Phase 1 Clinical Trial of Losmapimod in Facioscapulohumeral Muscular Dystrophy (FSHD): Safety, Tolerability and Target Engagement

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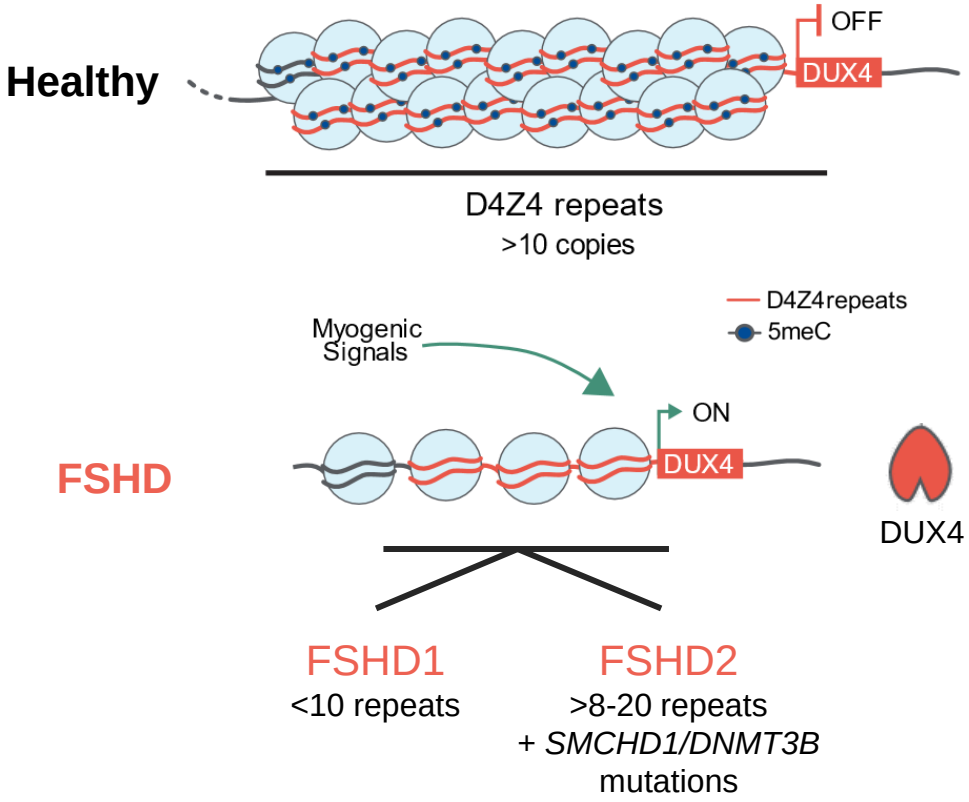
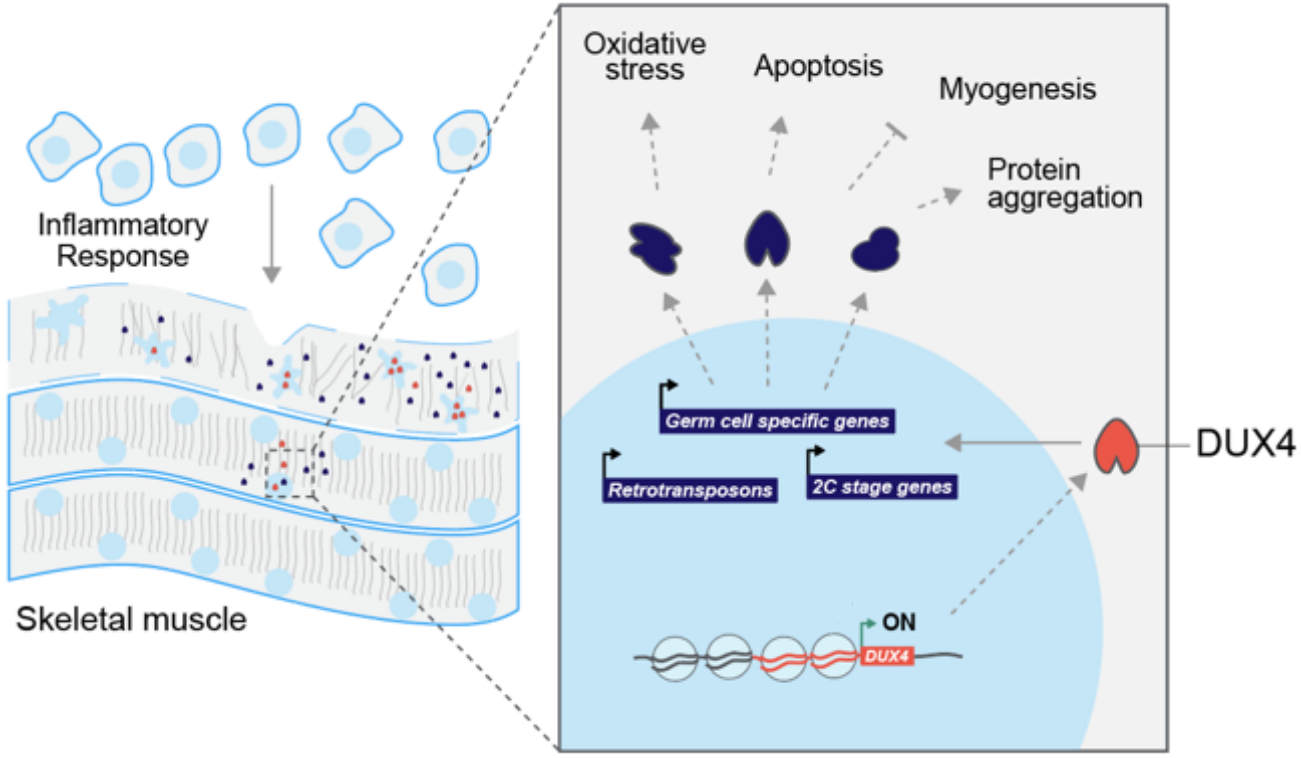
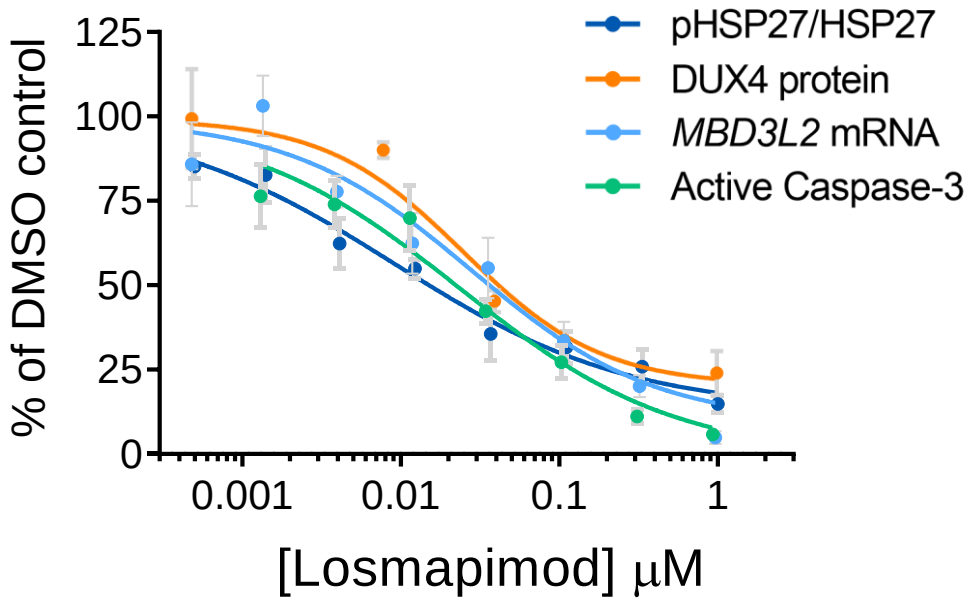
Aberrant expression of DUX4 causes FSHD

