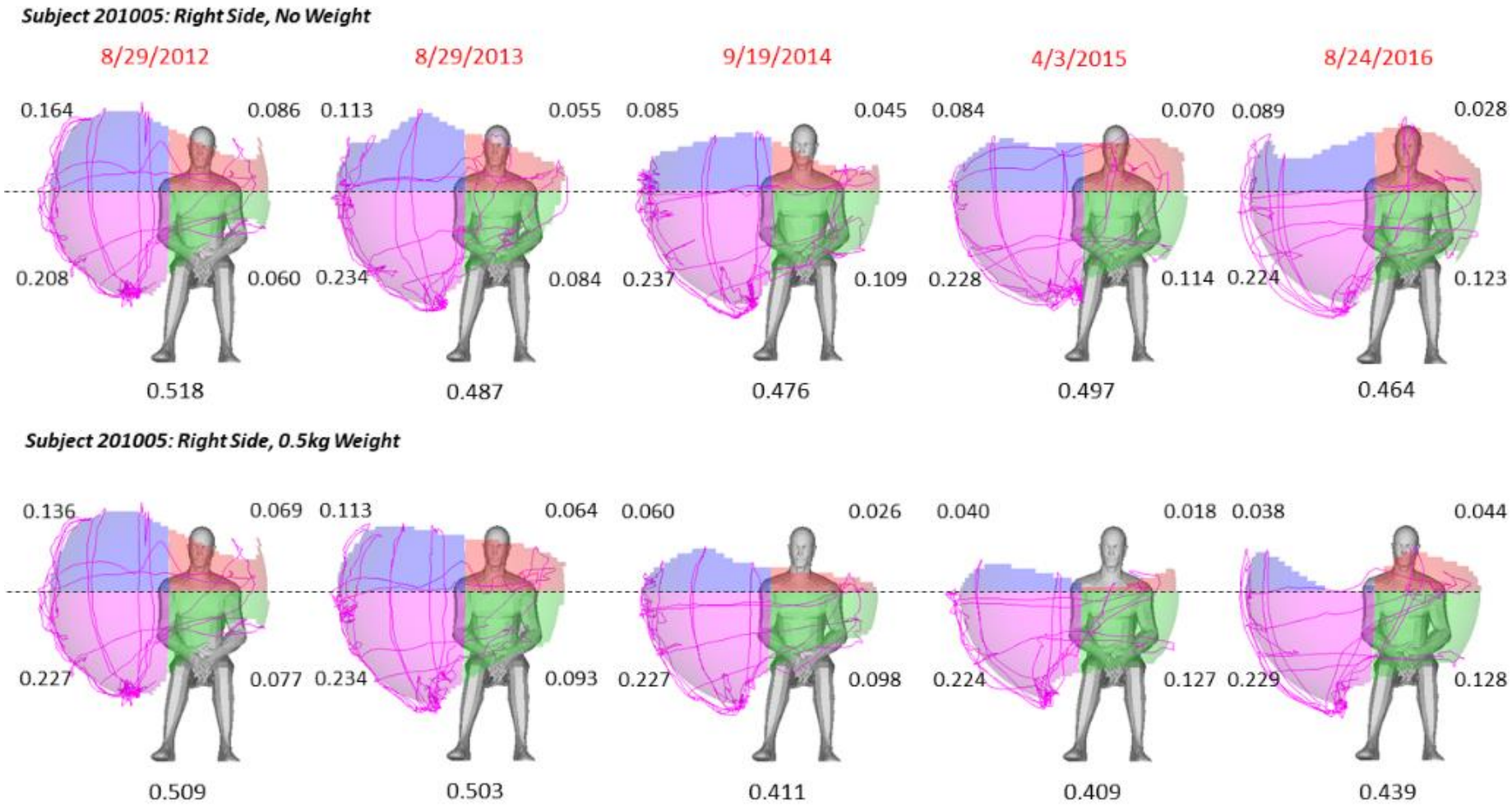
Han JJ, de Bie E, Nicorici A, Abresch RT, Bajcsy R, Kurillo G. Muscle Nerve. 2015 Dec;52(6):948-55.

