Interim Results from FORTITUDE™, a Randomized Phase 1/2 Trial Evaluating AOC 1020 in Adults with FSHD

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DISCLOSURES:

- Jeffrey M. Statland has received grants from the FSHD Society, Friends of FSH Research, MDA, FSHD Canada, NIH, CDC, Dyne Therapeutics, and Avidity Biosciences
- He has received consulting fees from Fulcrum Therapeutics, Avidity Biosciences, Dyne Therapeutics, Arrowhead Pharmaceuticals, Sarepta, Epic Bio, Roche, ML Bio, Lupin, Vertex, Vita Therapeutics, and Armatus
- He has payment or honoraria from MDA, SOLANE, AAN, and the FSHD Society
- He has received patents for long-acting formulation mexiletine
- He has received stock or stock options from Dyne Therapeutics.

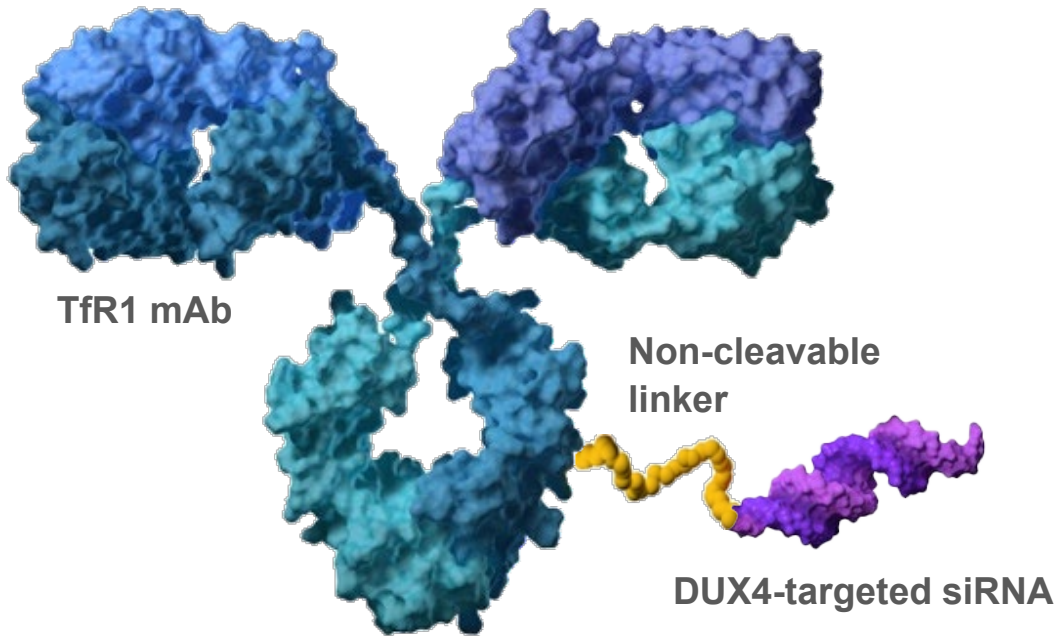
Development of AOC 1020: *delpacibart braxlosiran (del-brax)*

Three main components:

- **Antibody**: human transferrin receptor 1 (TfR1)-targeting, effector function-null, humanized IgG1 antibody
- **Non-cleavable linker**: MCC maleimide linker, enhanced for safety and durability
- **Oligonucleotide**: Stabilized siRNA targeting DUX4 mRNA; engineered and stabilized to withstand lysosomal enzymes, selected for potency and specificity, and modified to diminish off-target effects

Preclinical data has demonstrated:

- **Broad delivery to muscle**
- **Efficacy in FlexDux4 preclinical model**



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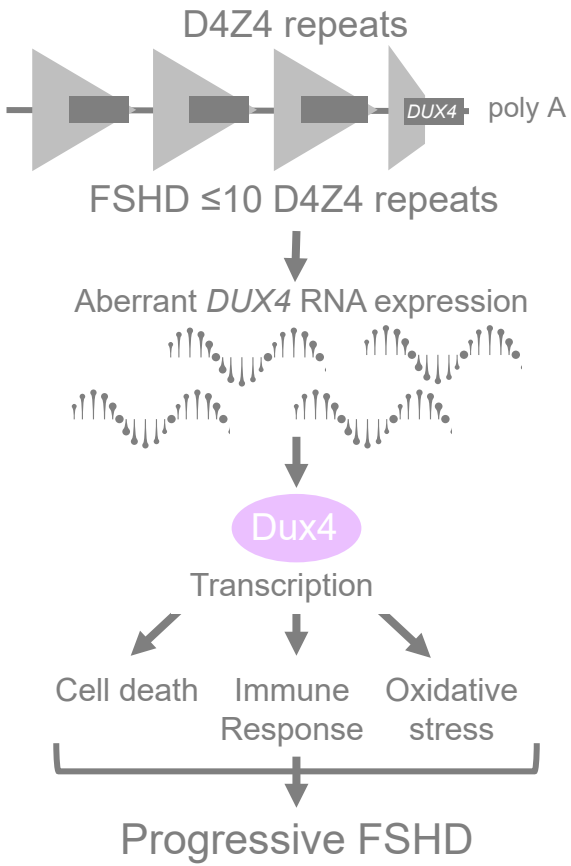
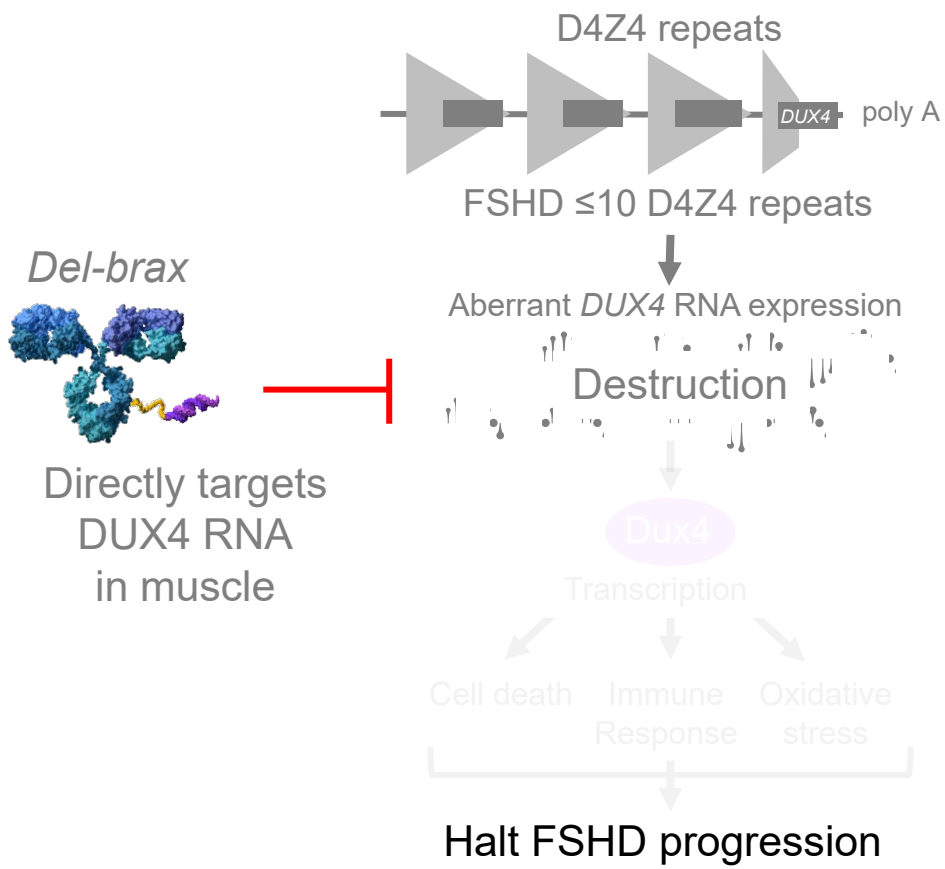
Del-brax: Targets DUX4, the Root Cause of FSHD

Target aberrant expression of DUX4 mRNA for destruction

FSHD disease pathology[1,2]



Del-brax Therapeutic Hypothesis[3,4]



1 Lemmers RJLF, et al. Science 329:1650–1653 (2010)
2 Snider L, et al. PLoS Genet. 2010;6(10):e1001181;

Phase 1/2 FORTITUDE™ Trial

Initial data from 2 mg/kg cohort at 4 months

Key Information

- Randomized, double blinded, placebo controlled
- Age 18-65
- 12-month multiple dose treatment/follow-up period
- Biopsies at baseline and Month 4

Cohort

- Cohort A*: First dose at 1 mg/kg; all subsequent doses at 2 mg/kg

Primary & Secondary Objectives

- Safety and tolerability of ascending doses of *del-brax* in participants with FSHD
- Pharmacokinetics

Key Exploratory Objectives

- Pharmacodynamics
  - Biomarkers
- Measures of clinical activity
  - Muscle strength
  - Muscle function
  - Muscle composition (MRI)
- Patient and Clinician reported outcomes

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*Cohort B data (4 mg/kg) not available

Baseline Demographics Generally Well Matched Between Groups

	Cohort A Placebo N=4 % or mean (SD)	*Del-brax* 2 mg/kg* N=8 % or mean (SD)
Sex, % Male	75	62.5
Age, years	53.5 (10.15)	51.6 (11.62)
Genetic Diagnosis, % FSHD 1	100	100
FSHD Clinical Score	9.3 (1.71)	9.3 (2.31)
D4Z4 Repeat Number	5.0 (2.45)	5.8 (2.60)
Age at First Symptom Onset (y)	25.3 (13.5)	28.6 (17.75)
Reachable Workspace RSA with weight (Q1+Q3) Reachable Workspace RSA without weight (Q1+Q3)**	0.118 (0.0661) 0.156 (0.0810)	0.088 (0.0598) 0.138 (0.0750)
Quantitative Muscle Testing - Percent Predicted Normal	33.97 (16.42)	30.14 (11.58)

*Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study
**Participants in FORTITUDE had >50% reduction in reachable workspace in Q1 & Q3 at baseline compared to normal controls (normal controls RWS (Q1+Q3) without weight: ~0.39, Han et al, 2015 Muscle Nerve)
Reachable Workspace (RWS) Relative Surface Area (RSA) (Q1+Q3) with or without weight was calculated using the average of both arms

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Del-brax: Favorable Safety and Tolerability

Subjects with ≥ 1 AE n (%)	Placebo N=13	2 mg/kg* N=8	4 mg/kg N=18
Any AE	11 (84.6%)	8 (100%)	17 (94.4%)
Related to study drug	3 (23.1%)	4 (50%)	9 (50%)
Severe AE	0	0	0
Serious AE (SAE)	0	0	0
AE leading to study discontinuation	0	0	0
AE leading to death	0	0	0

As of May 2024, data from FORTITUDE

All 39 patients enrolled remain in study

- No serious adverse events (AE), no severe AE
- No discontinuations
- All AE were mild or moderate
- Most common related AE occurring in 2 or more participants:
  - Fatigue
  - Rash
  - Hemoglobin decreased/anemia
  - Chills

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*Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study