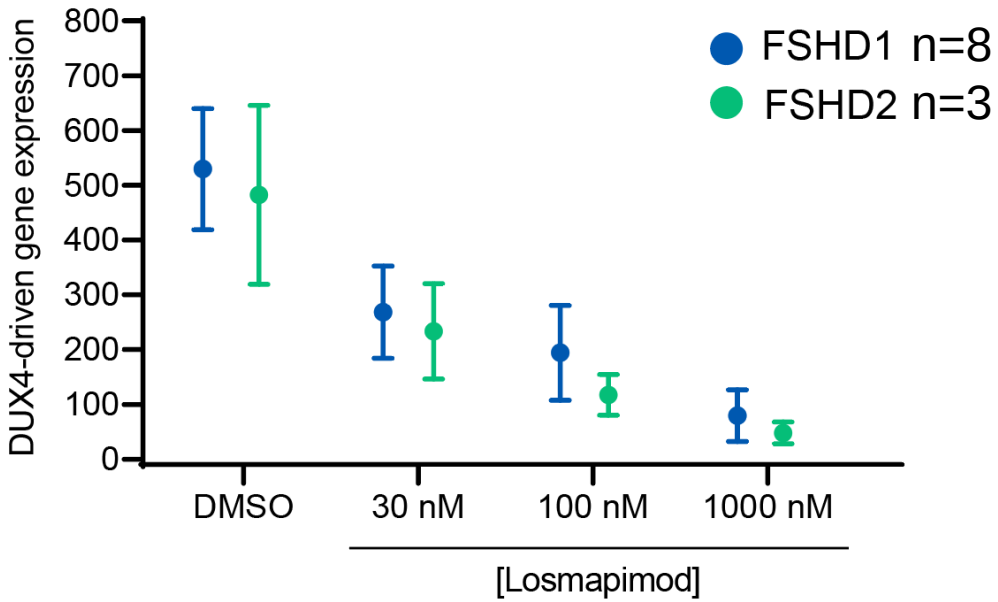




DUX4 is a homeodomain transcription factor

Losmapimod, a selective p38α/β MAPK inhibitor, reduced DUX4 expression in FSHD myotubes





- HSP27 is a substrate of p38 MAP kinase pathway
- *MBD3L2* is a DUX4-target gene

Phase 1 study: Objectives

Primary Objective: Safety and tolerability in FSHD patients

Safety and tolerability previously demonstrated in 25 studies in over 3,500 healthy adult volunteers and patients across multiple other indications. Never tested in FSHD patients

Secondary Objective: Drug levels and p38 inhibition in blood and muscle

Muscle biopsies performed at baseline and during treatment in FSHD patients

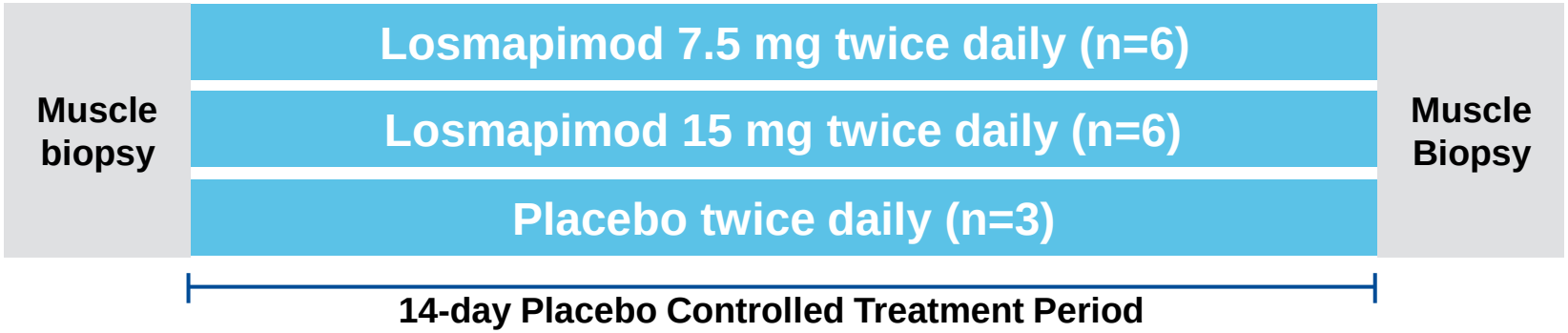
Phase 1 study: Study design

PART A

N=10 Healthy Volunteers; Single Ascending Dose; 4:1 randomization

PART B

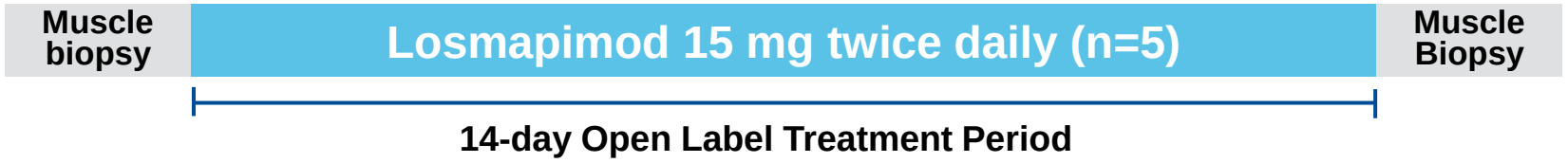
N=15 FSHD1 Patients; Double Blind; 2:2:1 Randomization; Placebo Controlled; Repeated Dose