Using simple wrist-weight increases ability to detect subtle differences in Reachability



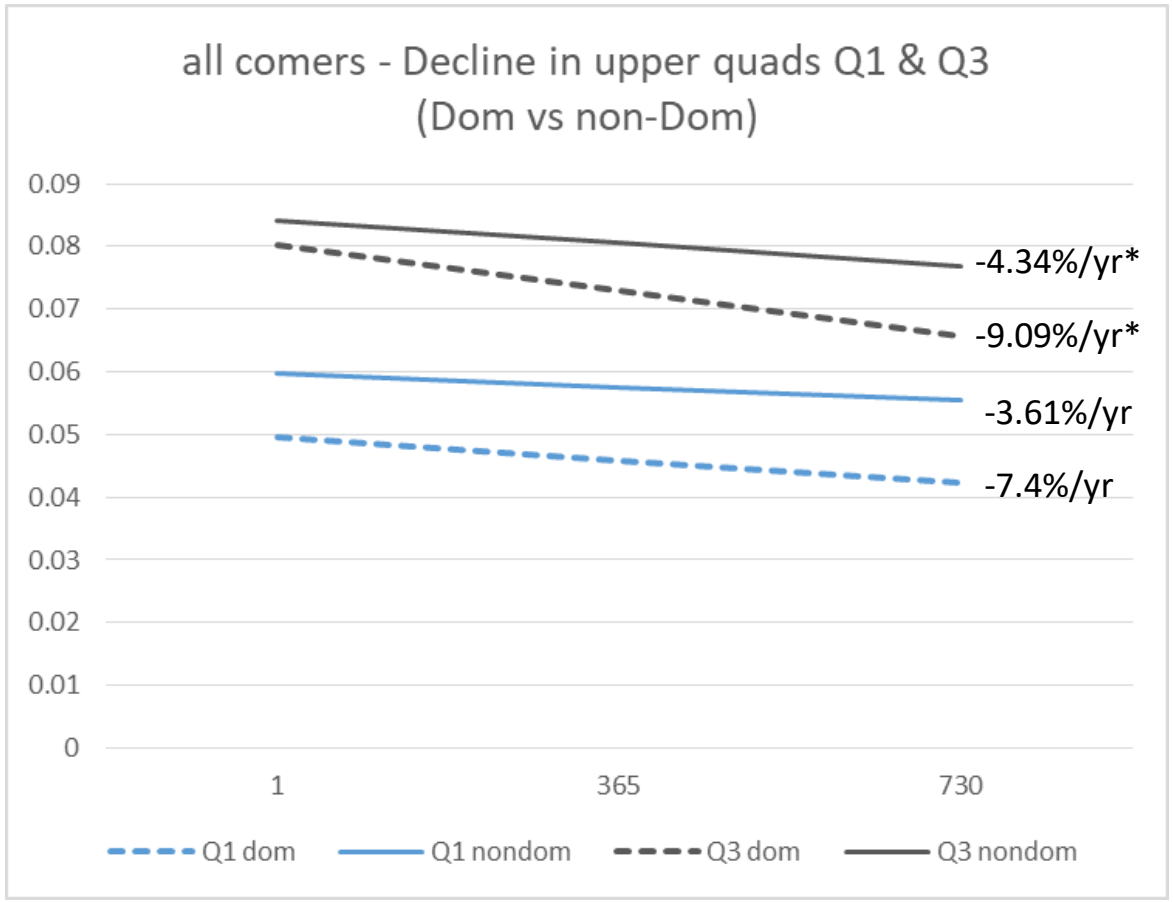
Han JJ, Kurillo G, Abresch RT, de Bie E, Nicorici Lewis A, Bajcsy R. Upper extremity 3D reachable workspace analysis in dystrophinopathy using Kinect. Muscle Nerve. 2015 Sep;52(3):344-55

FSHD: Longitudinal study (18 subjects: 8mo-5yrs, ave 2.5yrs)

