

Phase 1 clinical trial of losmapimod in FSHD: safety, tolerability and target engagement

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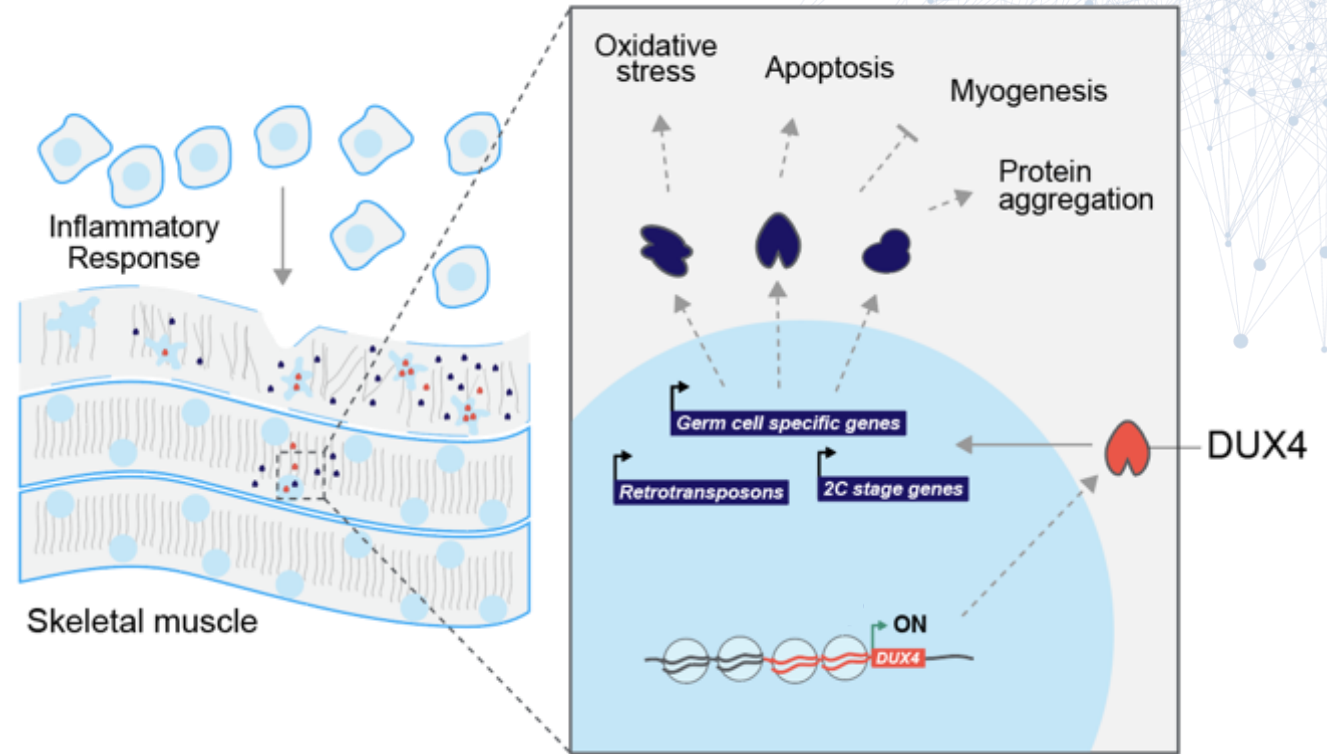
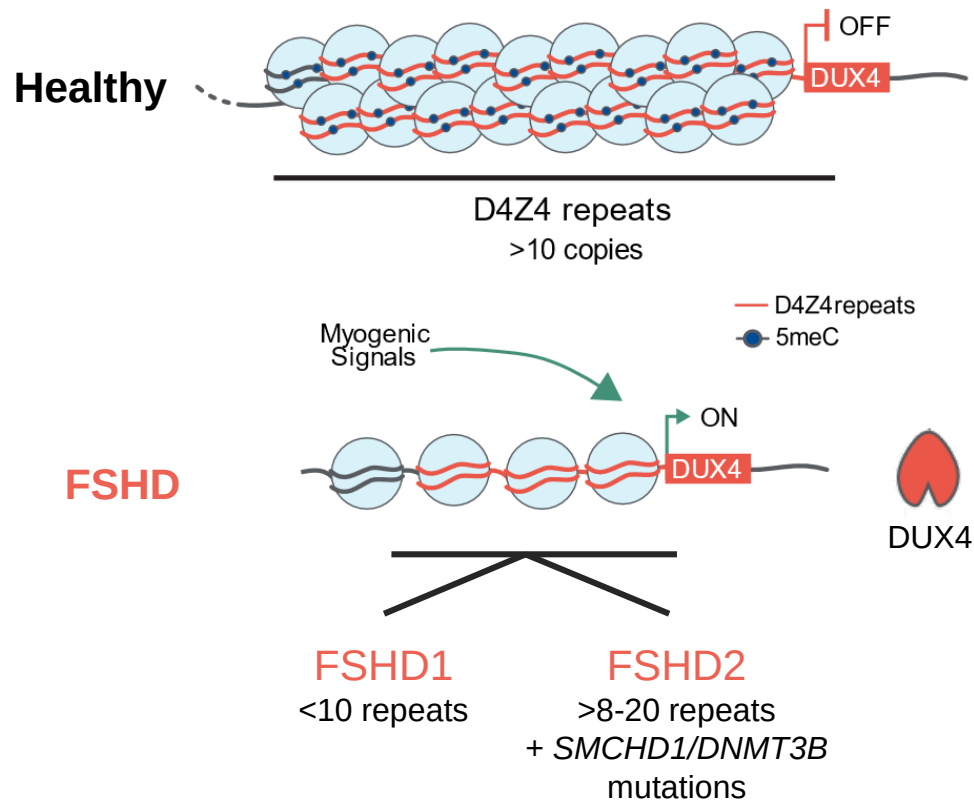
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Disclosures