Note: Lower extremity muscle biopsies were performed in normal appearing muscles identified by MRI

PART C

N=5 FSHD1 Patients; Open Label Extension; Repeated Dose



Note: Lower extremity muscle biopsies were performed in STIR+ muscles with MFF of 10-40% identified by MRI

Baseline Characteristics

	Age (years) Mean(SD)	Sex n, (%)	Race n, (%)	BMI (kg/m2) Mean (SD)	Ricci Score Mean (SD) [Range]
Part A (HV)					
Placebo (N=2)	26.5 (2.1)	2 (100): 0	White 2 (100)	22.0 (0.4)	NA
7.5 mg/15 mg (N=8)	32.6 (19.3)	4 (50):4 (50)	Asian 1 (12.5) White 7 (87.5)	22.9 (2.7)	NA
Part B (FSHD1)					
Placebo (N=3)	43 (14)	3 (100): 0	White 3 (100)	23.8 (3.4)	2.6 (0.7) [1.5 to 4]
7.5 mg (N=6)	47.3 (10.3)	1(16.6): 5(83.4)	White 6 (100)	26.4 (3.4)	
15 mg (N=6)	35.2 (10.1)	2(33.2): 4(66.8)	White 5 (83.3) Mixed 1 (16.7)	24.2 (2.1)	
Part C (FSHD1)					
15 mg (N=5)	48.6 (8.6)	3(60): 2(40)	White 5 (100)	24.4 (3.7)	3.1 (0.5) [2.5 to 4]

No Difference in Treatment Emergent Adverse Events

	Number of TEAEs	Subjects with at least 1 TEAE, n (%)
Part A (HV)		
Placebo (N=2)	2	1 (50)
7.5 mg (N=8)	8	4 (50)
15 mg (N=8)	5	4 (50)
Part B (FSHD1)		
Placebo (N=3)	8	3 (100)
7.5 mg (N=6)	6	4 (66.7)
15 mg (N=6)	13	4 (66.7)
Part C (FSHD1)		
15 mg (N=5)	3	2 (40)

