



Emerging Data from the First-in-Human Study of EPI-321, an Investigational Epigenetic Modulating Therapy for FSHD

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WMS2026
HIROSHIMA

**The 31st Annual Congress of
the World Muscle Society**

29 September - 3 October 2026, Hiroshima, Japan



Disclosure

- Biogen funded a natural history study of spinal muscular atrophy
- Roche funded first tranche of Biobank samples
- Clinical trials
 - Past: *Amicus, Roche, Stealth*
 - Current: *PTC, Dyne, Arrowhead/Sarepta, Edgewise, Epicrispr, Skyhawk, Design, Soufflé*
- Philanthropy: Duncan Trust, Stern Foundation
- Competitive Grants: MDANZ, HRC, Neurology Dept, Neurological Foundation
- Scientific advisory boards for Roche, Biogen and Larimar
- PI with PCRN/Momentum, NZCR and Optimal Clinical Trials

FSHD is a Progressive Disease with No Approved Treatment, Highlighting a Significant Unmet Need



Over 1 million patients globally



Typical onset in late teens – early 20s

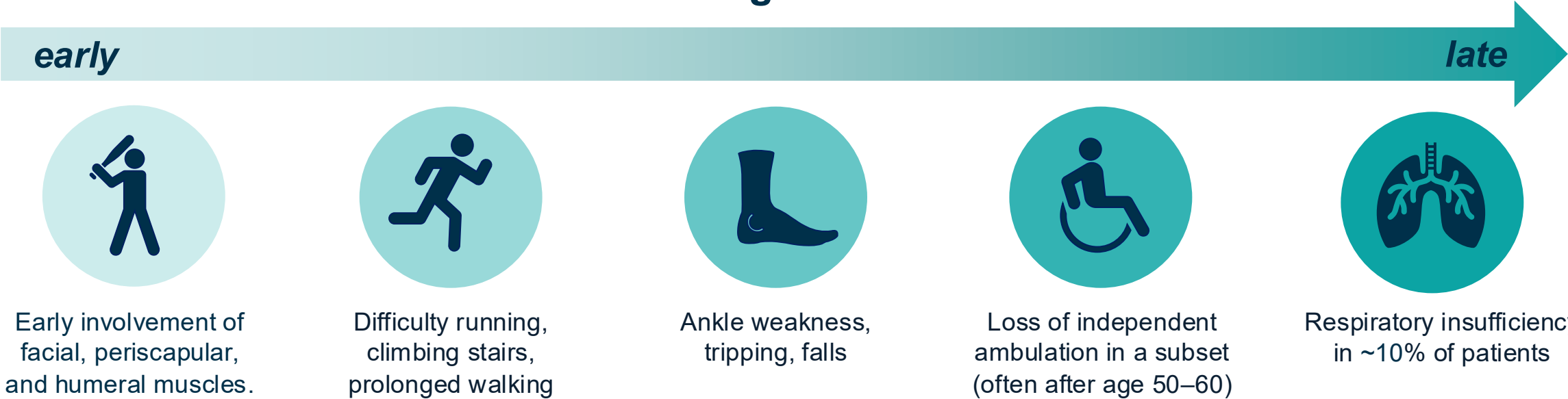


~24% patients become wheelchair dependent

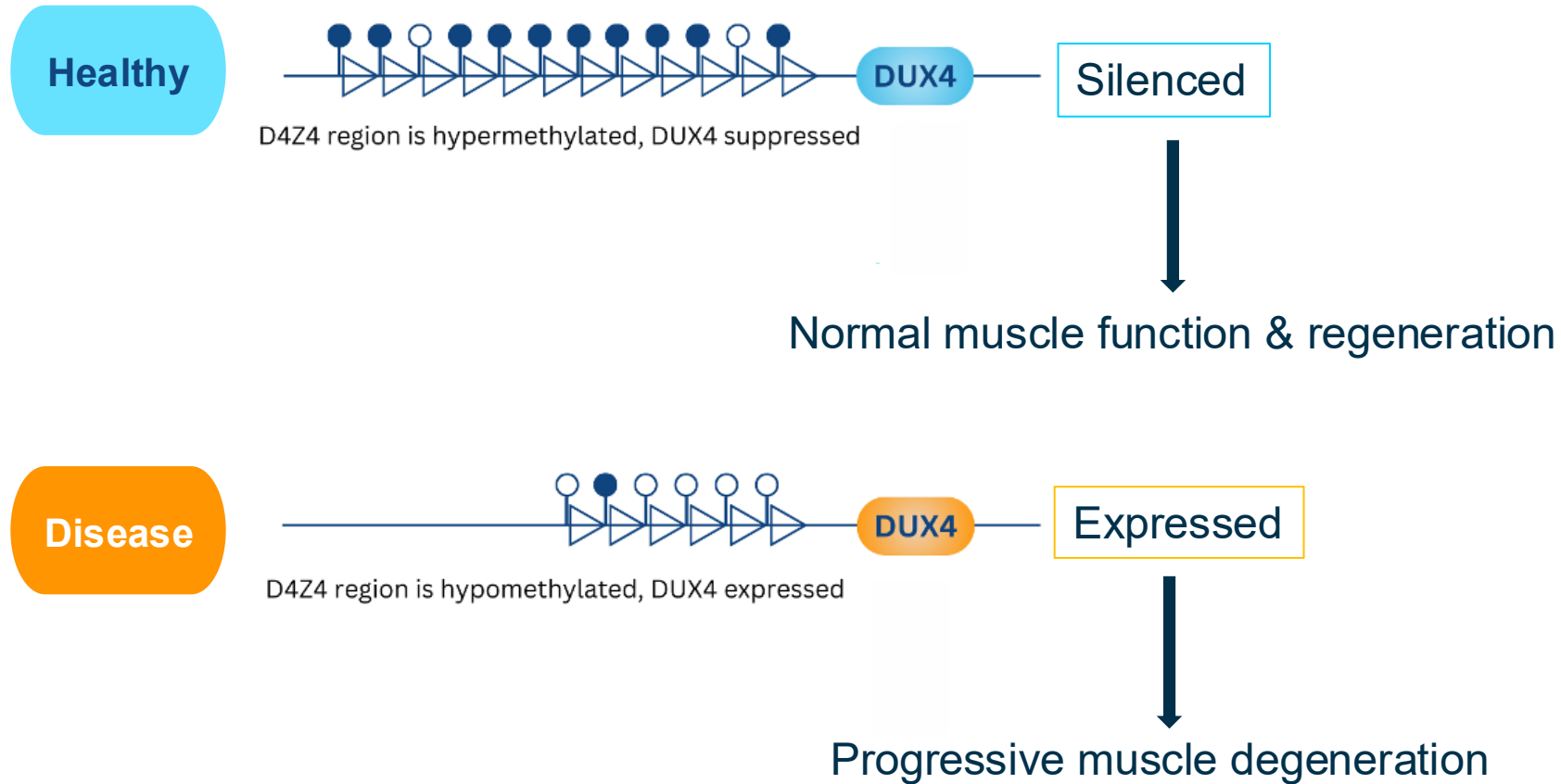


No approved therapies

Functional Progression of FSHD

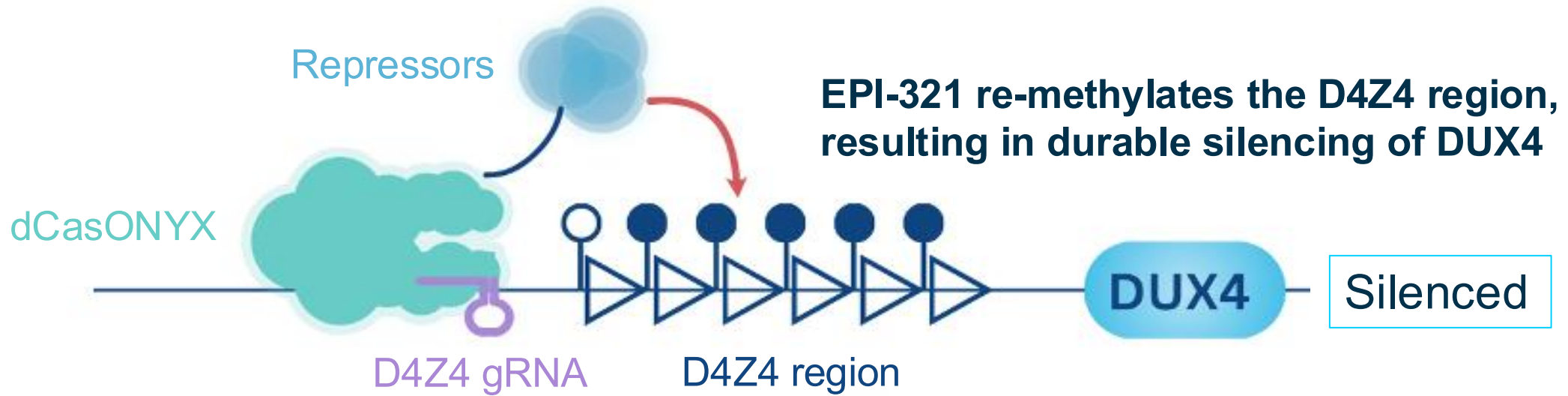


Epigenetic Dysregulation of DUX4 is the Underlying Cause of FSHD



Therapeutic hypothesis: Restoring DUX4 silencing is hypothesized to reduce muscle toxicity and improve muscle function.