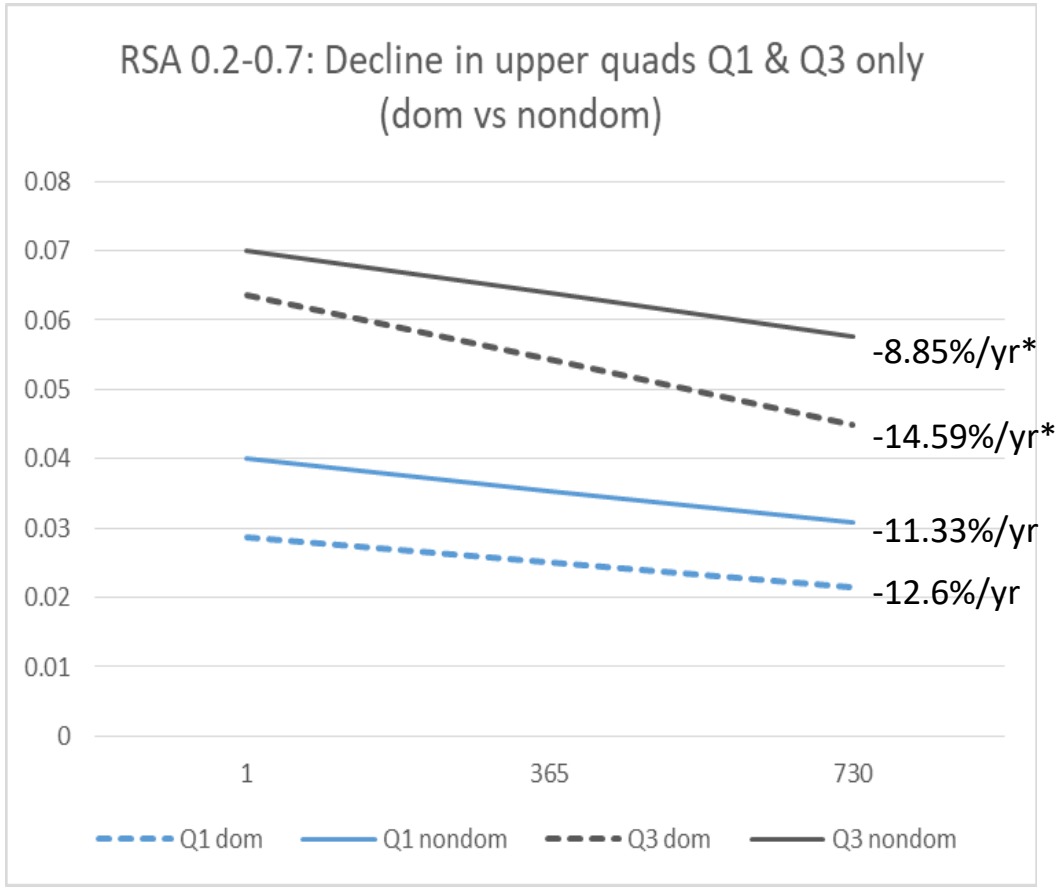


Hatch et al. Longitudinal Study of Upper Extremity Reachable Workspace in FSHD. Neuromuscular Disorders (2019). doi: https://doi.org/10.1016/j.nmd.2019.05.006

RWS sensitive to disease progression over time in FSHD patients who are most likely to progress