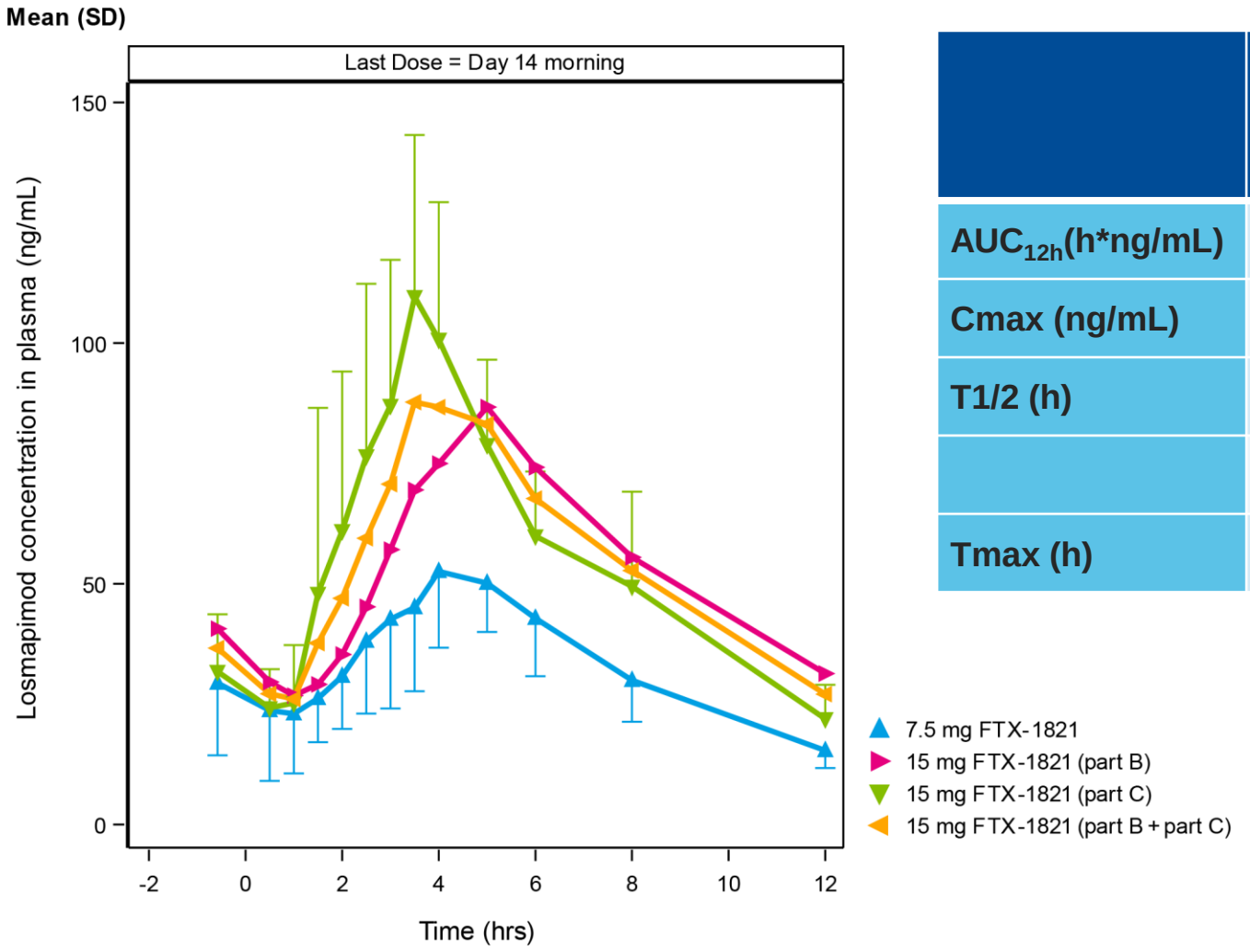
Adverse Events Summary

- **No serious adverse events**
  - Most Adverse Events were not considered related to study drug administration
- **No discontinuations due to AEs**
- **Mild Severity**
  - No clinically significant changes in vital signs, laboratory analyses, ECG or urinalysis
- **Most common**
  - Headache
  - Dizziness
  - Somnolence
  - GI disorders

Losmapimod Demonstrated a Similar PK Profile Across Cohorts at Day 1

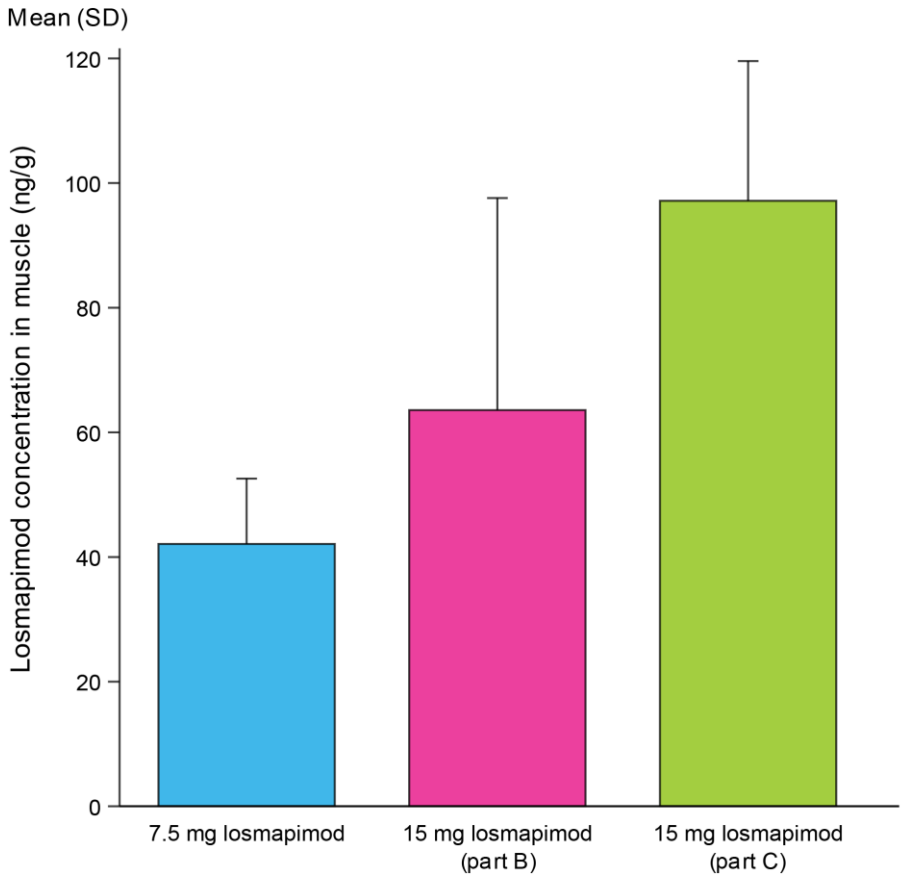
	Part A 7.5 mg (mean ± SD) (N=8)	Part B 7.5 mg (mean ± SD) (N=6)	Part A 15 mg (mean ± SD) (N=8)	Part B 15 mg (mean ± SD) (N=6)	Part C 15 mg (mean ± SD) (N=5)
AUC_{12h} (h*ng/mL)	195 ± 56.7	201 ± 74.6	367 ± 183	410 ± 50.3	403 ± 117
Cmax (ng/mL)	36.6 ± 10.7	40.9 ± 21.1	74.6 ± 29.8	85.0 ± 16.7	76.8 ± 17.7
T1/2 (h)	5.6 ± 1.1	5.2± 1.9	5.2 ± 0.8	4.1 ± 0.8	4.5± 1.1
	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)
Tmax (h)	4.5 (3.5-12)	4.5 (3.5-12)	4.3 (3.0-12)	4.6 (3.5-5.0)	5.0 (2.5-12)

