

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

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## 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.

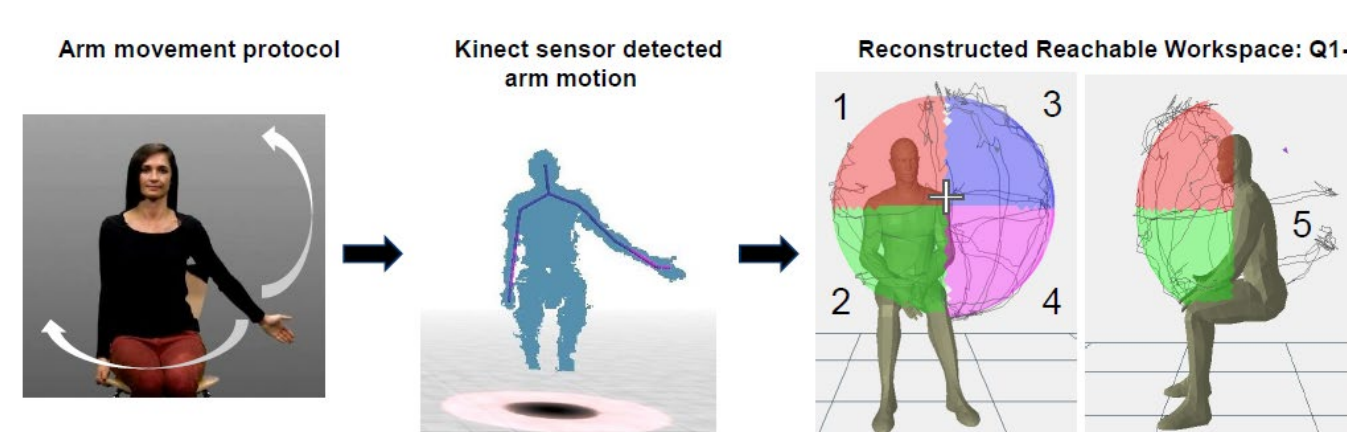
- Losmapimod is an investigational small molecule inhibitor of p38α/β Mitogen Activated Protein Kinase (MAPK).
- Clinical studies in over 3,600 subjects across a diversity of diseases evidenced acceptable safety and tolerability for up to one year of treatment at relevant doses.
- Patients with FSHD 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<sup>2</sup>) 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 Demographics and Baseline Characteristics

	ReDUX4		OLS
	Placebo BID (N=40)	Losmapimod 15 mg BID (N=40)	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
<b>DEMOGRAPHICS</b>			
Age (years)	N	40	40
	Mean (SD)	45.7 (+/- 12.69)	45.7 (+/- 11.61)
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)
Body Mass Index (BMI) (kg/m <sup>2</sup> )	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)
	2	0	0
Ricci Score n (%)	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)

## Results

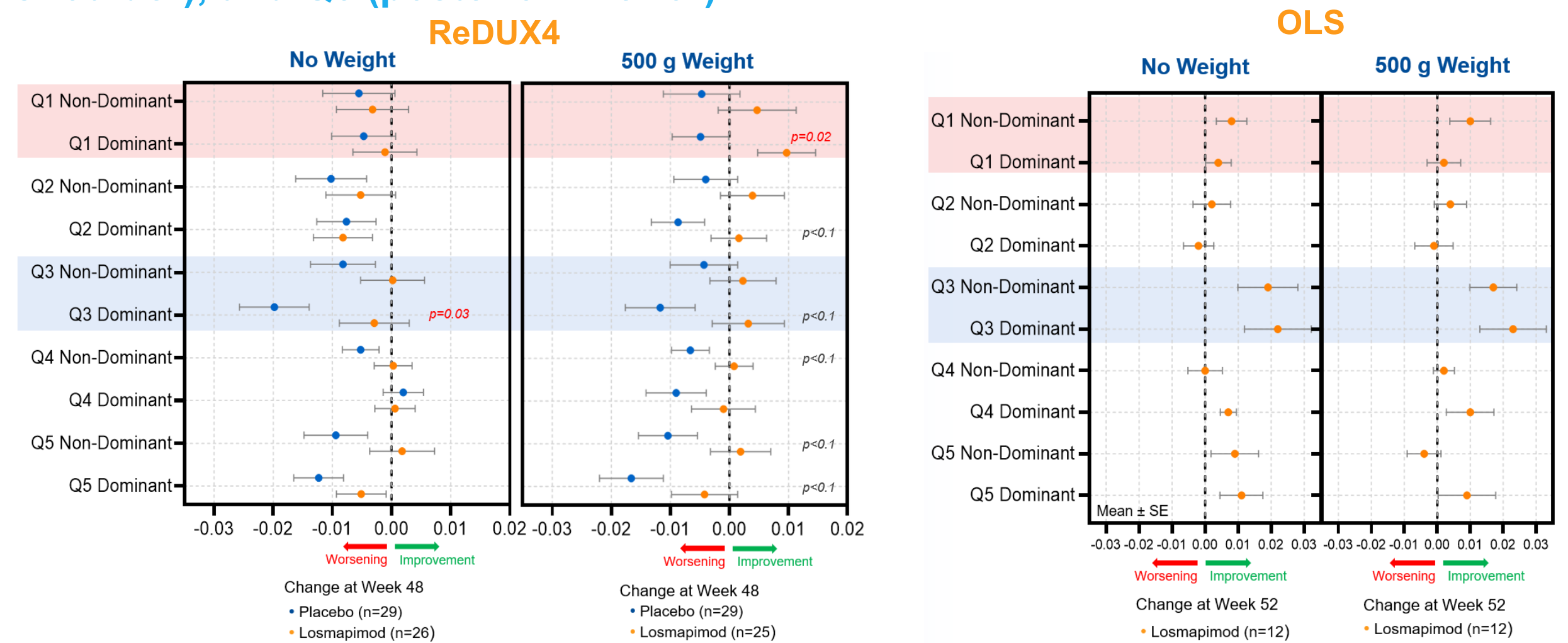
- Baseline Total RSA (Q1-5) ranged from 0.51 to 0.64 across studies