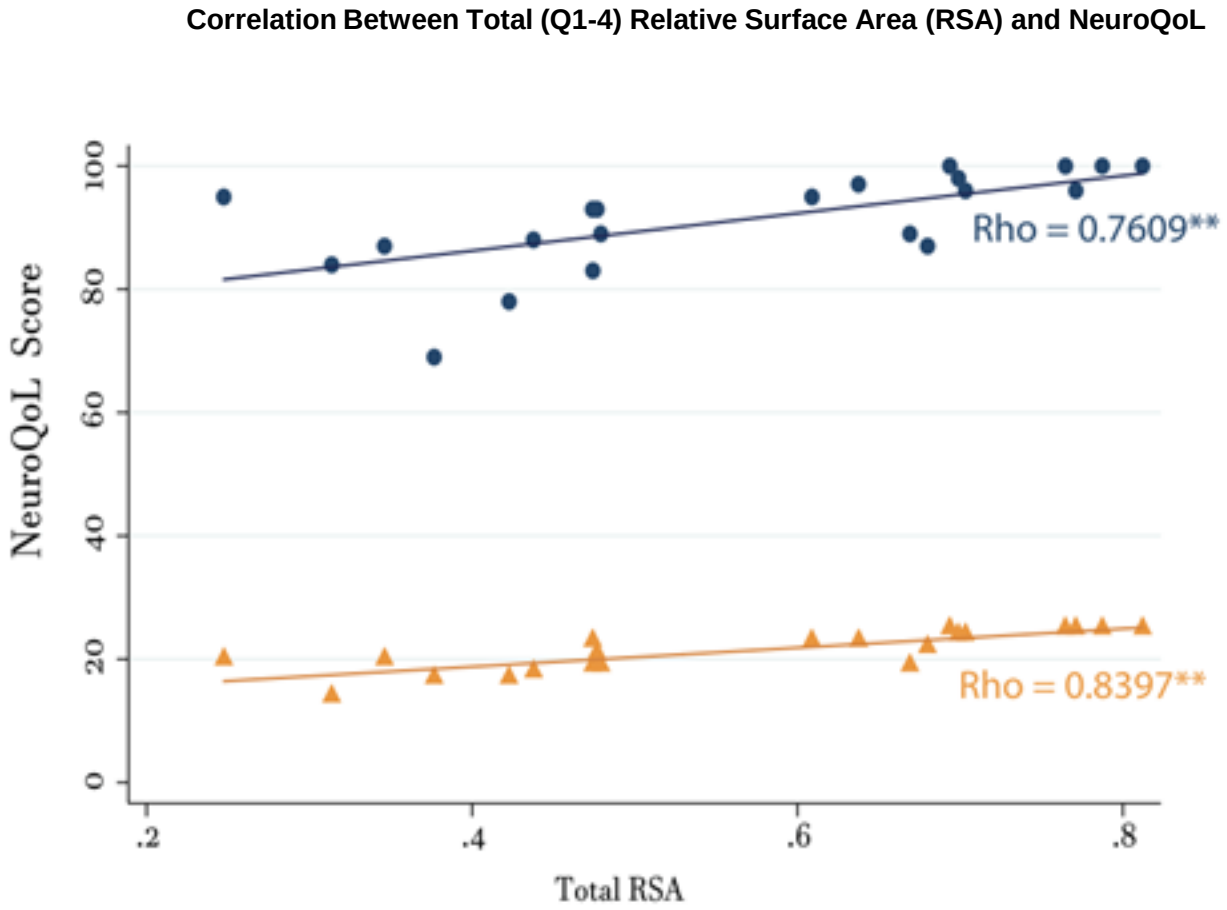


* p<0.05



* p<0.05

Reachable Workspace (RWS) is Strongly Associated with Neuro-QoL Upper Extremity (UE) Questionnaire



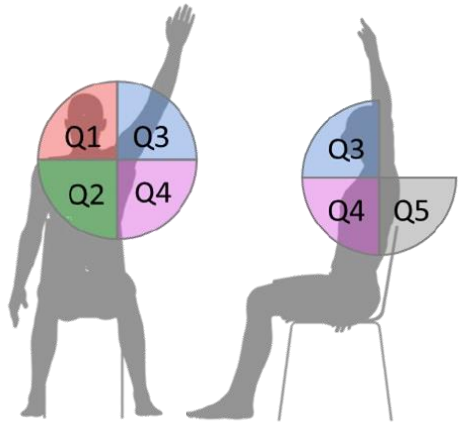
Blue: Sum of all 20 NeuroQoL questions

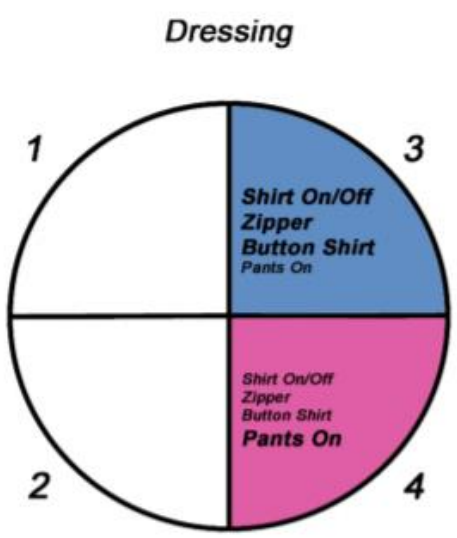
Orange: Sum of 5 sub-NeuroQol questions relating to proximal and shoulder function