PK of Losmapimod in FSHD Patients
Exposure higher with 15 mg than 7.5 mg



	Part B 7.5 mg (mean ± SD) Day 14 (N=6)	Part B 15 mg (mean ± SD) Day 14 (N=6)	Part C 15 mg (mean ± SD) Day 14 (N=5)
AUC_{12h}(h*ng/mL)	395 ± 92.8	632 ± 176	650 ± 182
Cmax (ng/mL)	56.3 ± 14.2	100 ± 34.4	113 ± 32.2
T1/2 (h)	4.0 ± 0.5	4.6 ± 0.8	4.1 ± 0.4
	Median(range)	Median(range)	Median(range)
Tmax (h)	4.5 (3.0-6.0)	5.0 (3.5-8.0)	3.5 (2.5-4.2)

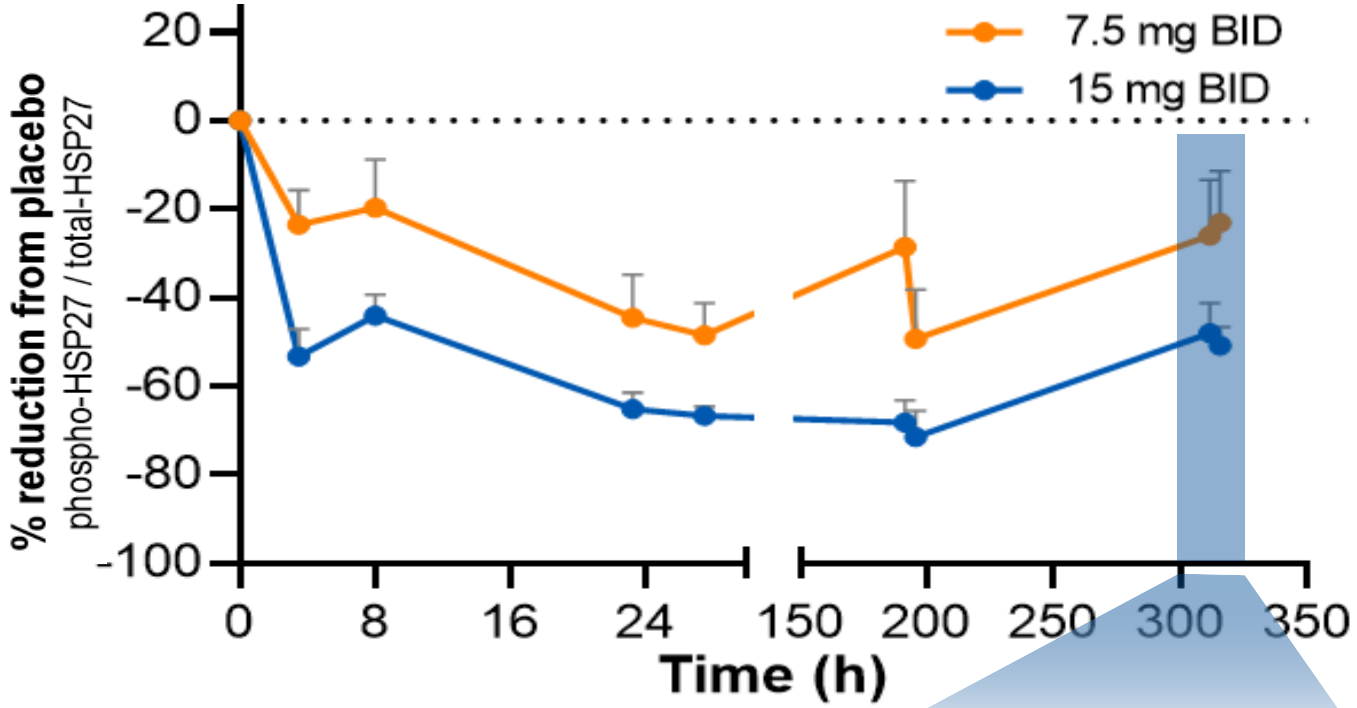
Losmapimod Showed Approximate Dose-Dependent Concentrations in Muscle