	ReDUX4	
	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)

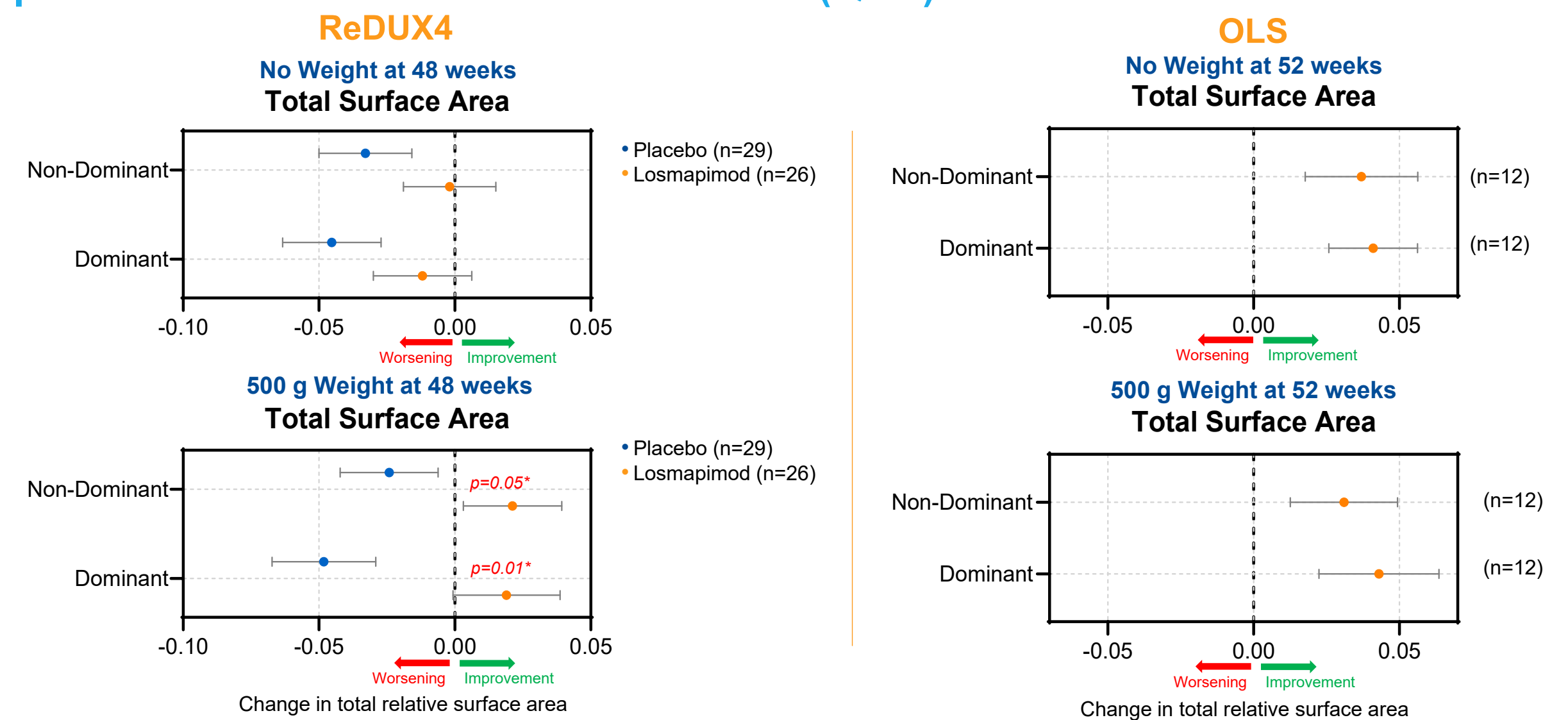
	OLS	
	Dominant	Non-Dominant
Losmapimod	Mean (SD)	Mean (SD)
With Weight (n=14)	0.52 (0.25)	0.62 (0.26)
Without Weight (n=14)	0.55 (0.24)	0.64 (0.24)