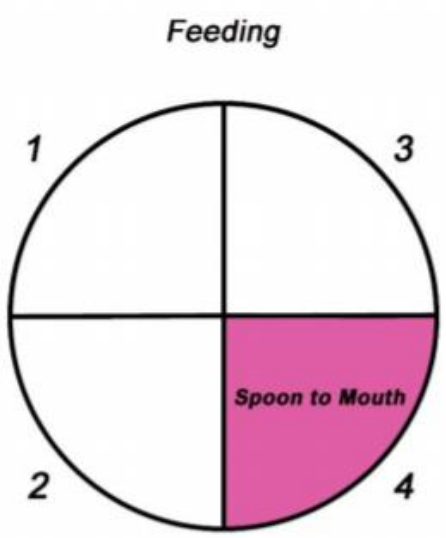
**p<0.01

Source: Hatch et al., 2020

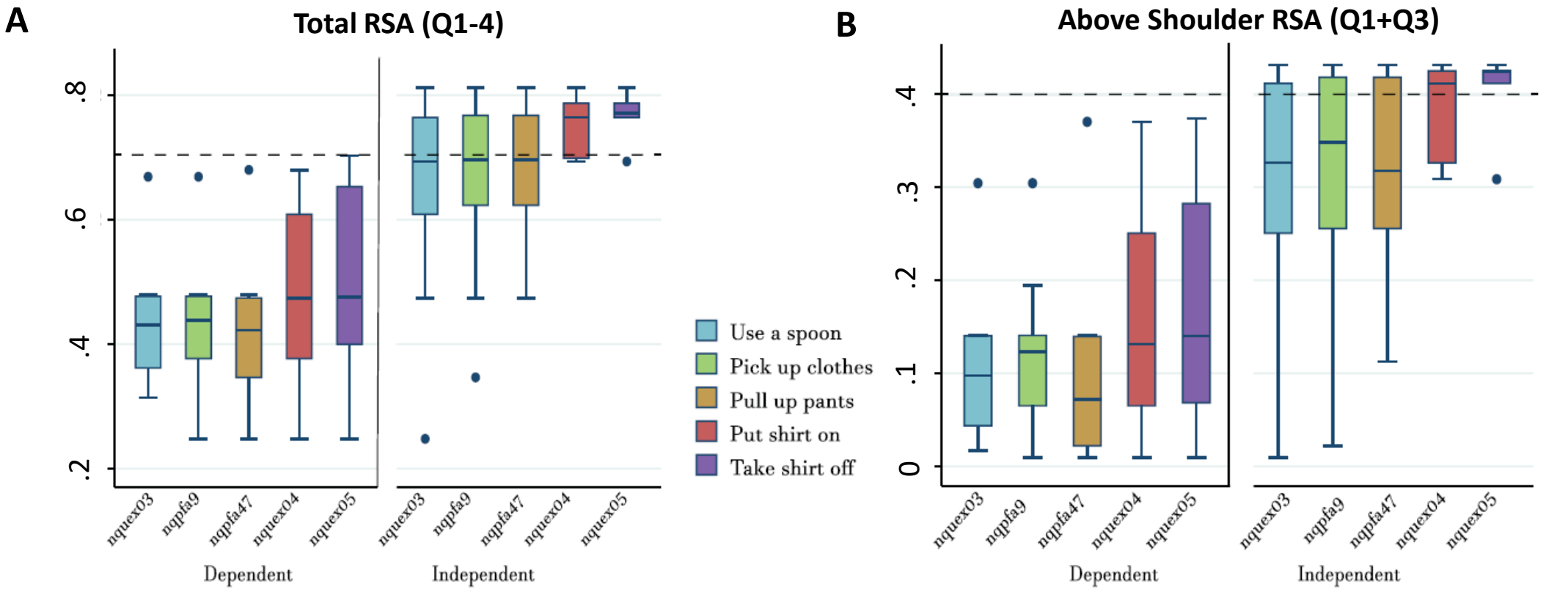
RWS assessment can map to Activities of Daily Living (ADL)







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

RWS is a functional measure of disease progression

- Reliability and validity established
  - CE Marked and FDA Class 1
- Well-characterized as being sensitive to disease progression over time
  - Capable of granular and quantitative tracking of reachability
  - Identification of:
    - Mildly affected
    - Moderately affected
    - Severely affected
  - Use of weights can improve sensitivity
- Highly correlated with abilities to perform activities of daily living and maintain independence
- Strongly associated with real-life function and how patients feel

Losmapimod:
First-to-market opportunity

Mel Hayes, Chief Commercial Officer

Fulcrum Therapeutics

Key Drivers for Fulcrum in FSHD

Urgent need for therapy
to slow or stop disease progression

Large addressable patient population as second most common muscular dystrophy

1st First to market launch
opportunity with no competitors in market and none in clinic

