Reachable Workspace to Evaluate Efficacy of Losmapimod in Subjects with FSHD in Two Phase 2 Studies

Rabi Tawil, MD[1], Kathryn Wagner, MD, PhD[2], Jeffrey Statland, MD[3], Leo Wang, MD, PhD[4], Angela Genge, MD[5], Sabrina Sacconi, MD, PhD[6], Hanns Lochmüller, MD, PhD[7], David Reyes Leiva, MD[8], Jordi Diaz-Manera, MD, PhD[8,9], Nuria Muelas, MD, PhD[10],Juan J. Vilchez, MD, PhD[11], Alan Pestronk, MD[12], Summer Gibson, MD[13], Namita A. Goyal, MD[14], Johanna Hamel, MD[1], Jay Han, MD[14], Lawrence Hayward, MD[15], Nicholas Johnson, MD[16], Samantha LoRusso, MD[17], Miriam Freimer, MD[17], Perry B. Shieh, MD, PhD[18], Sankarasubramoney H. Subramony, MD[19], Doris Leung MD, PhD[2], Baziel van Engelen MD, PhD[21], Joost Kools, MD[21], John Jiang, PhD[22], L. Alejandro Rojas, PhD[22], Anthony Accorsi, PhD[22],Christopher Morabito, MD[22], Jennifer Shoskes, PharmD[22], Michelle L. Mellion, MD[22] (first author)

[1]University of Rochester, [2]Kennedy Krieger Institute, Johns Hopkins University, [3]University of Kansas, [4]University of Washington, [5]Montreal Neurological Institute and Hospital, [6]Nice University Hospital, Peripheral Nervous System and Muscle Department, University Cote Azur, Nice, France, [7]Children's Hospital of Eastern Ontario Research Institute; Division of Neurology, Department of Medicine, The Ottawa Hospital; and Brain and Mind Research Institute, University of Ottawa, Canada, [8]Hospital Universitari Santa Creu i Sant Pau, Institut de Recerca IIB Sant Pau, Barcelona, Spain, [9]John Walton Muscular Dystrophy Research Center, Newcastle University, Newcastle, United Kingdom, [10]Hospital Universitari i Politecnic La Fe de Valencia. Instituto de Investigación Sanitaria IIS La Fe. CIBERER, [11]Neuromuscular and Ataxias Research Group, Instituto de Investigación Sanitaria La Fe, Valencia, Spain [12]Washington University, [13]University of Utah, [14]University of California Irvine, [15]University of Massachusetts, [17]University of Virginia [18]Ohio State University, Wexner Medical Center, [19]University of California Los Angeles, [20]University of Florida, [21]Radboud University Medical Center, Nijmegen [22]Fulcrum Therapeutics, Inc.

Introduction

- FSHD is a serious, rare, progressive and heterogeneous disease, caused by the aberrant expression of DUX4 in skeletal muscle leading to progressive muscle loss and accumulation of disability.
- Hallmark pattern of weakness is significant functional impairment occurring in the shoulder girdle and proximal arm
- Preserving upper extremity function is critical for maintaining independence and the ability for self-care and other activities of daily living (ADL) that directly influence quality of life
- Reachable workspace is a reliable and sensitive assessment that can quantitatively and reproducibly evaluate upper extremity function. This assessment provides an objective assessment of disease severity, progression and response to treatment.

Currently, there are with no approved disease modifying therapies for people living with FSHD that prevent and/or slow muscle wasting and weakness

Rationale

A treatment that reduces or prevents aberrant DUX4 activity in skeletal muscles may stop or prevent functional impairment and accumulation of disability and decrease/arrest replacement of muscle by fat.