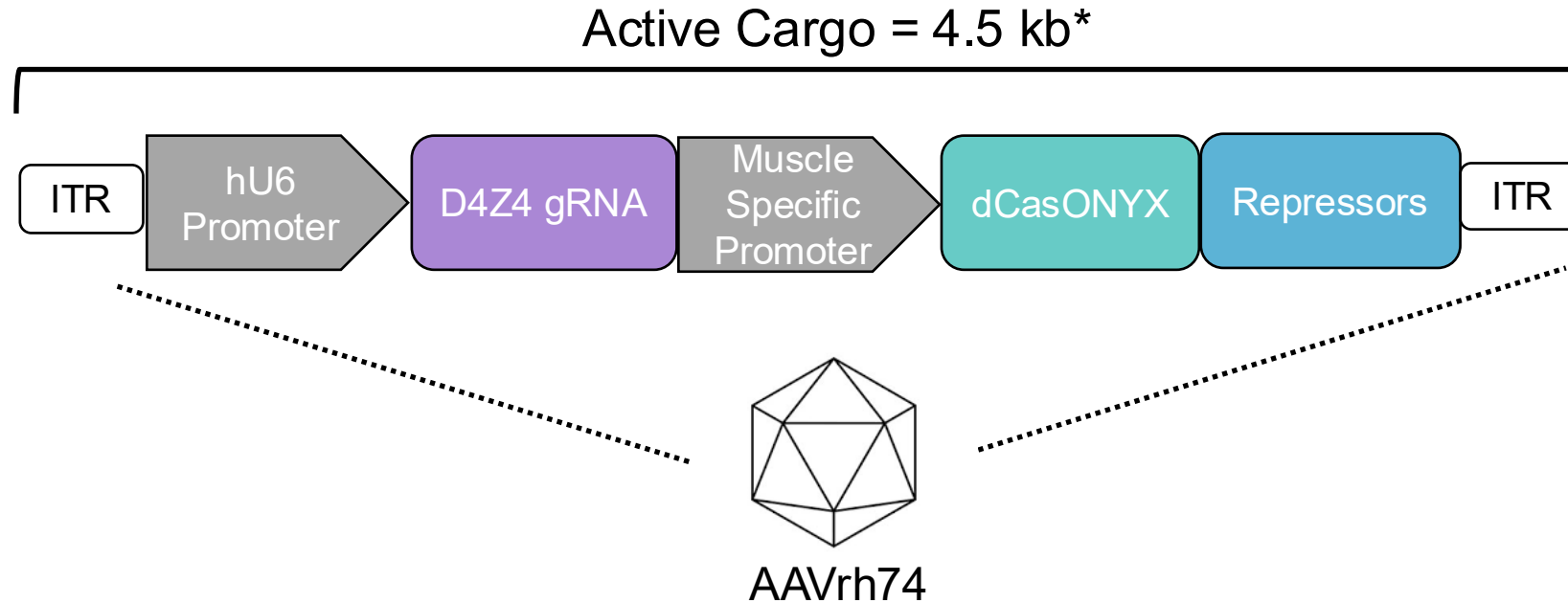
EPI-321: a Potentially Transformative Therapy Designed to Treat FSHD at its Epigenetic Root Cause



Unique Strengths of EPI-321

- ✓ One-time treatment
- ✓ Durable DUX4 silencing
- ✓ Improved muscle health

Complete EPI-321 Therapeutic Payload is Packaged in a Single Muscle-Tropic AAV Vector



Advantages of AAVrh74

- ✓ High muscle tropism
- ✓ Approved in other neuromuscular gene therapies

First-in-Human, Single-arm, Open-label Study to Assess Safety, Tolerability and Early Evidence for Efficacy of EPI-321

Study Design

- N = 12 Participants
- Adults: 18-75 years of age
- FSHD Type 1; Ricci 2-4 (of 5)
- Global, multi-centre
- Single intravenous (IV) infusion
- 2 Dose level cohorts:
 - 1) 2×10^{13} vg/kg (N=6)
 - 2) 4×10^{13} vg/kg (N=6)
- Prophylactic immune suppression:
 - Cohort 1: prednisone
 - Cohort 2: prednisone + sirolimus + rituximab

Primary Objective

Evaluate the **Safety and Tolerability** of EPI-321

Adverse events; clinically relevant changes in labs, vital signs, and physical exam

Secondary & Exploratory Objectives

	Baseline	3 Months	6 Months	1 Year	5 Years
Biomarker (Novel circulating cell-free DUX₂)	○	○	●	○	→
Biomarker (MRI)	○		●	○	→
Functional Assessments	○	○	●	○	→

EPI-321 Demonstrates Manageable Safety with No Serious Adverse Events (SAEs) Related to EPI-321 To Date

Adverse Event	Participants with ≥ 1 AE n (%)	
	2 x 10 ¹³ vg/kg IV (n=6)	4 x 10 ¹³ vg/kg IV (n=6)
Any Adverse Event	6 (100%)	3 (50%)
Related to EPI-321	6 (100%)	3 (50%)
Severe [#] Adverse Event	1 (16.7%)	1 (16.7%)
Serious Adverse Event	0 (0%)	1 (16.7%)*
EPI-321 Related Serious Adverse Event	0 (0%)	0 (0%)
Adverse events leading to death	0 (0%)	0 (0%)

EPI-321 related AEs (≥2 participants)