- Stock/Stock Options in Biogen, Vertex Pharmaceuticals, and Fulcrum
- Full-time employee as Medical Director at Fulcrum Therapeutics

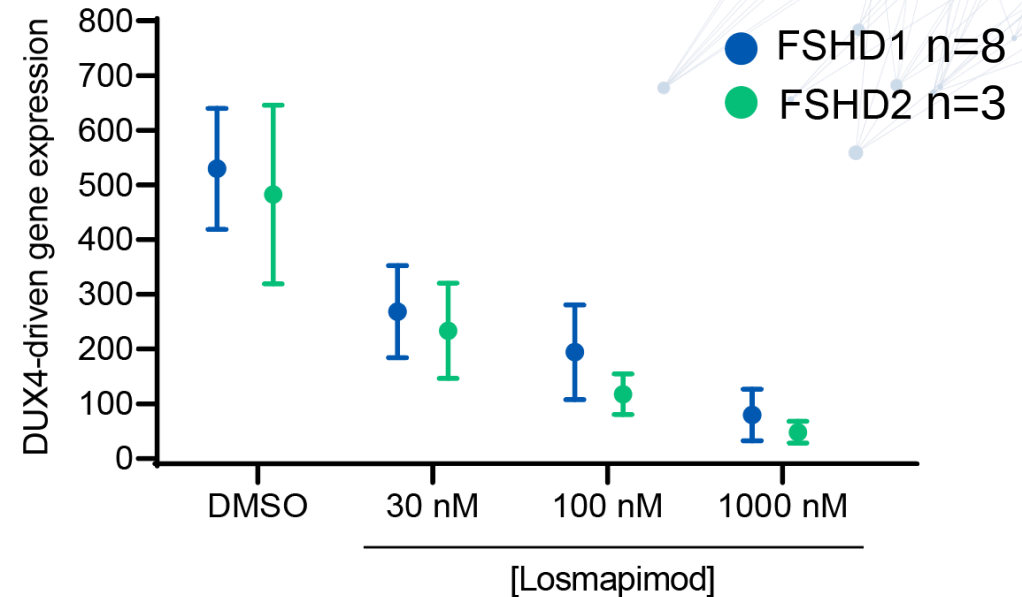
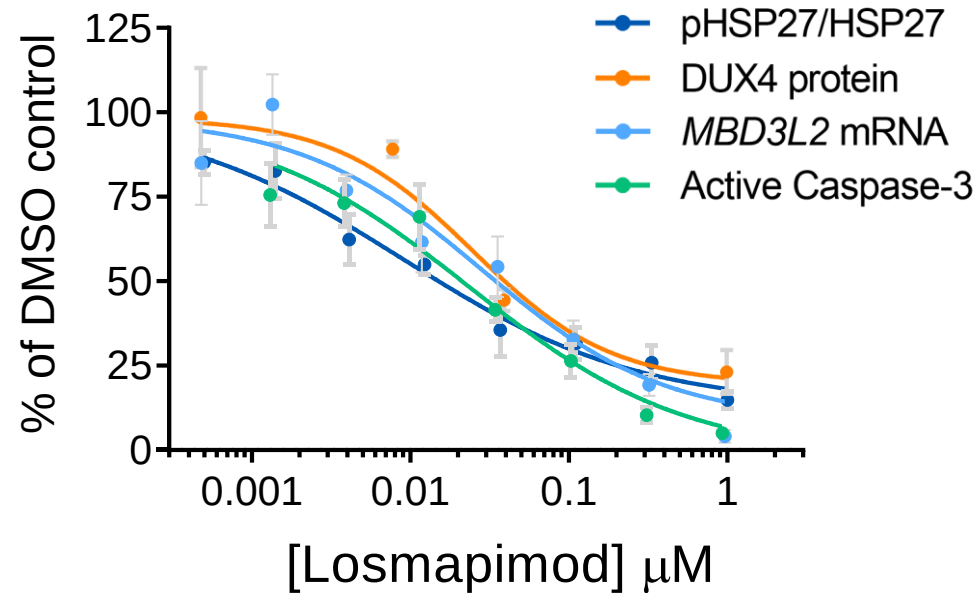


Aberrant expression of DUX4 causes FSHD



DUX4 is a homeodomain transcription factor

Losmapimod, a selective p38 α / β MAPK inhibitor, reduced DUX4 expression in FSHD myotubes