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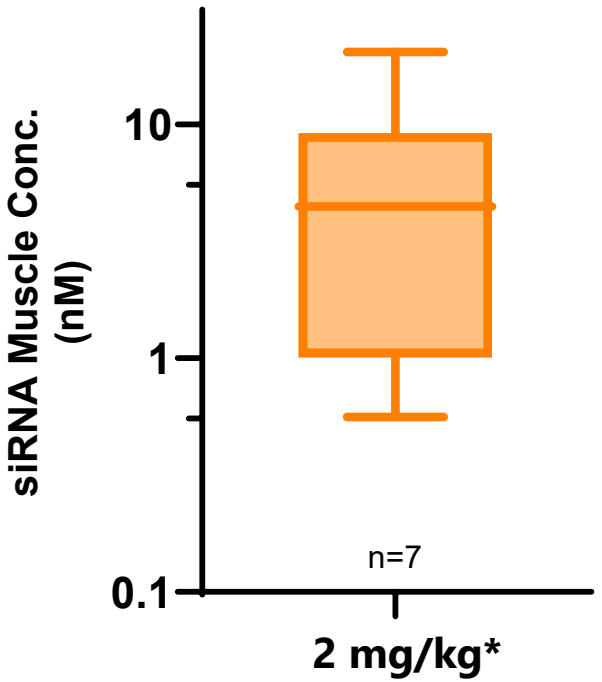
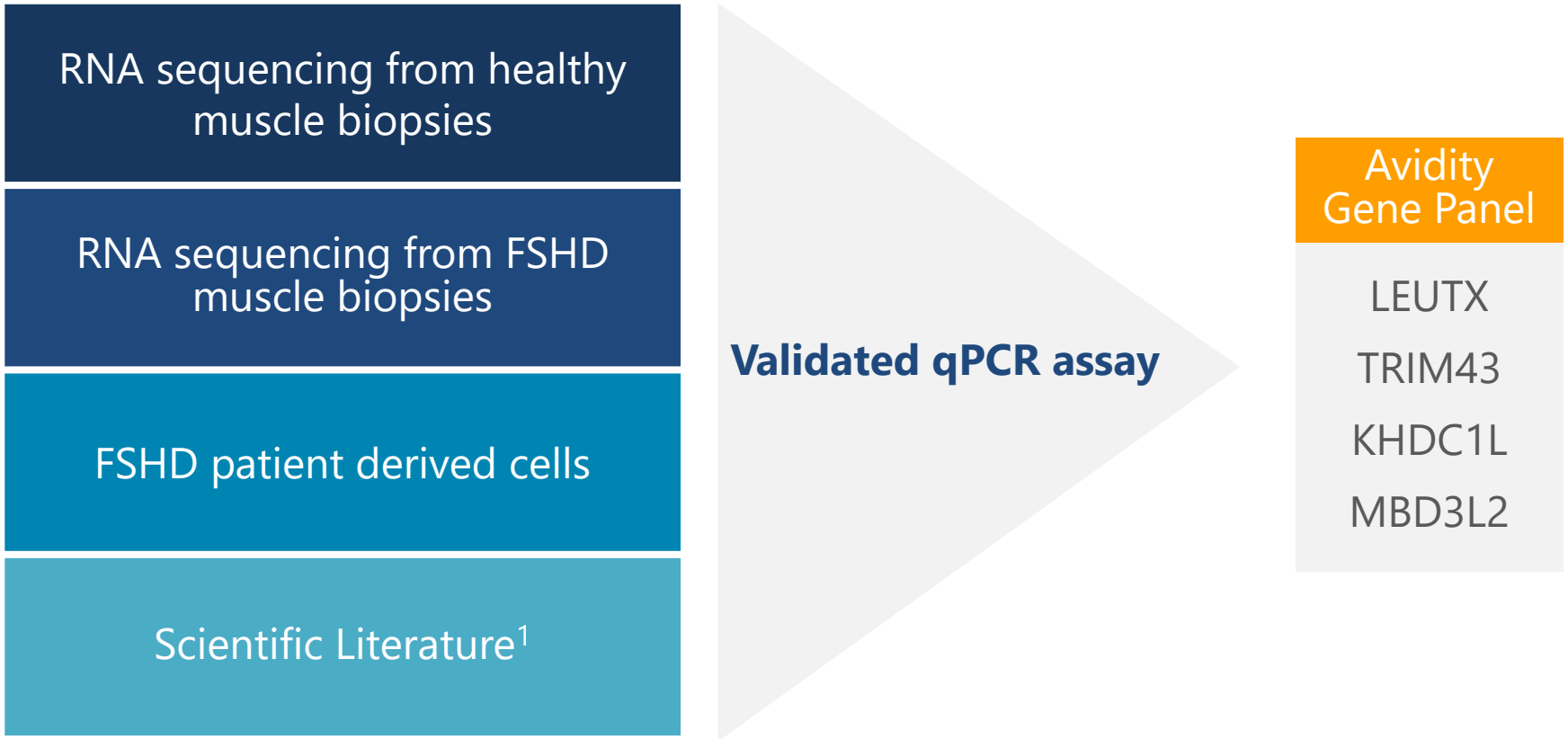
Del-brax: Consistent and Effective Delivery of siRNA to Muscle



Muscle biopsies were collected in leg muscles (vastus lateralis, vastus medialis, tibialis anterior, gastrocnemius medialis or gastrocnemius lateralis) with fat fraction 15-40%, 4 weeks after 3rd dose. *Doses were 1 mg/kg (D1), 2 mg/kg (D43 and D92). One participant in the del-brax treated group missed post-dose biopsy n=7

DUX4-Regulated Genes Selected for Robustness and Reproducibility

Procured muscle biopsies, RNA sequencing, patient-derived cells informed the panel