RSA = relative surface area

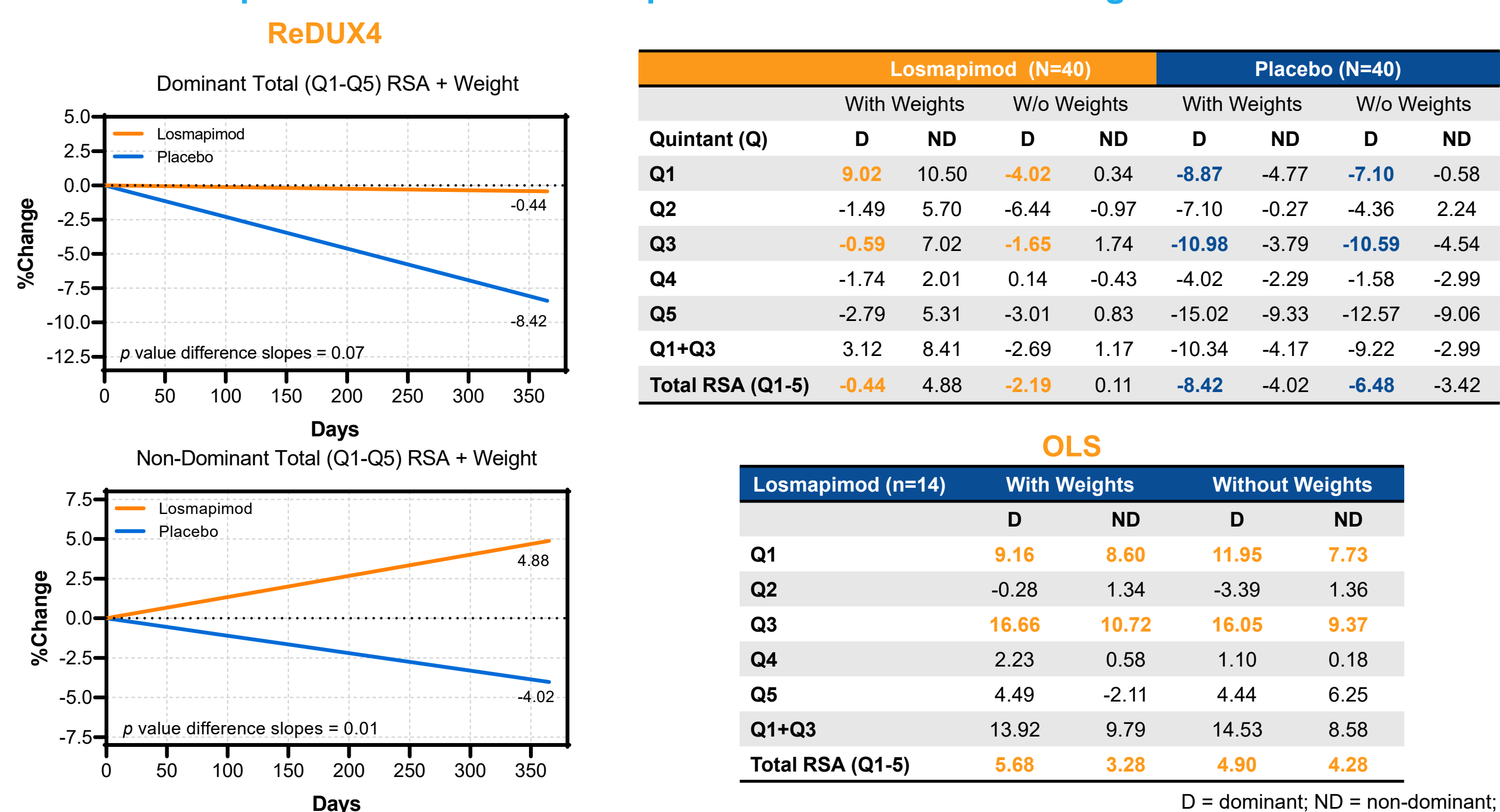
- Change from Baseline at 48- or 52-weeks RSA by domain showed that the losmapimod arm had either improvements or no worsening, particularly in Q1 and Q3 (above shoulder), and Q5 (posterior inferior).