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

Objectives

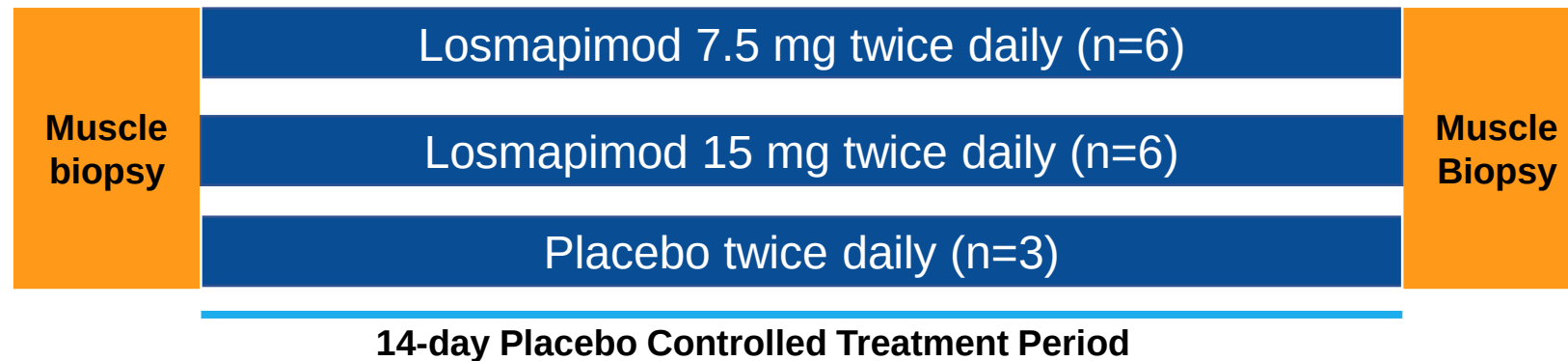
- **Primary Objective:** Initial Safety and Tolerability in FSHD
 - Note: Safety and tolerability previously demonstrated in 25 studies in over 3,500 healthy adult volunteers and patients across other multiple indications (see poster P.44, Cadavid D et al).
- **Secondary Objective:** PK and Target Engagement in blood and muscle
 - Note: Muscle biopsies performed at baseline and on treatment at approx. Cmax in FSHD patients

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

Demographics

	Part A Healthy Volunteers	Part B FSHD1
Gender (M:F)	6M:4F	6M:9F
Age Mean SD Min/Max	31.4 17.2 22/64	41.6 11.6 26/64
BMI Mean SD Min/Max	22.7 2.4 19.6/27.2	24.8 3.0 20.7/31.4
Ricci (FSHD Disability Score) Mean SD Min/Max	N/A	2.6 0.7 1.5/4

Safety and tolerability

- No Serious Adverse Events (SAE)