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1 Yao, Z et al. Hum Mol Genet. (2014), Tawil, R. et al., Lancet Neurol (2024)

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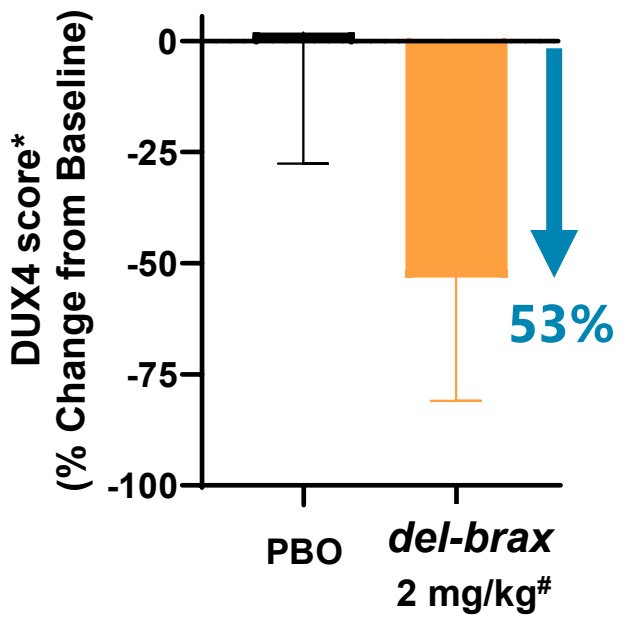
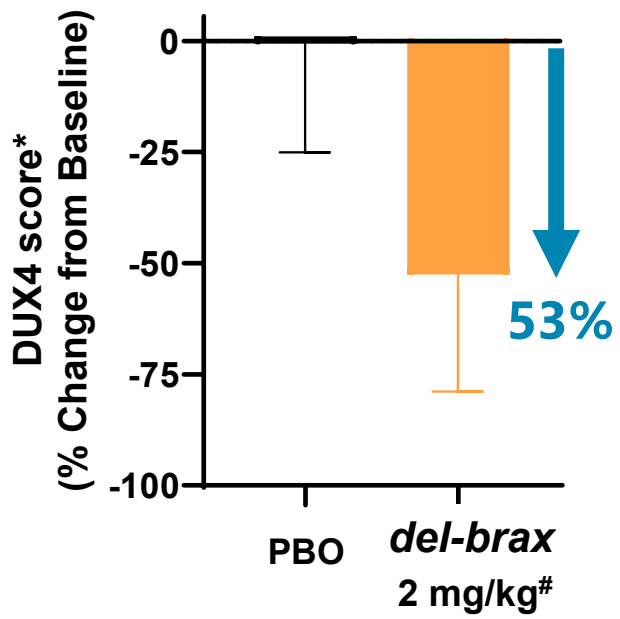
Del-brax Shows Consistent >50% Reductions in DUX4-regulated Genes as Measured by Multiple Gene Panels

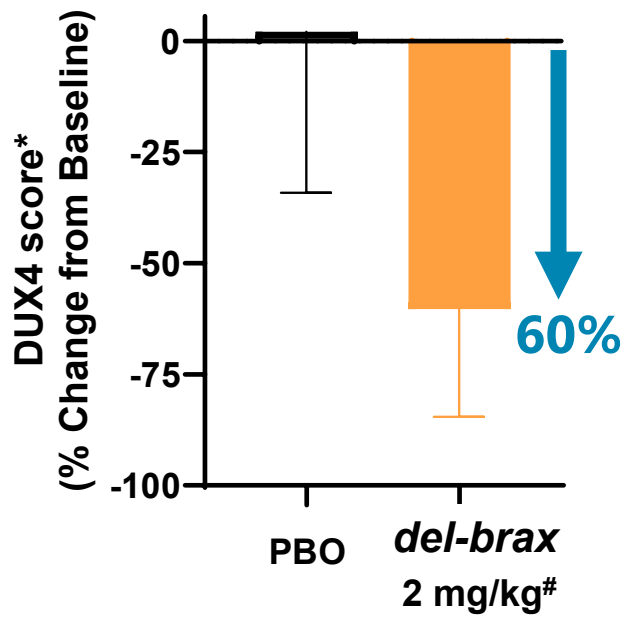
Avidity Panel[1]



ReDUX4 Panel[2]



41-Gene Panel[3]



[1] Avidity 4-Gene panel (LEUTX, TRIM43, MBD3L2, KHDC1L; Reference genes: TBP, STATA5)
[2] ReDUX4 6-Gene panel (CCNA1, ZSCAN4, MBD3L2, KHDC1L, SLC34A2, PRAMEF6); Tawil, R. et al., *Lancet Neurol* **23**:477 (2024)
[3] Van den Heuvel, A. et al., *Scientific Reports* **12**:1426 (2022)
* DUX4 score in MRI informed muscle biopsy were determined utilizing qPCR (Avidity panel) or RNASeq (ReDux and 41-Gene). DUX4 score calculated as cumulative expression of each gene and data presented as change at 4M treatment relative to cohort normalized baseline. Mean +/- SEM, N=7 *del-brax*, N=4 PBO. One participant in treated group did not receive post-treatment biopsy.
#Doses were 1 mg/kg (D1), 2 mg/kg (D43 and D92) with biopsy 1 month after 3rd dose.