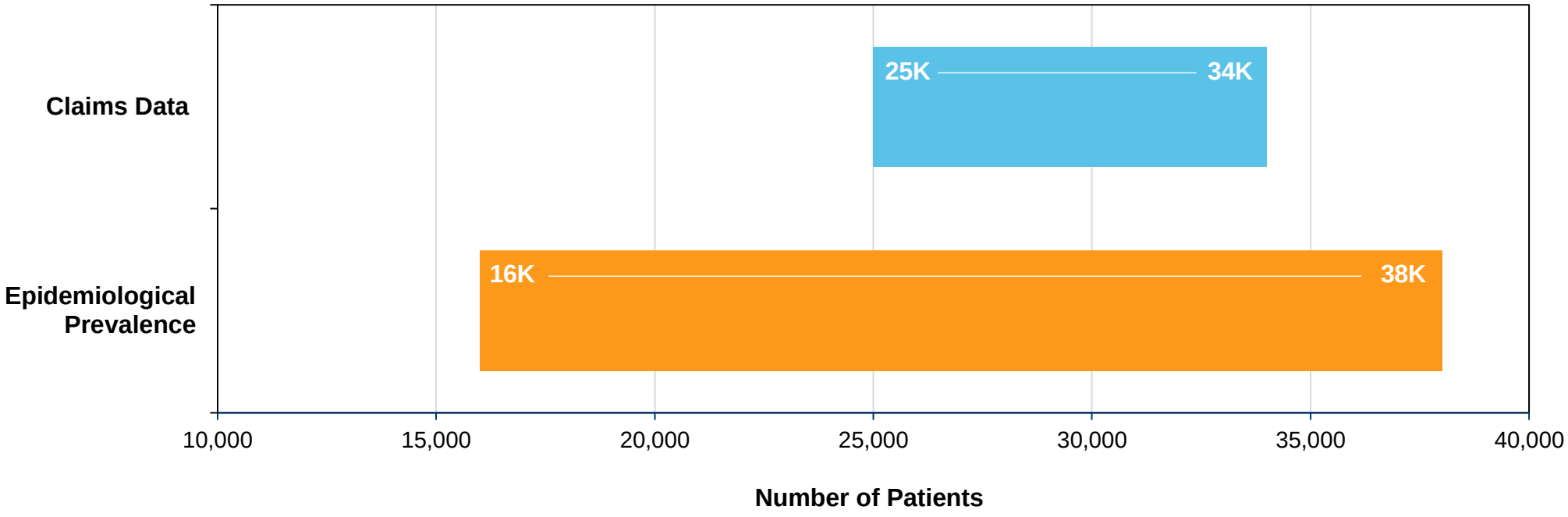
Fast track status

Passionate and persistent patient community with strong advocacy relationships

Favorable safety and potentially disease modifying (3600 patients; slows and improves functional endpoints)