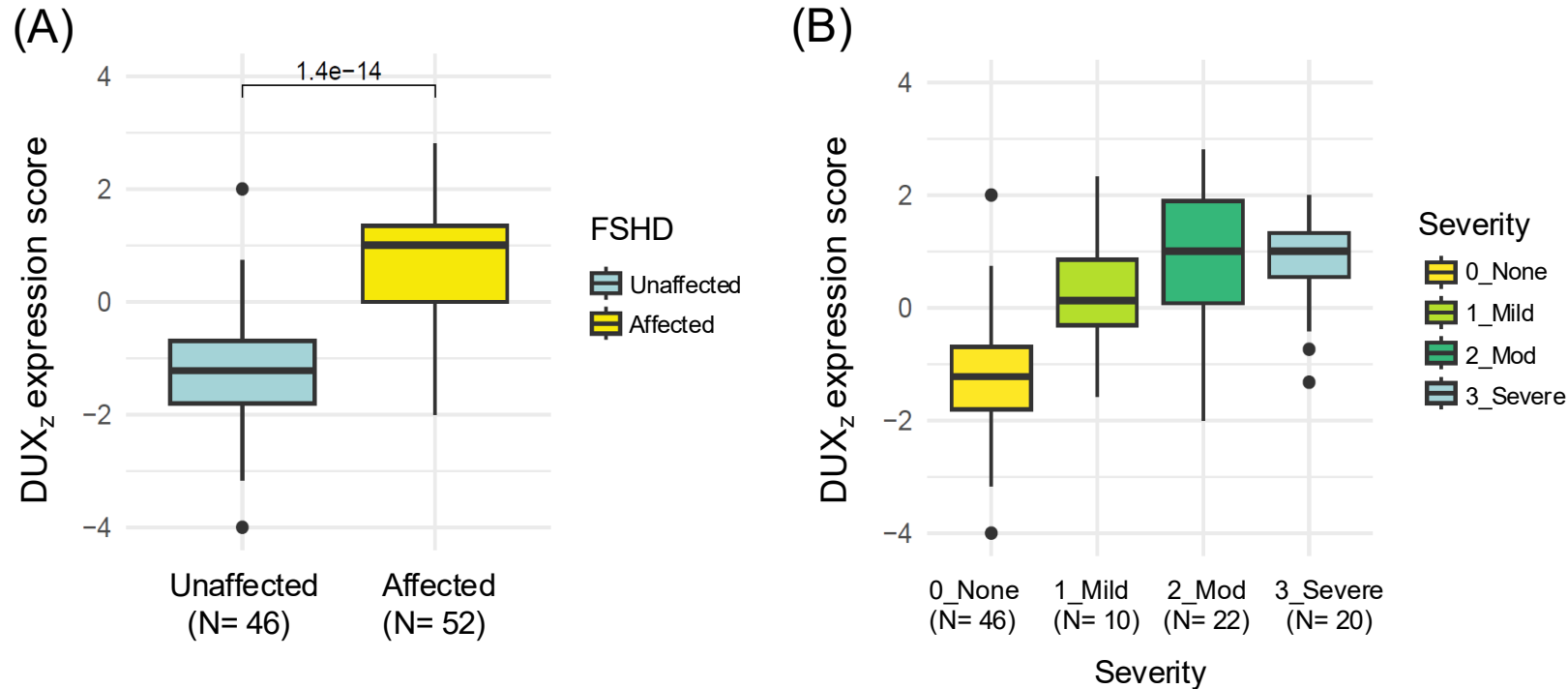
- Elevated soluble C5b-9
- AST or ALT elevation
- Elevated Troponin-I
- Headache
- Nausea
- Thrombocytopenia
- Fatigue

1 participant experienced 2 severe AEs related to AAV:

- ALT and AST elevation
- Cohort 1 (prednisone prophylaxis only)
- Responded to high-dose methylprednisolone (1g IV x 3 days)
- No clinical sequelae

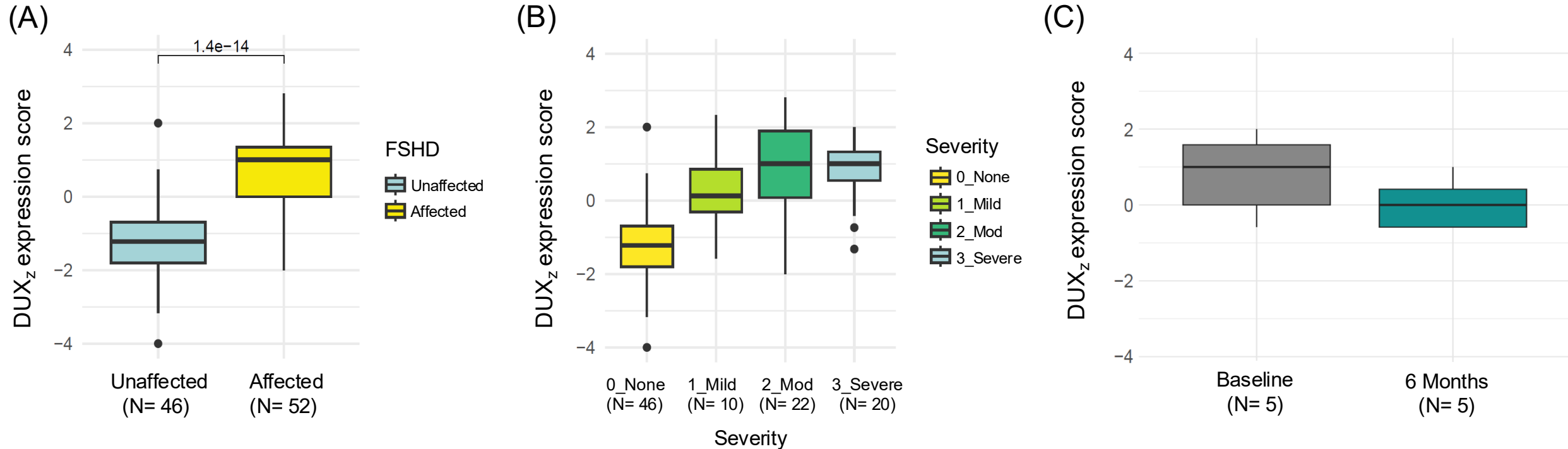
**Severe AE and SAE occurred in 1 participant in Cohort 2 (Grade 3 hypertension with headache, hospitalized) assessed as not related to EPI-321*