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



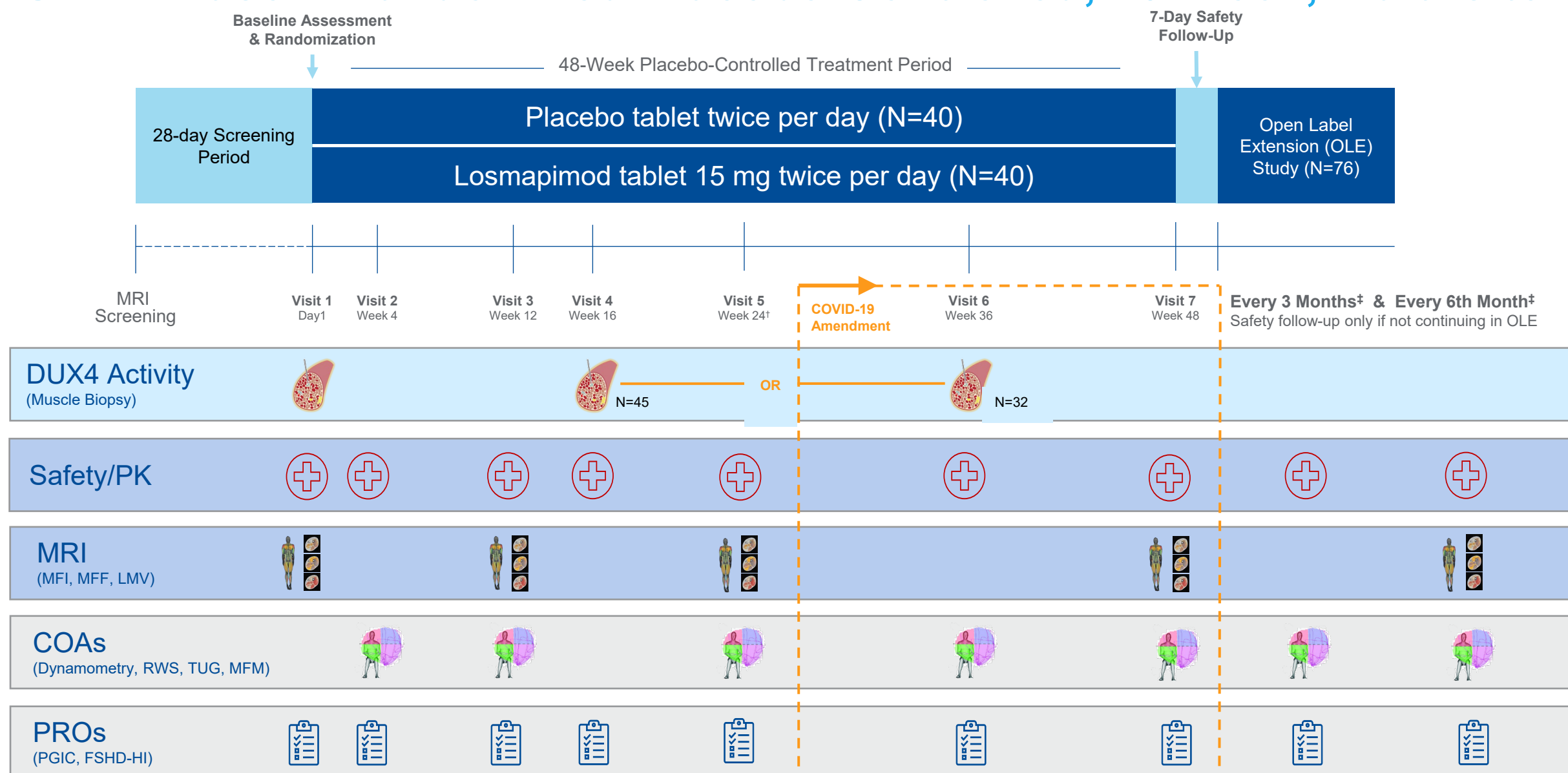
- Annualized Reachable Workspace (percent change from baseline per year) showed that losmapimod arm had either improvements or no worsening