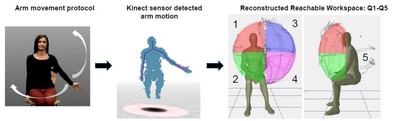
- **Losmapimod** is an investigational small molecule inhibitor of p38α/β Mitogen Activated Protein Kinase (MAPK).
- Clinical studies in over 3,600 subjects across a diversity of diseases evidenced acceptable safety and tolerability for up to one year of treatment at relevant doses.
- Patients with FSHD consistently rank difficulty with use of shoulder and proximal arm as the most prevalent and severe impairment leading to limitations in their daily activities

Objective

- **Assess clinical efficacy of losmapimod to slow or stop disease progression with Reachable Workspace (RWS)**

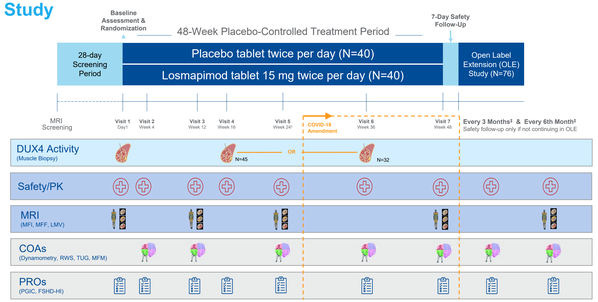
Methods – Reachable Workspace

- Reachable Workspace (RWS) is a centrally read evaluation of individual global upper extremity function, including shoulder and proximal arm, which tracks 3D upper limb trajectory using the Microsoft Kinect device
  - Divided into 5 regions; shoulder as origin (each quintant = 0.25, total scale 0-1.25)
  - Calculation of total RWS surface envelope area (m^2) and areas for each quintant
- Evaluation performed with and without 500 g weights with the Dominant (D) and Non-dominant (ND) arms
- Scaling of data by each subject's arm length allows normalization and comparison between subjects (Relative Surface Area: RSA)
- Annualized rate of change (%) was calculated using a linear mixed-effects model to estimate percent change per year

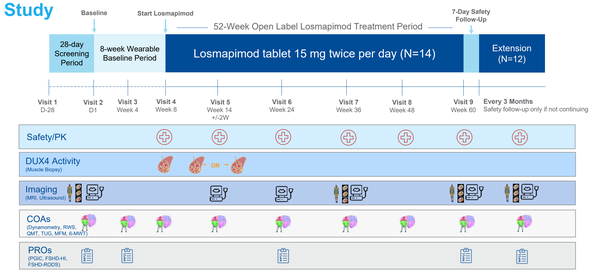


Study Designs

ReDUX4: Phase 2 Randomized Placebo-Controlled, 48-Week, Multi-site Study



Open-Label Study (OLS): Phase 2 Open-Label Single-Center, 52-Week Study



Main Inclusion Criteria for Both Studies:	Main Exclusion Criteria for Both Studies:
▪ Age 18-65 years ▪ Genetically confirmed diagnosis of FSHD1 ▪ Ricci score 2-4 ▪ STIR+ muscle, as determined by a central reader, safely accessible by needle biopsy	▪ Medical conditions that can confound results of the study ▪ Contraindication to MRI ▪ Contraindication to muscle biopsy

Study Demographics and Baseline Characteristics

		ReDUX4 Placebo BID (N=40)	ReDUX4 Losmapimod 15 mg BID (N=40)	OLS Open-Label Study Losmapimod 15 mg BID (N=14)
Completed		38 (95%)	39 (97.5%)	14 (100%)
Discontinued		2 (5.0%)	1 (2.5%)	0
DEMOGRAPHICS				
Age (years)	N	40	40	14
	Mean (SD)	45.7 (+/- 12.69)	45.7 (+/- 12.44)	45.7 (+/- 11.61)
Race n (%)	White	39 (97.5)	31 (77.5)	13 (92.9)
	Asian	0	5 (12.5)	0
	Other	0	1 (2.5)	1 (7.1)
	Not Applicable	1 (2.5)	3 (7.5)	0
Body Mass Index (BMI) (kg/m²)	N	39	40	14
	Mean (SD)	26.19 (+/- 3.914)	25.71 (+/- 5.434)	24.04 (+/- 2.939)
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)	3 (21.4)
	4-9 Repeats	34 (85.0)	33 (83.50)	11 (78.6)
Ricci Score n (%)	2	0	0	0
	2.5	7 (17.5)	5 (12.5)	1 (7.1)
	3	18 (45.0)	19 (47.5)	5 (35.7)
	3.5	7 (17.5)	11 (27.5)	2 (14.3)
	4	**8 (20.0)**	**5 (12.5)**	**6 (42.9)**