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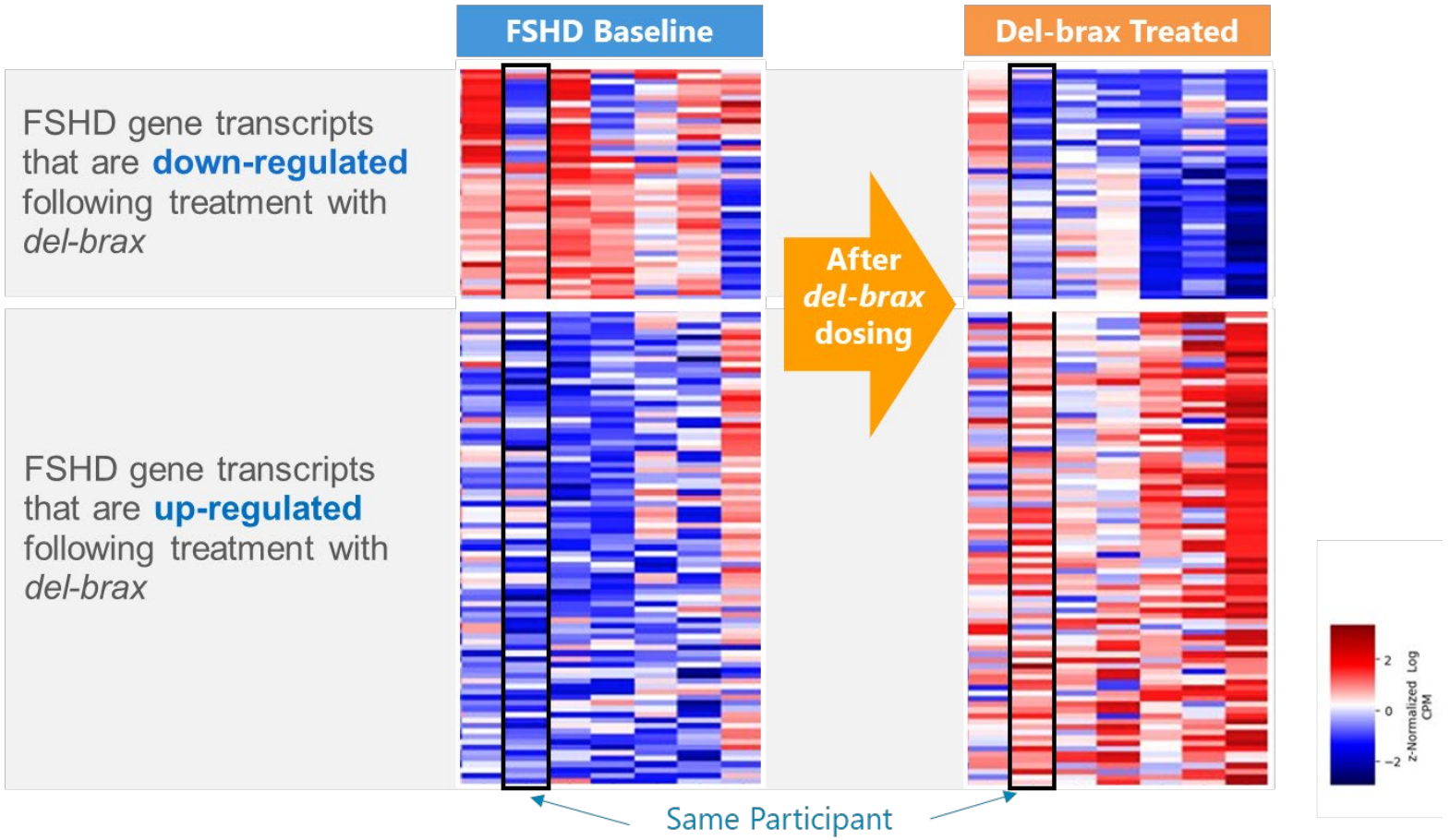
Del-brax Impacts Underlying FSHD Disease Biology

Broad biological effects following *del-brax* treatment



Each column is a participant's disease signature at baseline compared to 1 month post 3rd dose

Differential gene expression (excluding DUX4 regulated genes) in muscle utilizing RNASeq.
N=7 del-brax 1 mg/kg (D1), 2 mg/kg (D43 and D92). One participant missed post-dose biopsy.

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Novel DUX4-Regulated Circulating Biomarker

Potential accelerated approval endpoint

Multi-year Discovery Process

FSHD & Healthy Biopsies

Plasma from FSHD & Healthy Volunteers

Advisors & Disease Expertise

Novel DUX4-Regulated Circulating Biomarker

Potential Accelerated Approval Endpoint

- Significantly elevated in patients with FSHD as compared to healthy individuals
- Allows rapid and continuous monitoring of how participants are responding to *del-brax*
- Non-invasive, patient-friendly
- Guides selection of dose regimen