Circulating Biomarker DUX_z Associates with FSHD (A), Tracks Disease Severity (B), and Decreases Following EPI-321 Treatment (C)



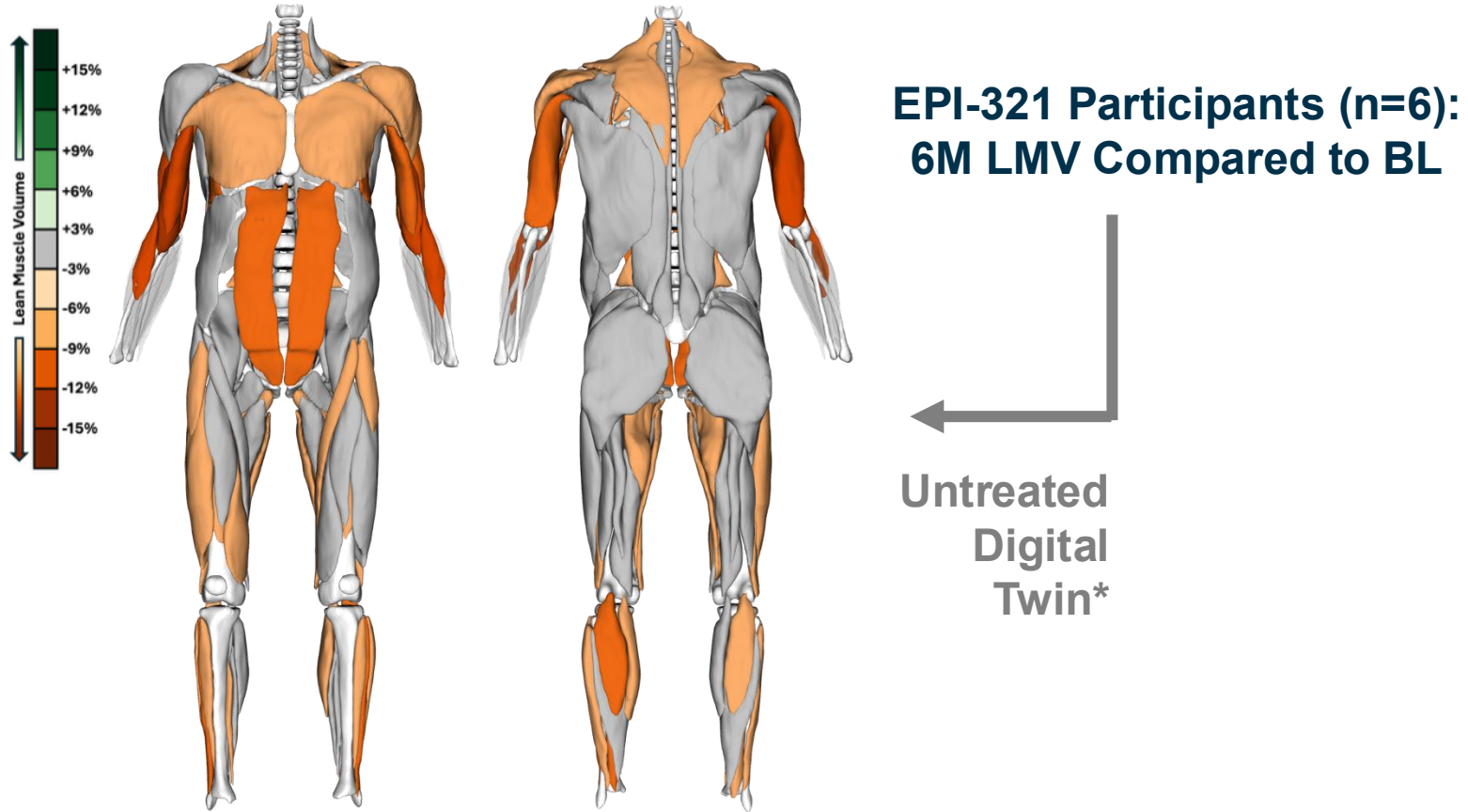
DUX_z = cfDNA fragment signature for *ZBTB17*, a direct transcriptional target of DUX4