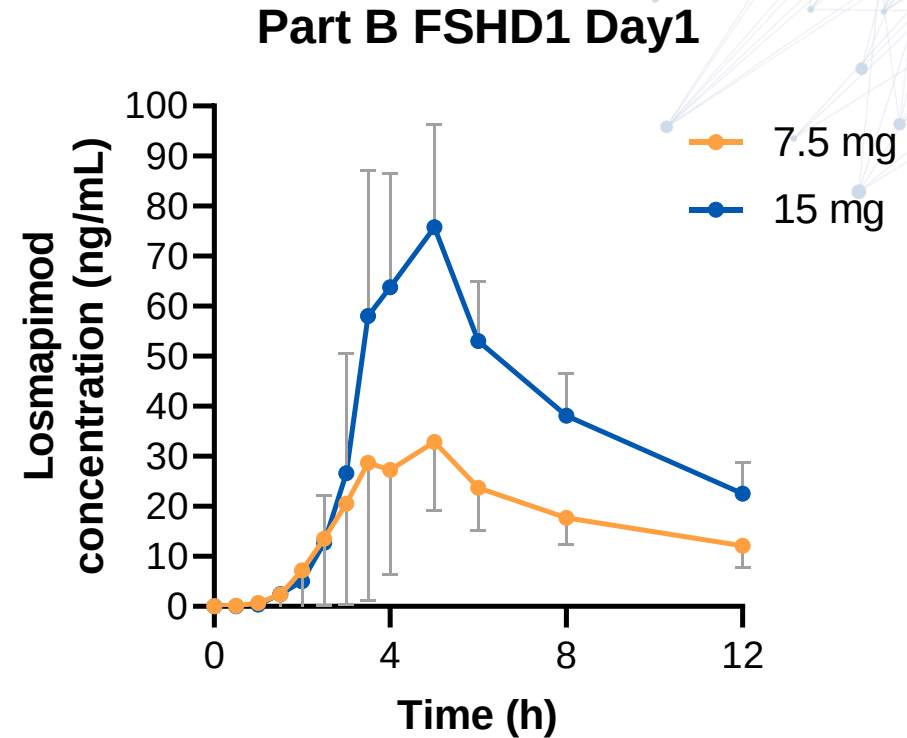
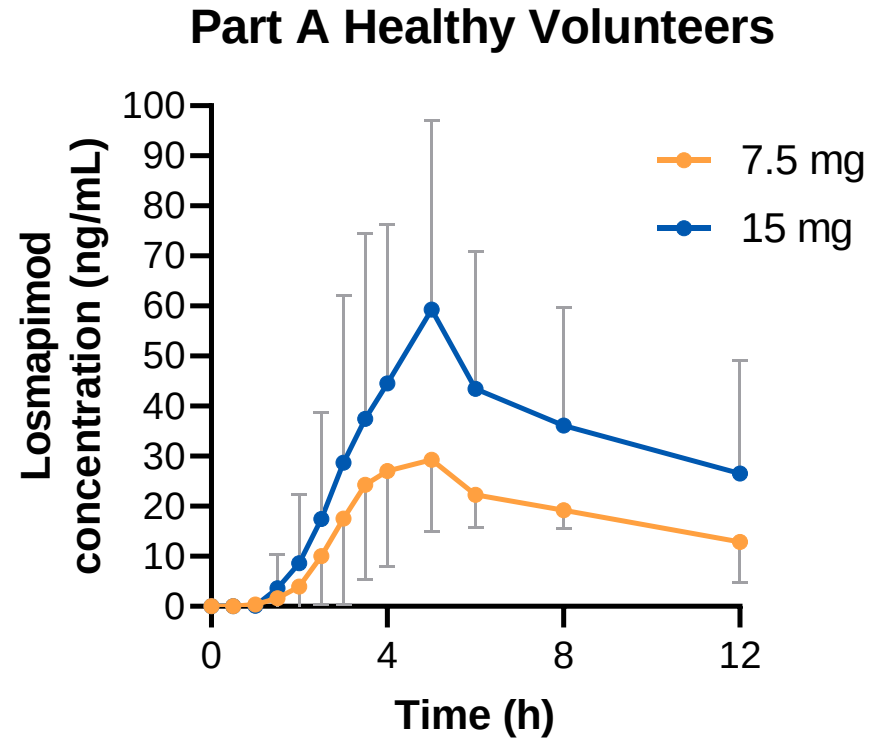
	Adverse Effects (AE) (n)
Part A	Somnolence (5) Headache (4) Dizziness (2)
Part B	Headache (4) Backpain (3) Fatigue (3) Constipation (1) Dizziness (1) Pain (1)

- No clinically significant changes in vital signs, laboratory analyses, ECG or urinalysis
- Muscle needle biopsies were well tolerated

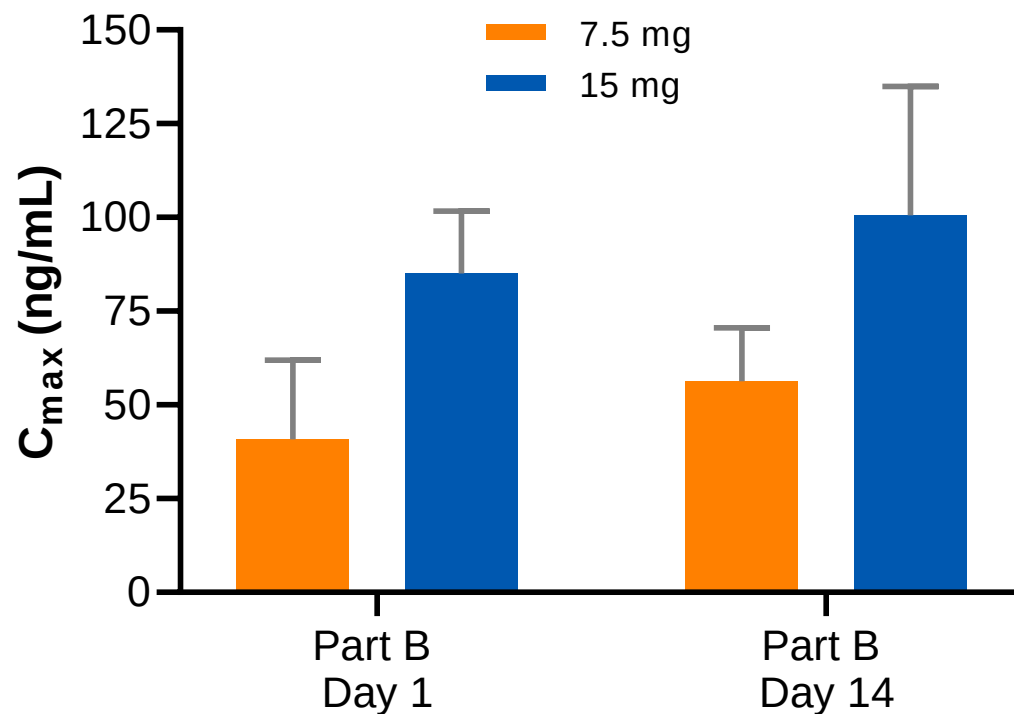
Assessment of Pharmacokinetics (PK)