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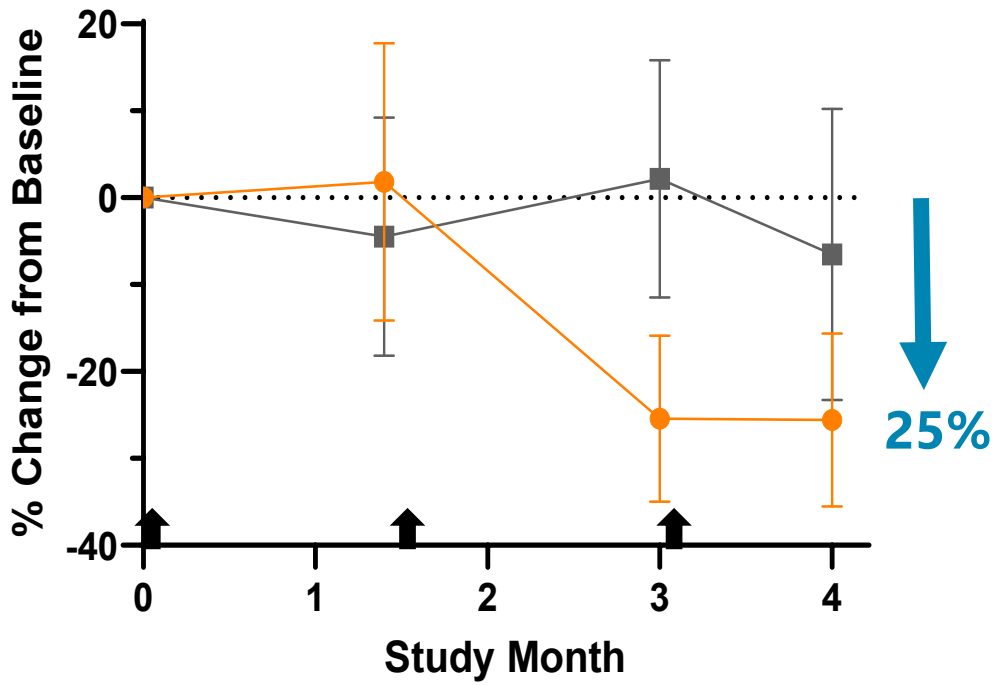
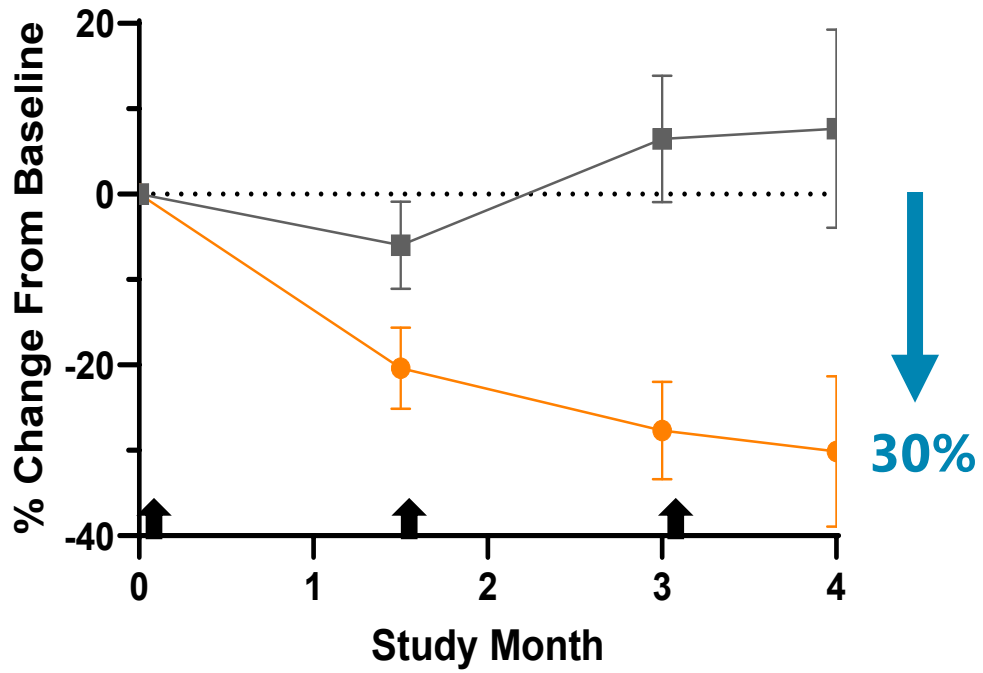
Consistent and Confirmatory Decrease in Both Novel and Creatine Kinase Circulating Biomarkers