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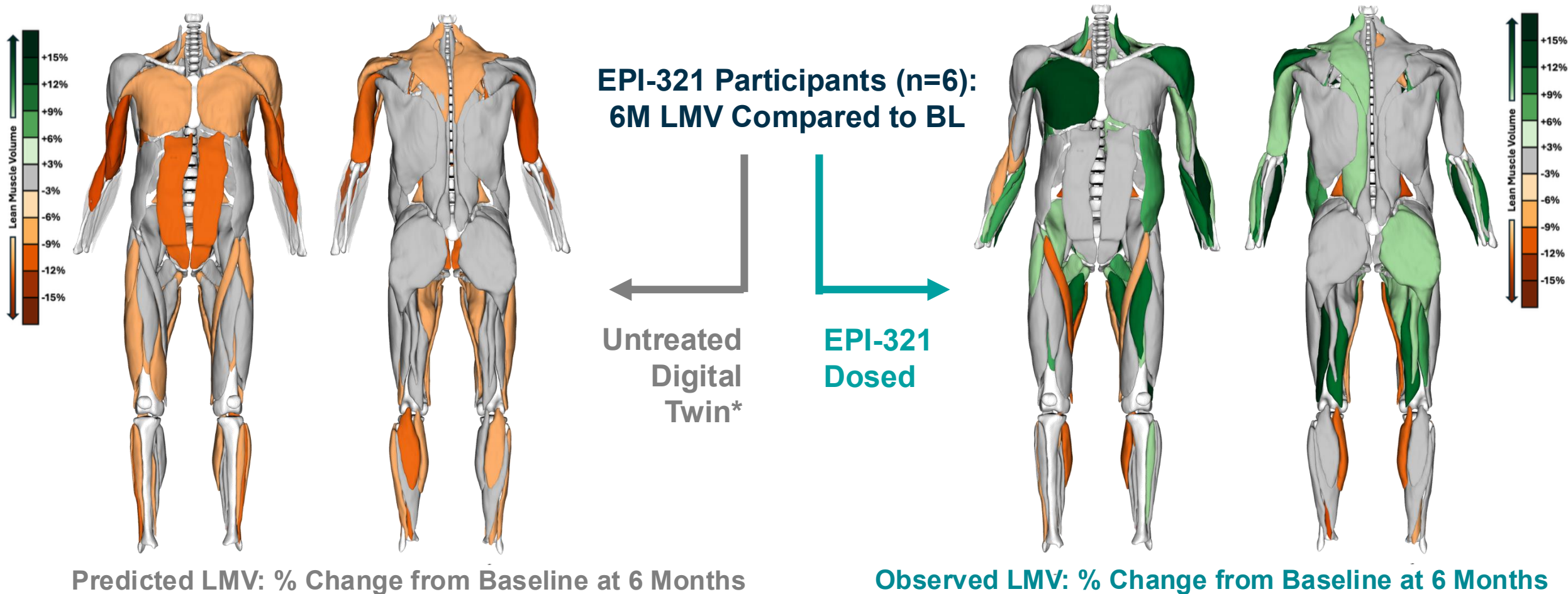
Striking Whole Body Lean Muscle Volume (LMV) Increases at Month 6 After EPI-321 Treatment (n=6)



Predicted LMV: % Change from Baseline at 6 Months

*Untreated Digital Twin 6-month LMV changes are based on Springbok Analytics' digital twin predictive model, informed by extensive, longitudinal FSHD MRI natural history data¹.