Similar PK profile in HV and FSHD1 subjects



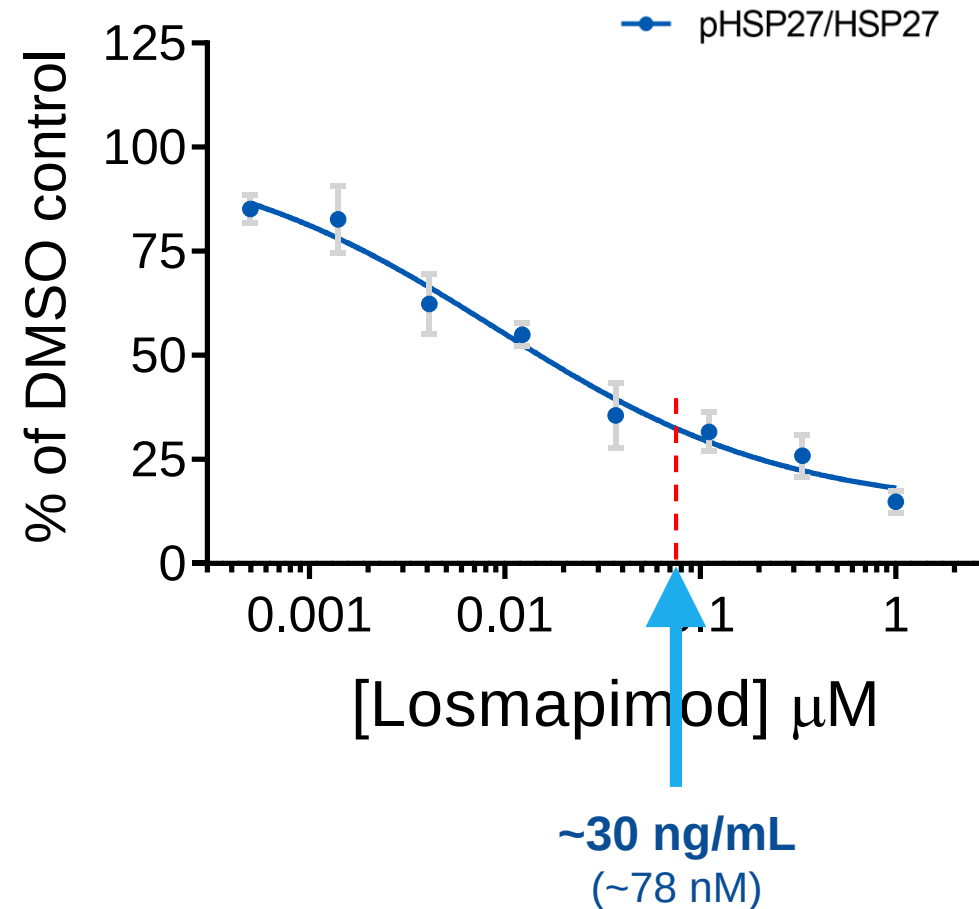
Accumulation observed with repeated dosing



	C_{max} (ng/ml)		AUC_{0-12} (ng*hr/ml)		T_{max} (hr)
	mean (SD)	CV %	mean (SD)	CV %	median
Part B (Day 1)					
7.5 mg	40.8 (21.1)	51.7	201.5 (74.6)	37.0	4.5
15 mg	85.0 (16.7)	19.7	410.2 (50.3)	12.0	4.6
Part B (Day 14)					
7.5 mg	56.3 (14.2)	25.3	394.6 (92.8)	23.5	4.5
15 mg	100.5 (34.4)	34.3	632.7 (175.4)	27.7	5.0

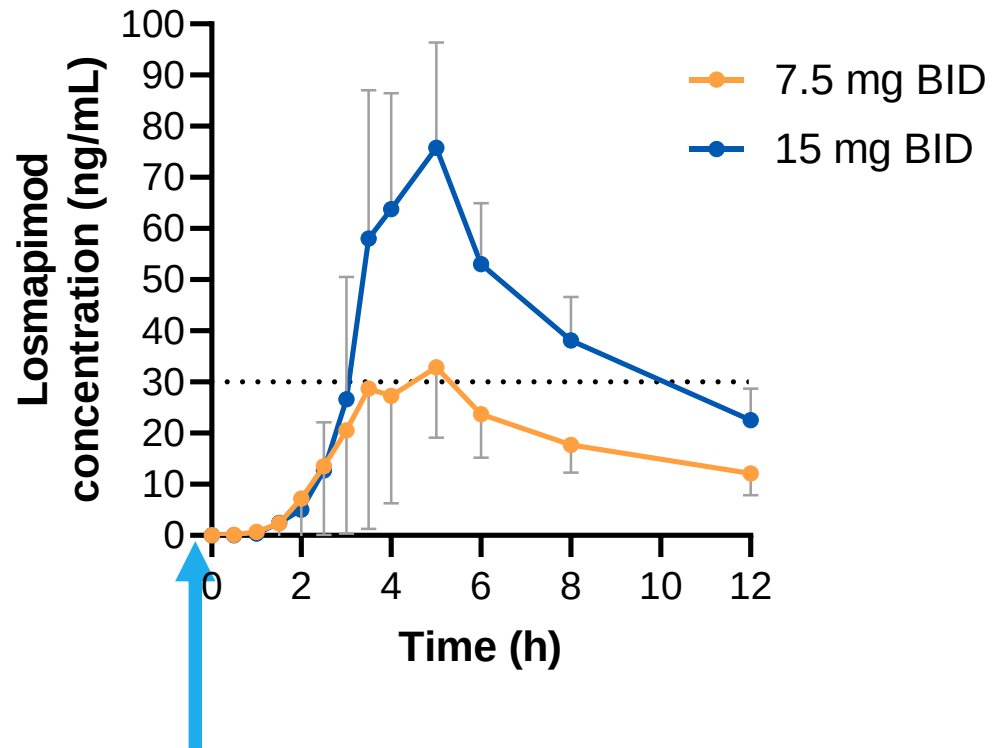
Accumulation Ratio: 7.5 mg: 2.0
15 mg: 1.5