Decreases in creatine kinase, an indicator of muscle damage

Novel DUX4-regulated biomarker



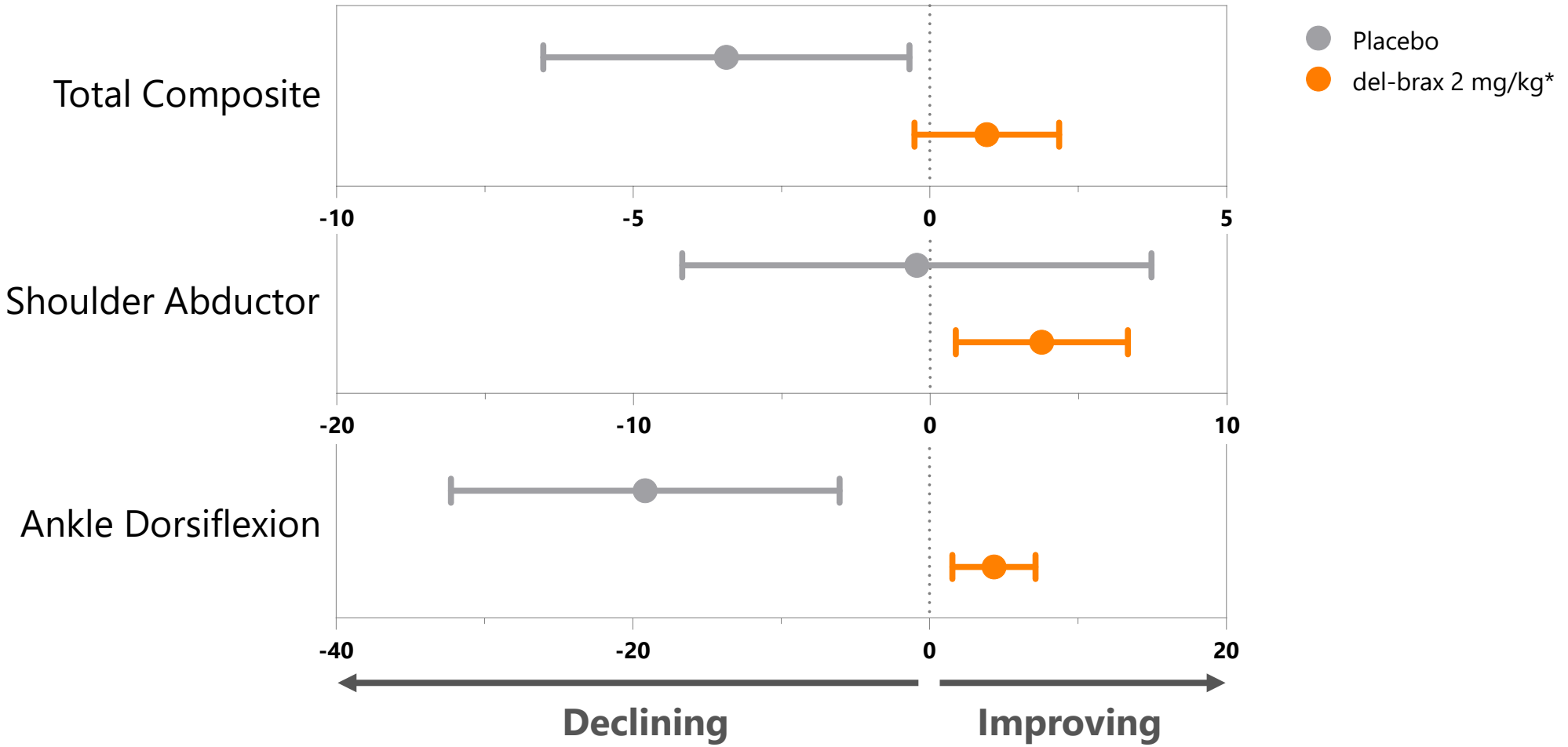
Creatine kinase biomarker



Timecourse of circulating biomarker at baseline and several timepoints post dose
*del-brax dose shown by black arrows 1mg/kg D1, 2 mg/kg D43 and D92. Placebo n=4 and del-brax treated n=8; Mean +/- SEM.

Exploratory measures of efficacy

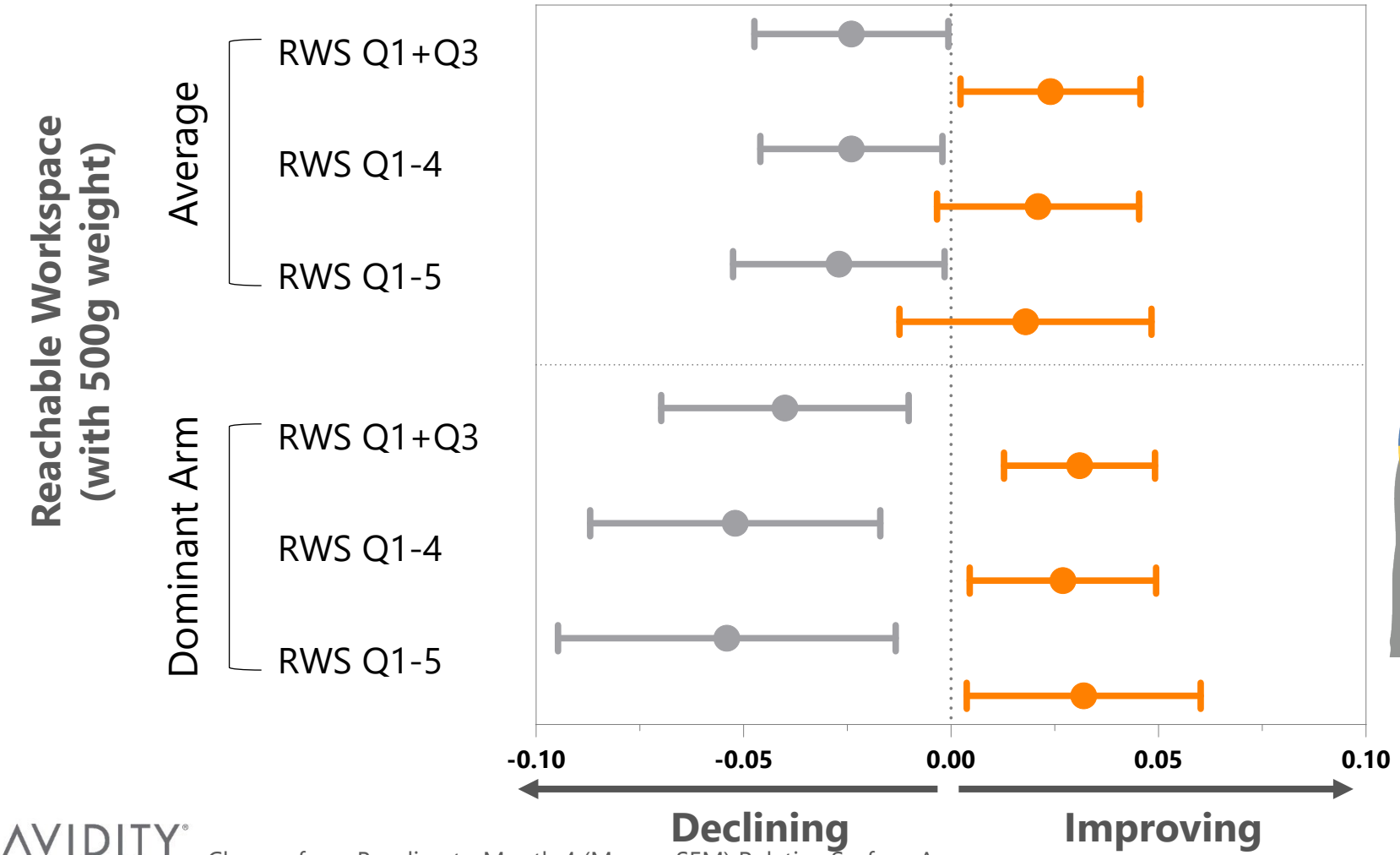
Del-brax Improved Muscle Strength in Both Upper and Lower Limb