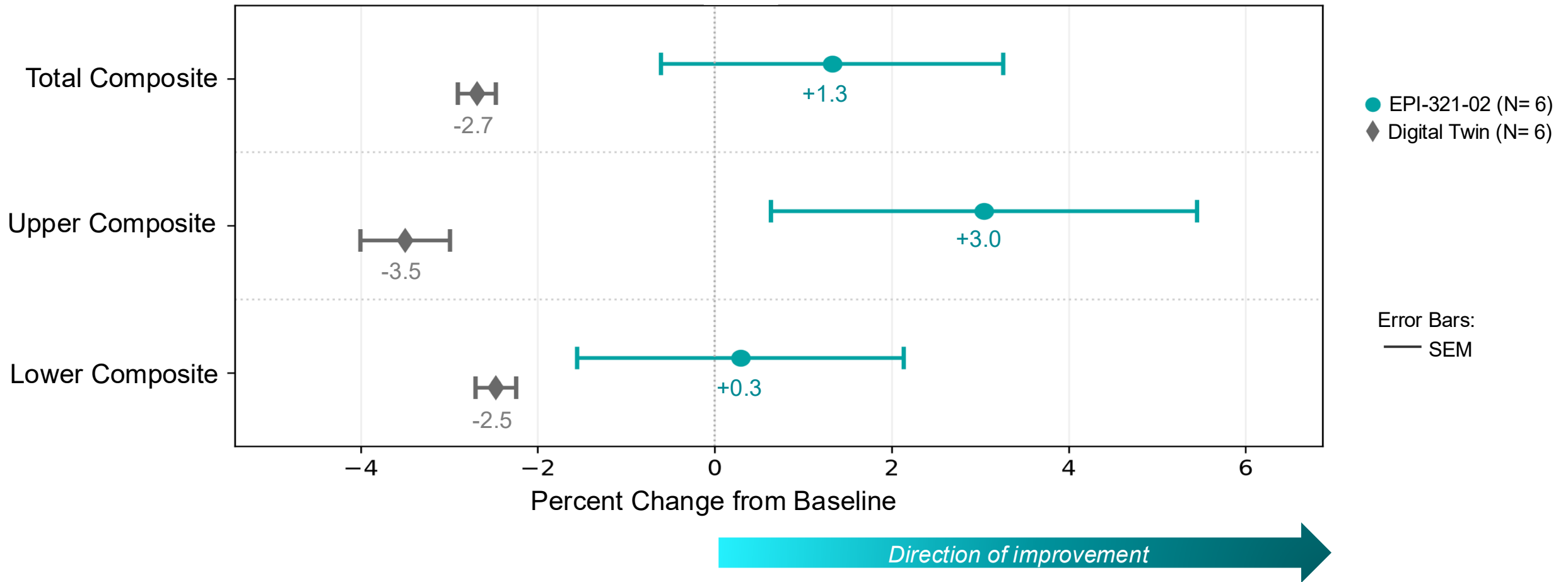
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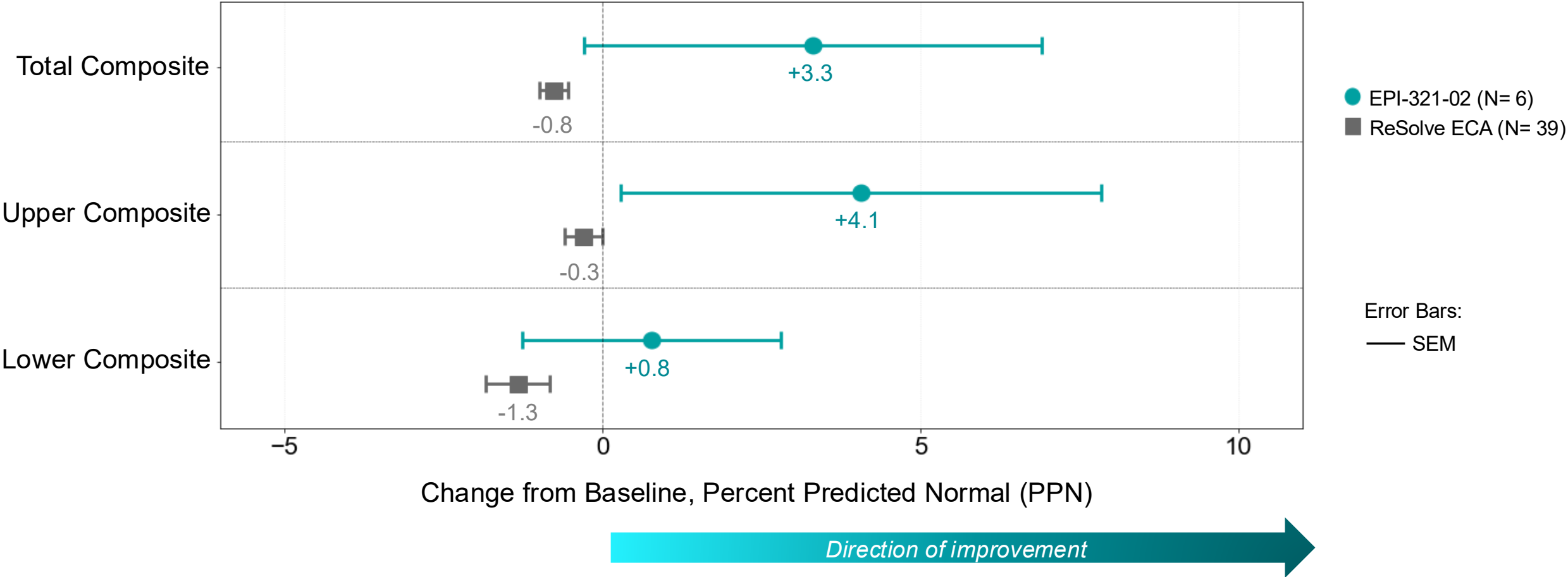
Whole Body LMV Gains After EPI-321 Compared with Matched Untreated Digital Twins at Month 6