Robust In Vitro inhibition of p38 activity at ≥ 30 ng/mL



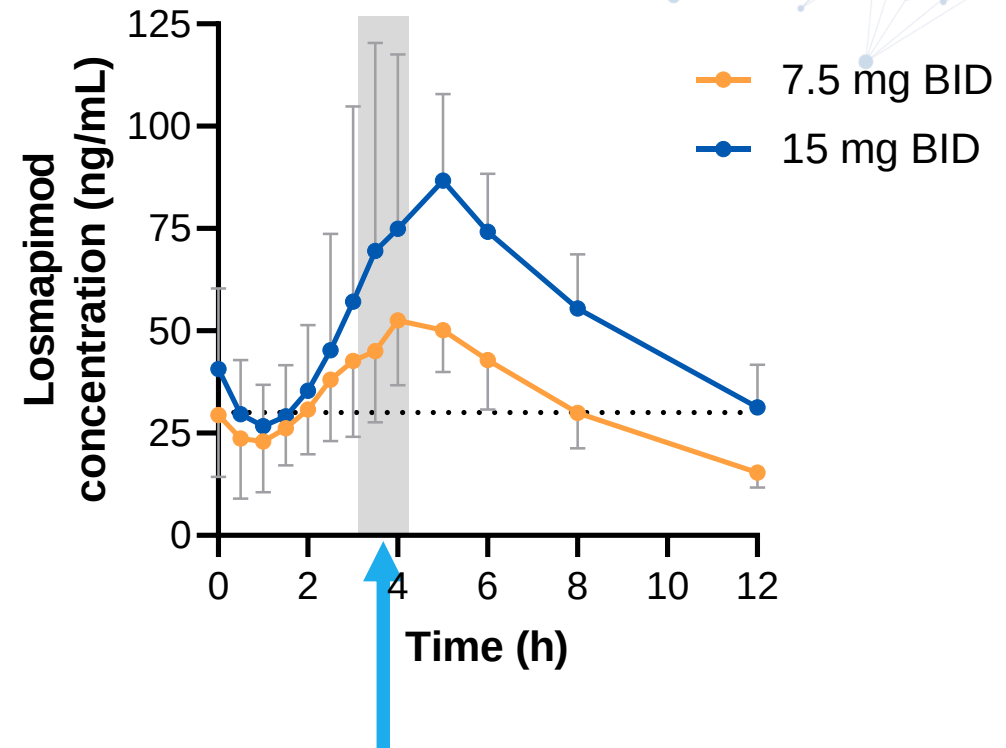
Losmapimod 15 mg BID sustained concentrations for robust target engagement