Robust Claims Data Validates Epidemiology Assumptions

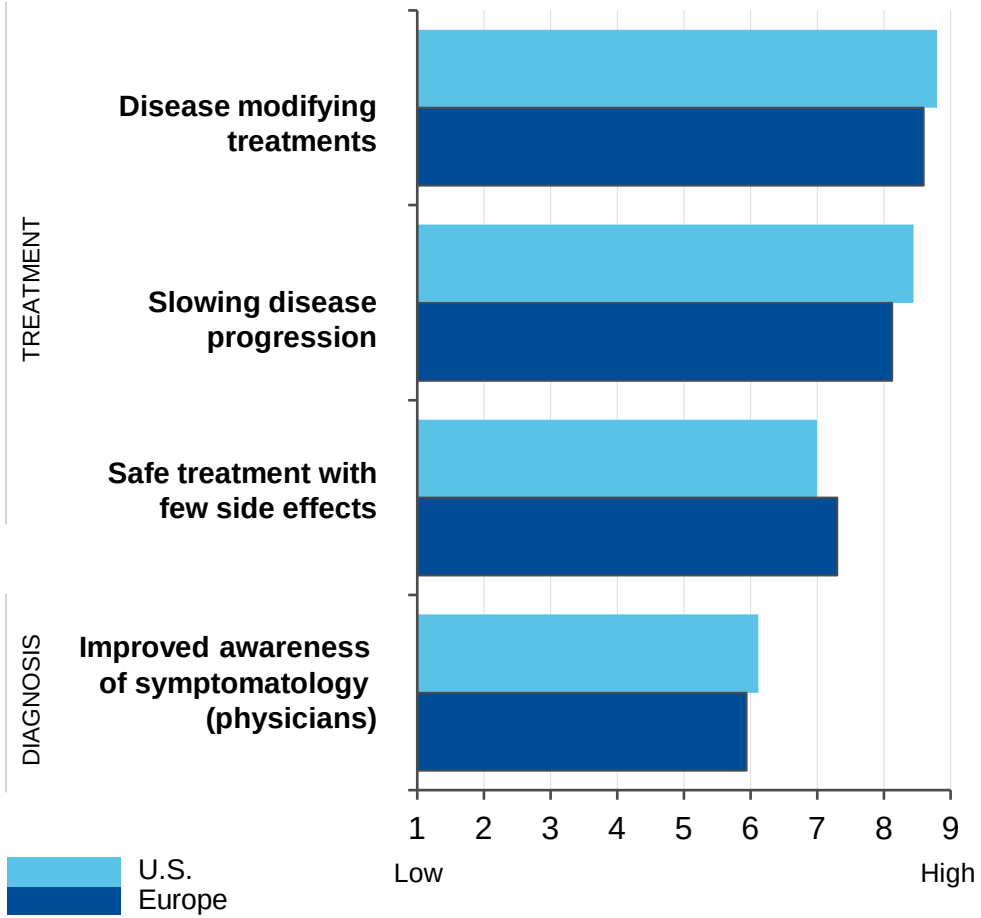
US FSHD Market Size Analysis



- Introduction of diagnostic code for FSHD in Oct. 2018 allows us to find and map patients
- Robust claims data analysis, predictive modeling and geo targeting gives us high confidence that US FSHD patient population is ~25,000 patients (conservative) to ~34,000 patients (opportunistic)
- Validates epidemiology assumptions

Physicians Rate Disease-modifying Therapy and Slowing of Disease Progression as Most Important Unmet Need

Level of unmet needs (N=29)



- High unmet need for disease-modifying treatments to reduce disease burden
- Current treatments are limited to supportive therapies

"There is no treatment, so anything that improves the perceived strength is better than what we currently have. Then, the patient can weigh the risks."

— Neurologist, The Walton Centre

Sources: L.E.K. interviews, research and analysis. This included an interview campaign with 29 neuromuscular specialists and 14 payers across regions to achieve an extensive understanding of the disease landscape and individual market dynamics in each of the 7 countries (G7)

Patients are Clear: Most Important Attribute in a Therapy is to Slow Disease Progression

Patients rank upper extremity function ranks as one of top needs, regardless of level of mobility

Important Qualities in Treatment
(from an aided list)

	Do not use a mobility aid	Use a mobility aid
1	Slowing Disease Progression	Slowing Disease Progression
2	Upper Extremity Function	Improved Mobility
3	Strong Safety and Lack of AEs	Upper Extremity Function
4	Improved Mobility	Strong Safety and Lack of AEs
5	Low OOP Cost	Low OOP Cost
5	Ability to Show Emotion in Face	6 Ability to Show Emotion in Face

(Identical Rankings)

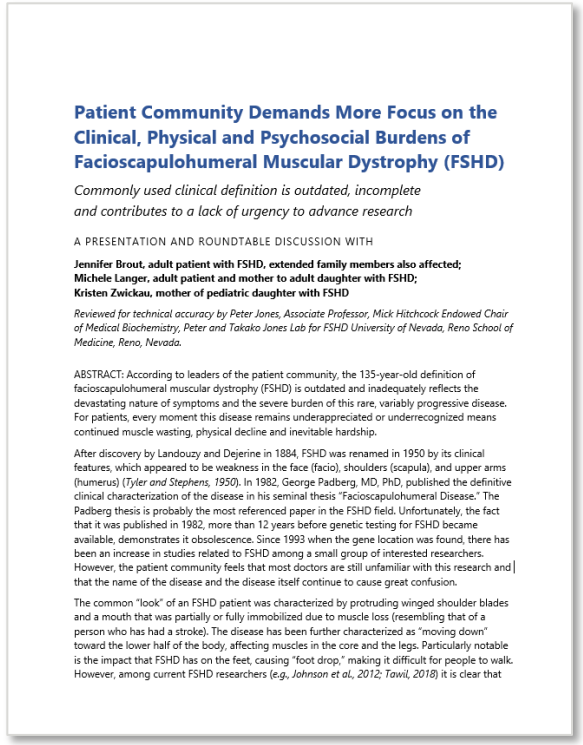
Trinity Qualitative Research, July-August 2021; N=12 EU HCPs and N=9 EU patients