Results

- **Baseline Total RSA (Q1-5) ranged from 0.51 to 0.64 across studies**

ReDUX4

Baseline Total RSA (Q1-5)	Dominant	Non-Dominant
Losmapimod	Mean (SD)	Mean (SD)
With Weight (n=39)	0.51 (0.24)	0.55 (0.27)
Without Weight (n=39)	0.56 (0.24)	0.62 (0.26)
Placebo		
With Weight (n=40)	0.53 (0.25)	0.55 (0.26)
Without Weight (n=40)	0.57 (0.24)	0.60 (0.25)

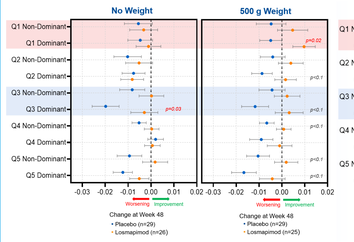
OLS

Baseline Total RSA (Q1-5)	Dominant	Non-Dominant
Losmapimod	Mean (SD)	Mean (SD)
With Weight (n=14)	0.52 (0.25)	0.62 (0.26)
Without Weight (n=14)	0.55 (0.24)	0.64 (0.24)

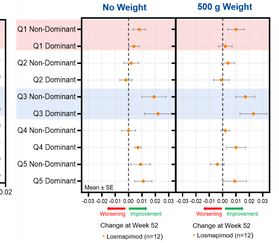
Q = quintant; RSA = relative surface area

- **Change from Baseline at 48- or 52-weeks RSA by domain showed that the losmapimod arm had either improvements or no worsening, particularly in Q1 and Q3 (above shoulder), and Q5 (posterior inferior)**

ReDUX4



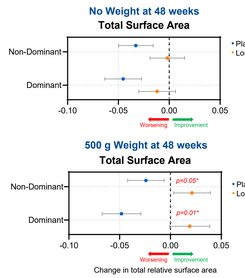
OLS



Results continued

- **Improvements or stabilization in Total RWS (Q1-5) were observed across studies**

ReDUX4



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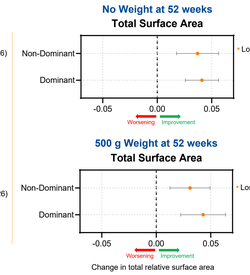
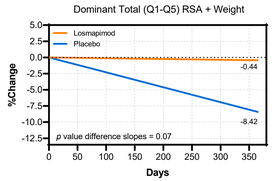
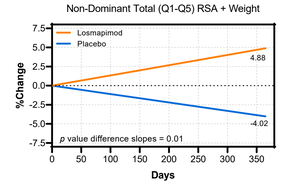


- **Annualized Reachable Workspace (percent change from baseline per year) showed that losmapimod arm had either improvements or no worsening**

ReDUX4





ReDUX4

%/year	Losmapimod (N=40)				Placebo (N=40)			
	With Weights		W/o Weights		With Weights		W/o Weights	
	D	ND	D	ND	D	ND	D	ND
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
Total RSA (Q1-5)	-0.44	4.88	-2.19	0.11	**-8.42**	-4.02	**-6.48**	-3.42

OLS

%/year	Open Label Losmapimod (n=14)			
	Without Weights		With Weights	
	Dom	Non-Dom	Dom	Non-Dom
Q1	11.95	7.73	9.16	8.60
Q2	-3.39	1.36	-0.28	1.34
Q3	16.05	9.37	16.66	10.72
Q4	1.10	0.18	2.23	0.58
Q5	4.44	6.25	4.49	-2.11
Q1+Q3	14.53	8.58	13.92	9.79
Total RSA	4.90	4.28	5.68	3.28

Dom = dominant; Non-Dom = non-dominant; RSA = relative surface area; Q = Quintant, W/o = Without

Conclusions

- RWS is a clinically meaningful upper extremity assessment of function, relevant to activities of daily living, that can be used to assess disease progression and treatment efficacy accurately
- RWS demonstrated that losmapimod significantly preserves or improves function across multiple domains