Part B FSHD1 Day 1



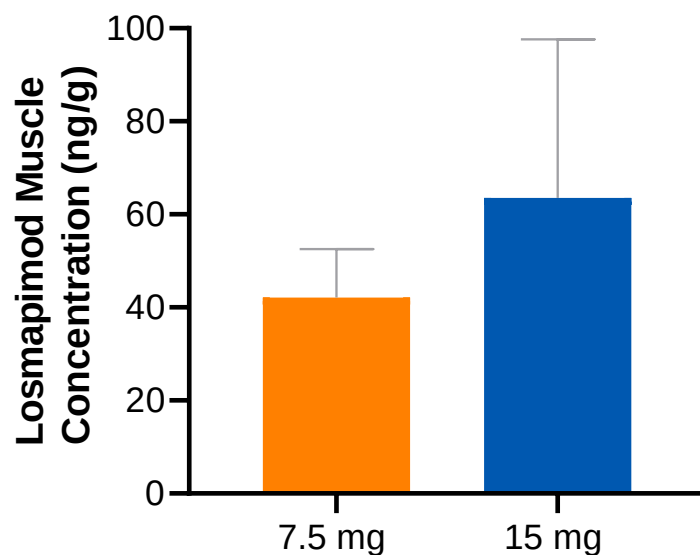
Pre-treatment muscle biopsy

Part B FSHD1 Day 14



On-treatment muscle biopsy

Losmapimod showed dose dependent concentrations in muscle



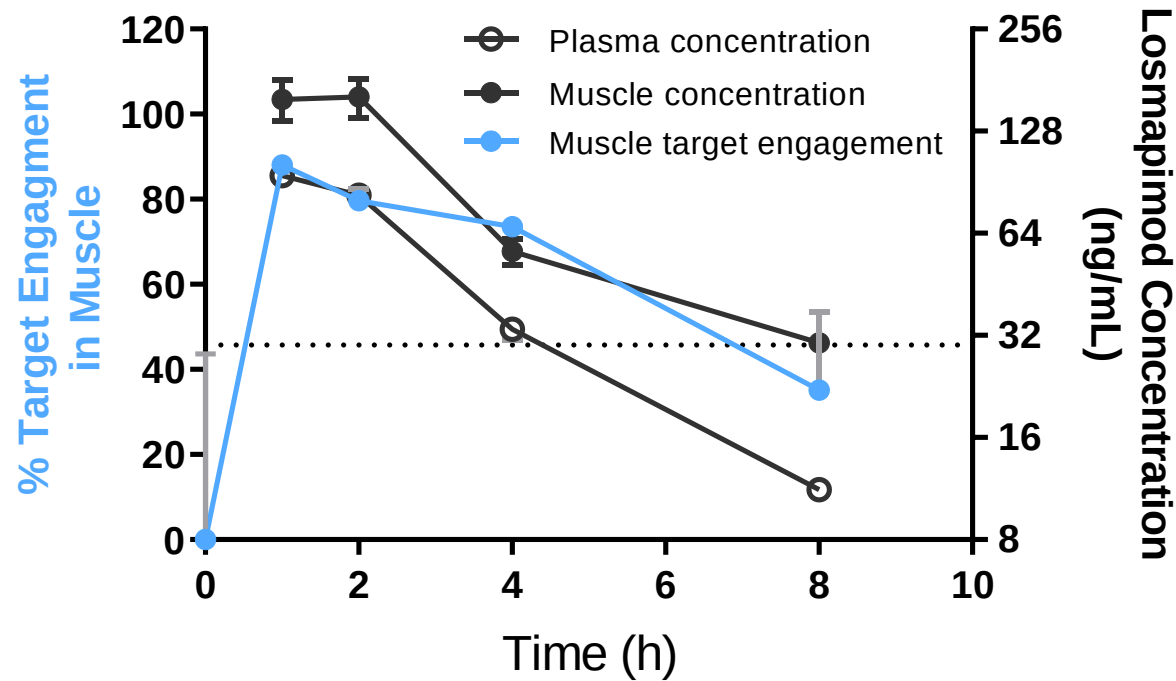
		Muscle		Plasma	
	N	Mean ng/g (SD)	CV(%)	Mean ng/ml (SD)	CV(%)
7.5 mg	6	42.1 (10.5)	24.9	52.6 (15.7)	30.2
15 mg	6	63.6 (34.0)	53.5	75.0 (42.5)	56.7

Ratio to Plasma approximately 1:1

Assessment of Pharmacodynamics (PD)