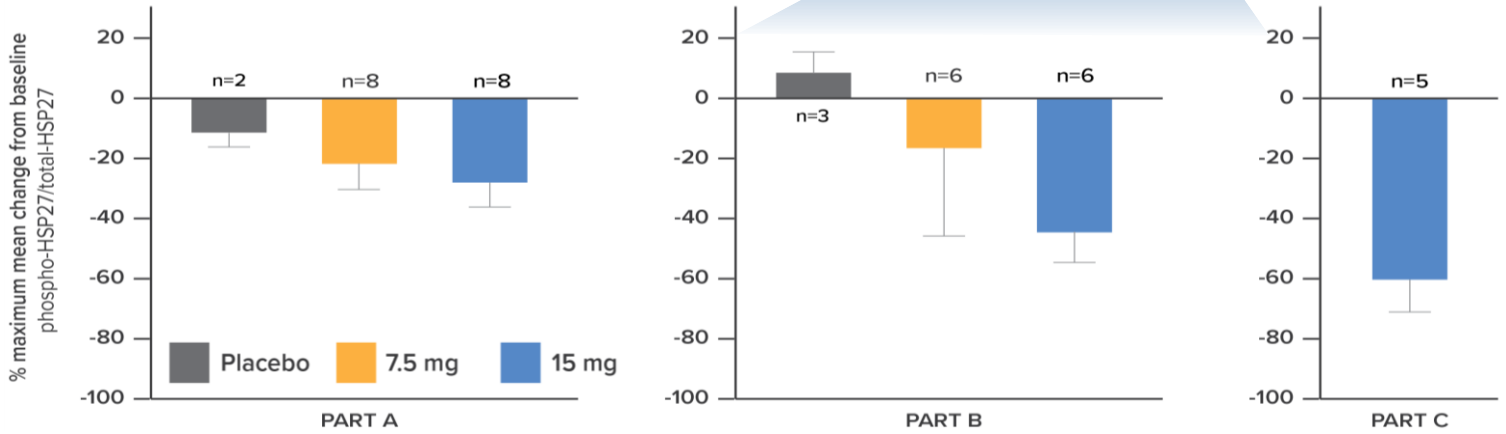
Treatment	N	Concentration, ng/g Mean (SD)
7.5 mg losmapimod	6	42.10 (10.47)
15 mg losmapimod (part B)	6	63.57 (34.03)
15 mg losmapimod (part C)	5	97.16 (22.42)

Time course of blood target engagement
Ex-vivo sorbitol stimulated pHSP27/total HSP27 assay

Part B: Estimated difference from Placebo (95%CI)