Trinity Qualitative Research, June-July 2021; N=20 HCPs and N=30 patients

Fulcrum Has Been Actively Partnering and Engaging with the FSHD Community

Recent engagement with the Community

- Externally led PFDD (Patient-Focused Drug Development) meeting, supported by FSHD Society
- White paper- patient-driven, emerging from conversation with patient advisory board members
- Funding initiatives to drive genetic testing, HEOR, PRO development, with organizations in and outside the US (FSHD UK and FSHD Society)
- Established “Co-Creation", activities with patients and HCPs to drive disease awareness with patients and caregivers



Patient Community Demands More Focus on the Clinical, Physical and Psychosocial Burdens of Facioscapulohumeral Muscular Dystrophy (FSHD)

Commonly used clinical definition is outdated, incomplete and contributes to a lack of urgency to advance research

A PRESENTATION AND ROUNDTABLE DISCUSSION WITH

Jennifer Brout, adult patient with FSHD, extended family members also affected;
Michele Langer, adult patient and mother to adult daughter with FSHD;
Kristen Zwickau, mother of pediatric daughter with FSHD

Reviewed for technical accuracy by Peter Jones, Associate Professor, Mick Hitchcock Endowed Chair of Medical Biochemistry, Peter and Takako Jones Lab for FSHD University of Nevada, Reno School of Medicine, Reno, Nevada.

ABSTRACT: According to leaders of the patient community, the 135-year-old definition of facioscapulohumeral muscular dystrophy (FSHD) is outdated and inadequately reflects the devastating nature of symptoms and the severe burden of this rare, variably progressive disease. For patients, every moment this disease remains underappreciated or underrecognized means continued muscle wasting, physical decline and inevitable hardship.

After discovery by Landouzy and Dejerine in 1884, FSHD was renamed in 1950 by its clinical features, which appeared to be weakness in the face (facio), shoulders (scapula), and upper arms (humerus) (*Tyler and Stephens, 1950*). In 1982, George Padberg, MD, PhD, published the definitive clinical characterization of the disease in his seminal thesis "Facioscapulohumeral Disease." The Padberg thesis is probably the most referenced paper in the FSHD field. Unfortunately, the fact that it was published in 1982, more than 12 years before genetic testing for FSHD became available, demonstrates it obsolescence. Since 1993 when the gene location was found, there has been an increase in studies related to FSHD among a small group of interested researchers. However, the patient community feels that most doctors are still unfamiliar with this research and that the name of the disease and the disease itself continue to cause great confusion.

The common "look" of an FSHD patient was characterized by protruding winged shoulder blades and a mouth that was partially or fully immobilized due to muscle loss (resembling that of a person who has had a stroke). The disease has been further characterized as "moving down" toward the lower half of the body, affecting muscles in the core and the legs. Particularly notable is the impact that FSHD has on the feet, causing "foot drop," making it difficult for people to walk. However, among current FSHD researchers (*e.g., Johnson et al., 2012; Tawil, 2018*) it is clear that

Reachable Workspace Resonates with Patients!

"It makes a lot of sense to use Reachable Workspace as a primary outcome measure for the Phase 3 trial because it is ***an easy and straightforward way to measure meaningful changes*** *over time concerning practical upper body movements that are critical and often compromised for people with FSHD.* ***I'm excited about the Phase 3 trial*** *and that they have decided to use such a practical and meaningful measure of change."*

– DY, FSHD patient

Reachable Workspace Resonates with Patients!

*"Over the past two years, I've experienced **significant decrease of function in my arms**. Not only is it more difficult to reach outward to retrieve or lift objects, I also have more difficulty brushing my teeth and hair, shaving, and eating. **My deficit in these areas has had a significant impact on my ability to function independently**. An endpoint that measures shoulder and arm function is meaningful for our community."*

– LG, FSHD patient

Reachable Workspace Resonates with Patients!

*"The progressive **loss of range of motion in my shoulders and arms has had a tremendous impact on my life**. Reaching out to open a door, putting a pot of water on the stove, dressing myself, or picking up my cat has all become harder. As I continue to decline, **I am looking ahead to needing caretaking, and that is scary.** Reachable Workspace recognizes the impact that this loss of range of motion in our shoulders and arms and is **critical for developing a drug that slows progression and allows me to keep my independence longer**."*

– CW, FSHD patient and member of Fulcrum's patient advisory board

Q&A

Fulcrum Therapeutics