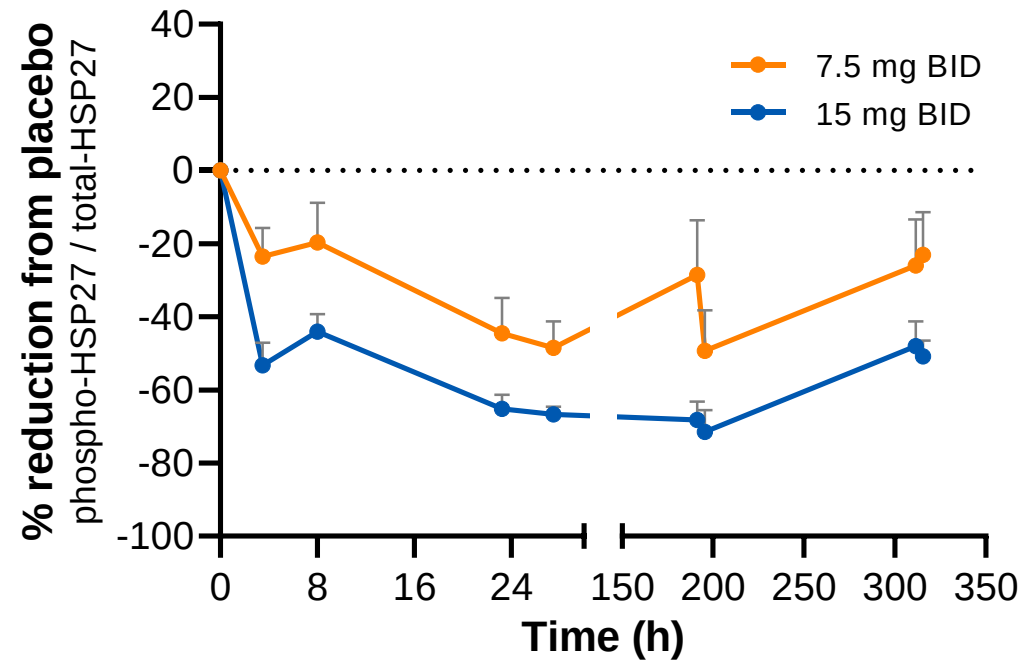
Losmapimod: in vivo PK/PD in rodents



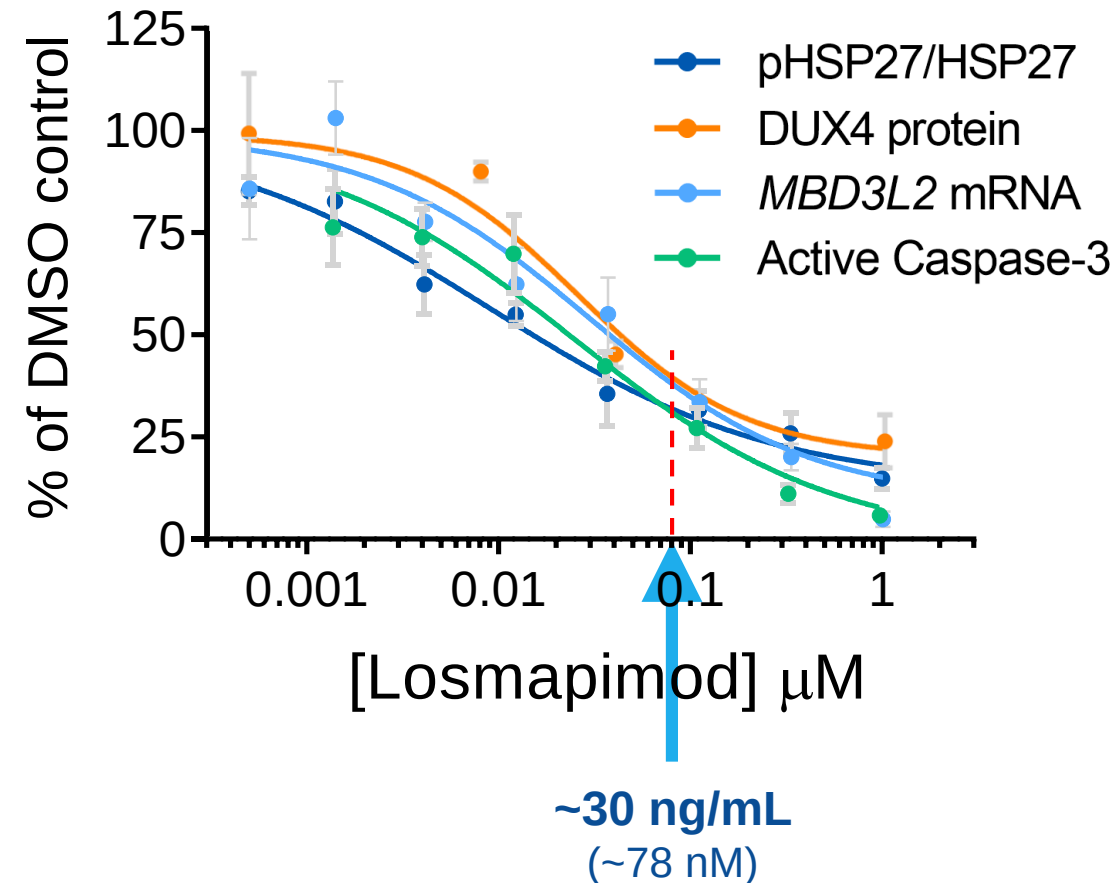
- Muscle:plasma exposure ratio is approximately 1 in rodents
- Losmapimod inhibits p38 in muscle rapidly following acute dosing.

Sustained and dose dependent target engagement in blood

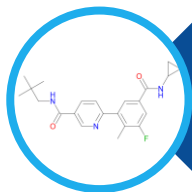
15 mg PO BID dose resulted in greater inhibition of p38 activity



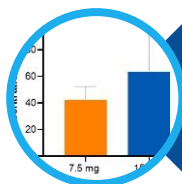
In Vitro inhibition of p38 MAPK resulted in a reduction of DUX4 activity and muscle cell death



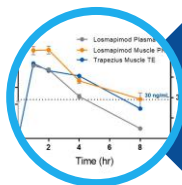
Conclusions



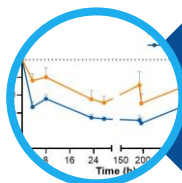
Losmapimod was safe and well tolerated in FSHD patients



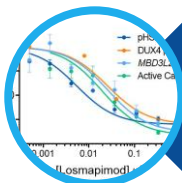
Achieved clinically relevant, dose-dependent concentrations in muscle



Similar exposures in plasma and muscle as shown in pre-clinical models



15mg PO BID dose showed sustained and robust target inhibition



Data supports the design of the ongoing Phase 2 clinical trials currently enrolling

- Placebo-controlled 24-week study ReDUX4 (NCT 04003974)
- Open label 64-week study (NCT 04004000)

Acknowledgements

- Healthy volunteers and FSHD patients who participated in the study
- Fulcrum's phase 1 study FIS 001-2018 management team
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- Fulcrum's FSHD Clinical Advisory Board
- Centre for Human Drug Research (CHDR)
- Leiden University Medical Center
- Radboud University Medical Center
- Vendors:
 - MRI imaging analysis vendor AMRA
 - PK vendor PPD
 - Target engagement vendor CBI