pHSP27 / total-HSP27 % change from baseline across Phase I cohorts

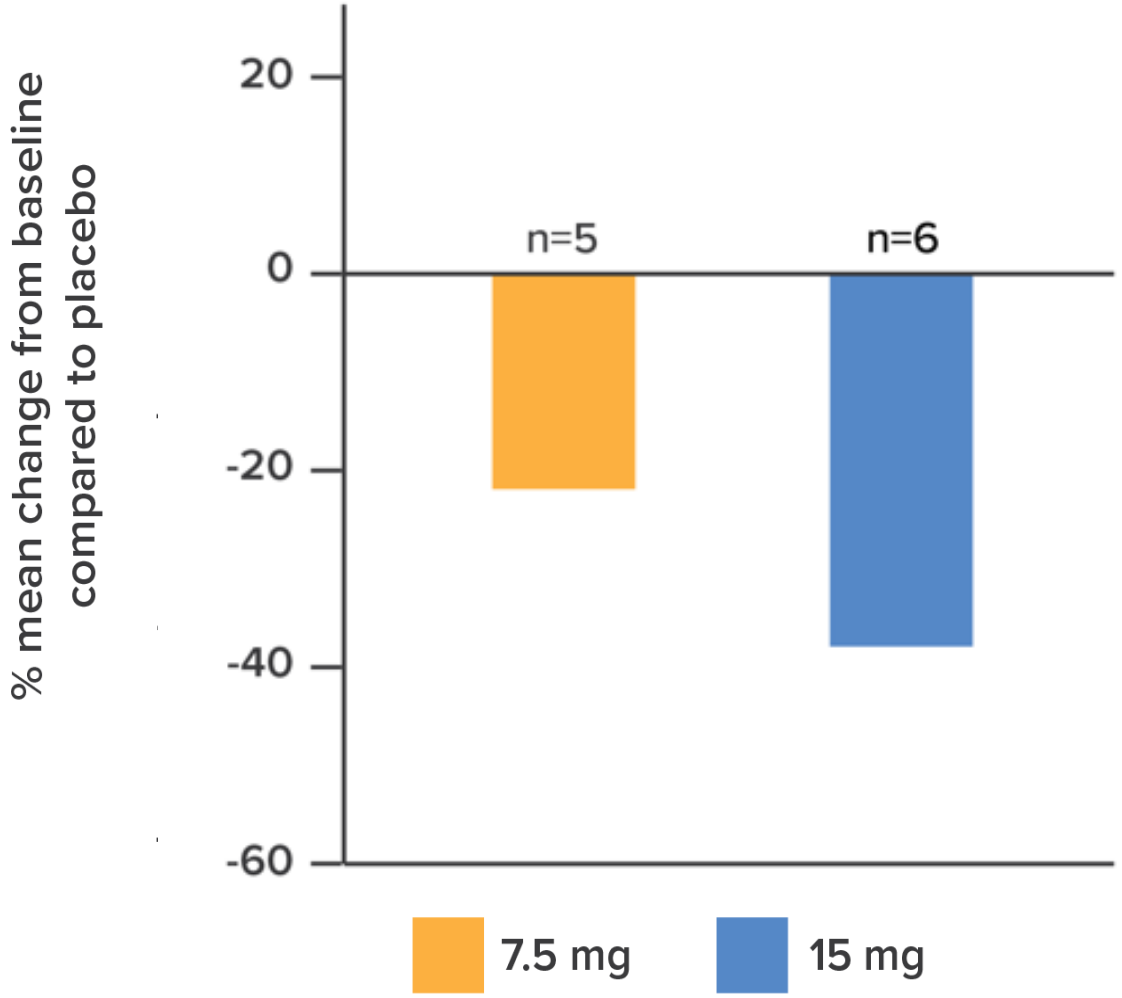


Part A: 1-day timepoint
Part B & C: 14-day timepoint

Losmapimod Showed Target Engagement in Skeletal Muscle

Data Normalized to Placebo

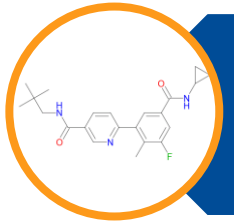
*pHSP27/HSP27 ratio at single time point (day 13) in **non-sorbitol stimulated** muscle*



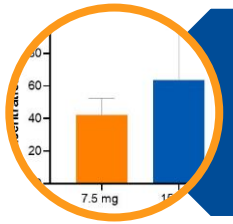
Placebo	N=1
7.5 mg BID	N=5
15 mg BID	N=6

**Note: Ex-vivo sorbitol stimulation is not feasible in muscle*

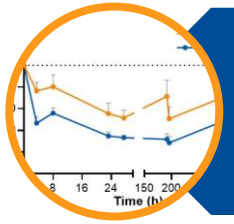
Conclusions



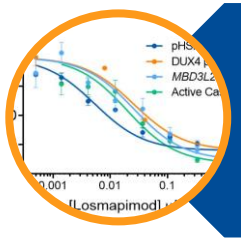
Losmapimod was well tolerated in FSHD patients



Achieved clinically relevant, approximate dose-dependent concentrations in muscle



15 mg PO BID dose showed sustained and robust target inhibition in blood and muscle



Data supports the design of the ongoing Phase 2 clinical trials; enrollment complete

- ReDUX4 (NCT 04003974) - A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 24-Week, Parallel-Group Study with OLE
- Open label 64-week study (NCT 04004000)

Acknowledgements

- Healthy volunteers and FSHD patients who participated in the study
- Center for Human Drug Research (CHDR, Leiden, Netherlands)
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- Fulcrum's FSHD Clinical Advisory Board
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- Radboud University Medical Center
- Vendors:
  - MRI imaging analysis vendor AMRA
  - Bioanalytical vendor PPD
  - Target engagement vendor CBI/Immunologix

Thank you!