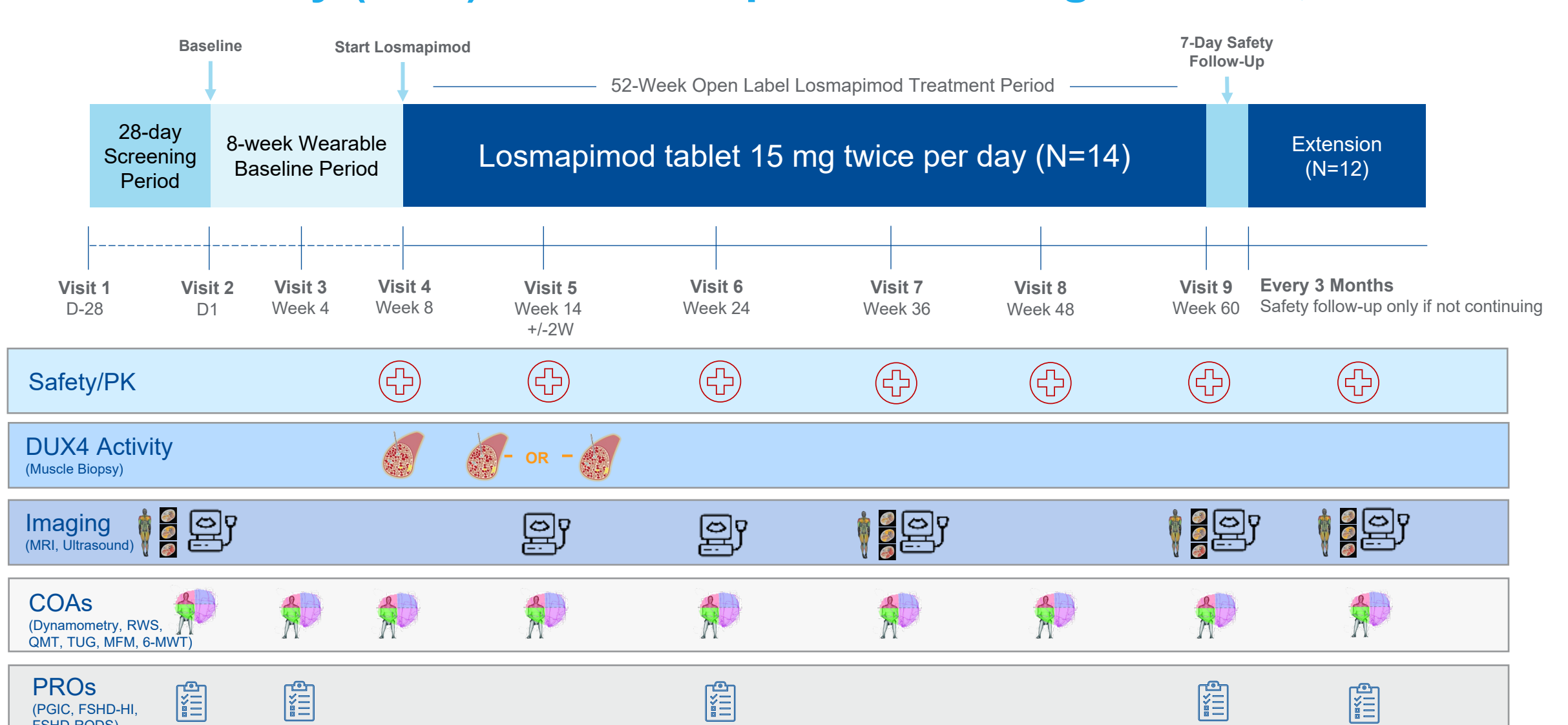
D = dominant; ND = non-dominant;

## 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:
<ul style="list-style-type: none"> <li>Age 18-65 years</li> <li>Genetically confirmed diagnosis of FSHD1</li> <li>Ricci score 2-4</li> <li>STIR+ muscle, as determined by a central reader, safely accessible by needle biopsy</li> </ul>	<ul style="list-style-type: none"> <li>Medical conditions that can confound results of the study</li> <li>Contraindication to MRI</li> <li>Contraindication to muscle biopsy</li> </ul>

## Conclusion

- 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