Lean Muscle Volume: Percent Change from Baseline at Month 6

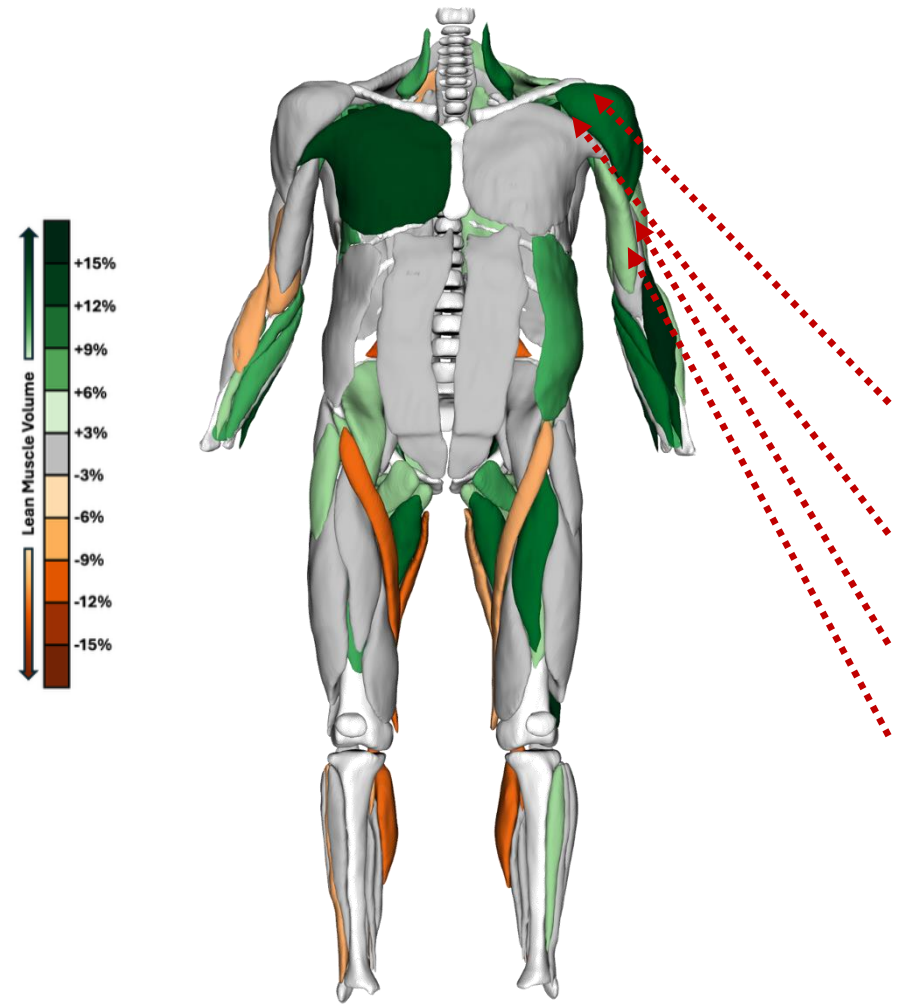


EPI-321 Treated Participants Gain Strength on Quantitative Muscle Testing (QMT) Compared with External Comparator Arm (ECA) at Month 6

Quantitative Muscle Testing: Change from Baseline at Month 6



Lean Muscle Volume (LMV) Gains in Strength-Related Muscles Track With Improvements in QMT at 6M after EPI-321



Muscle / Manoeuvre	LMV: % Change from Baseline		QMT: Change in % Predicted Normal	
	EPI-321 N=6	Digital Twin N=6	EPI-321 N=6	ReSolve ECA N=39
Shoulder Abduction	+4.0	-3.2	+1.0	+2.2
Shoulder External Rotation	+1.9	-1.9	+2.2	-1.6
Elbow Extension	+3.2	-9.0	+8.1	-1.1
Elbow Flexion	+1.7	-9.3	+0.7	-0.2
Total Upper Body	+2.8	-4.0	+3.0	-0.2

EPI-321 Shows a Manageable Safety Profile with Evidence for Improvement Across Efficacy Readouts: DUX_z, LMV, and LMV-Strength Correlations



Enrolment of 6 participants in Cohort 1 (2×10^{13} vg/kg) and 6 participants in Cohort 2 (4×10^{13} vg/kg) completed.



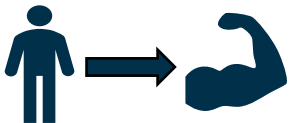
EPI-321 appears safe and well-tolerated with a manageable safety profile at both dose levels.



Early circulating biomarker data show reduction of DUX_z, indicating suppression of DUX4 pathway.



Early MRI data show increases in lean muscle volume at Month 6, indicating gain in muscle mass.



Early lean muscle volume changes track with strength measurements, supporting the potential for EPI-321 to provide a transformative therapy for FSHD.



Future plans include initiation of a Phase 2b study, expected to open in early 2027.

Acknowledgements

Participating Sites

- Rare Disease Research, USA (PI: Dr. Renata Shih)
- Momentum Clinical Research and University of Auckland, New Zealand (PI: Dr. Richard Roxburgh)
- University of California, Los Angeles, USA (PI: Dr. Perry Shieh)
- University of Utah, USA (PI: Dr. Russell Butterfield)
- UMass Chan Medical School, USA (PI: Dr. Lawrence Hayward)
- Sydney Local Health District, Australia (PI: Dr. Katrina Morris)
- Kennedy Krieger Institute, USA (PI: Dr. Doris Leung)

Collaborators

- Springbok Analytics
- University of Colorado Anschutz*
- Solve FSHD
- FSHD Society
- FSHD Global

A huge thank you to the EPI-321 trial participants.