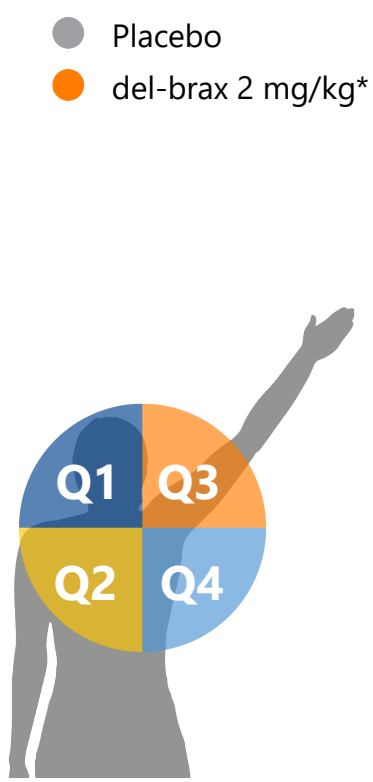


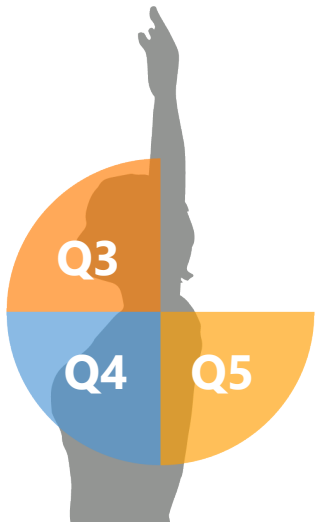
Change from Baseline to Month 4 (Mean ± SEM) Percent Predicted Normal
QMT by hand-held device
Total composite score: shoulder abductors, shoulder external rotators, elbow flexors, elbow extensors, knee flexor, knee extensor and ankle dorsiflexion
* Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study

Del-brax Improved Reachable Workspace Compared to Placebo

Improved range of motion and function; similar trends observed without weight

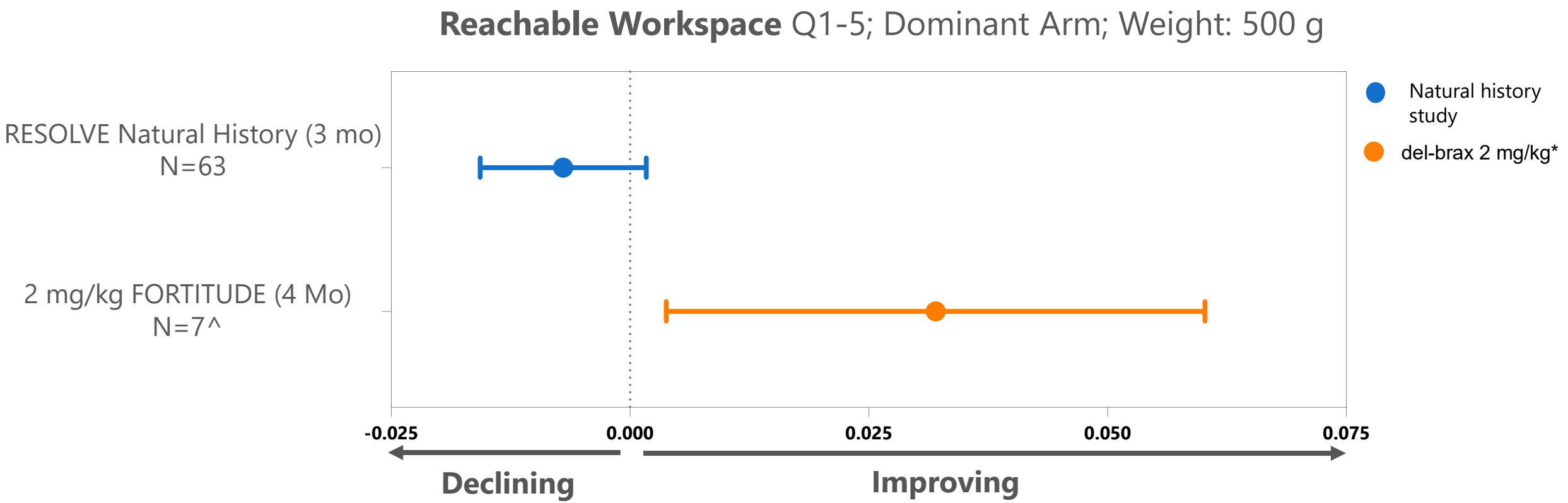






Change from Baseline to Month 4 (Mean ±SEM) Relative Surface Area.
Average n=8 & dominant arm n=7 in the *del-brax* group
*Participants receive a first dose of 1 mg/kg and then receive the 2 mg/kg dose for the remainder of the study.

Del-brax Improved Reachable Workspace Compared to Matched Natural History Data



Thanks to RESOLVE physicians for reviewing and approving use of this Avidity analysis. RESOLVE subpopulation matched to FORTITUDE (age 18-65, FCS 2-14, RWS (no weight) Q1+3 >0 and ≤0.4)
Q1-5; Dominant Arm; 500 g
RSA (Relative Surface Area) (Mean ±SEM)
^One patient excluded from AOC 1020 "dominant arm" group due to rotator cuff tear and clavicle fracture which occurred after the Baseline assessment;
* Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study

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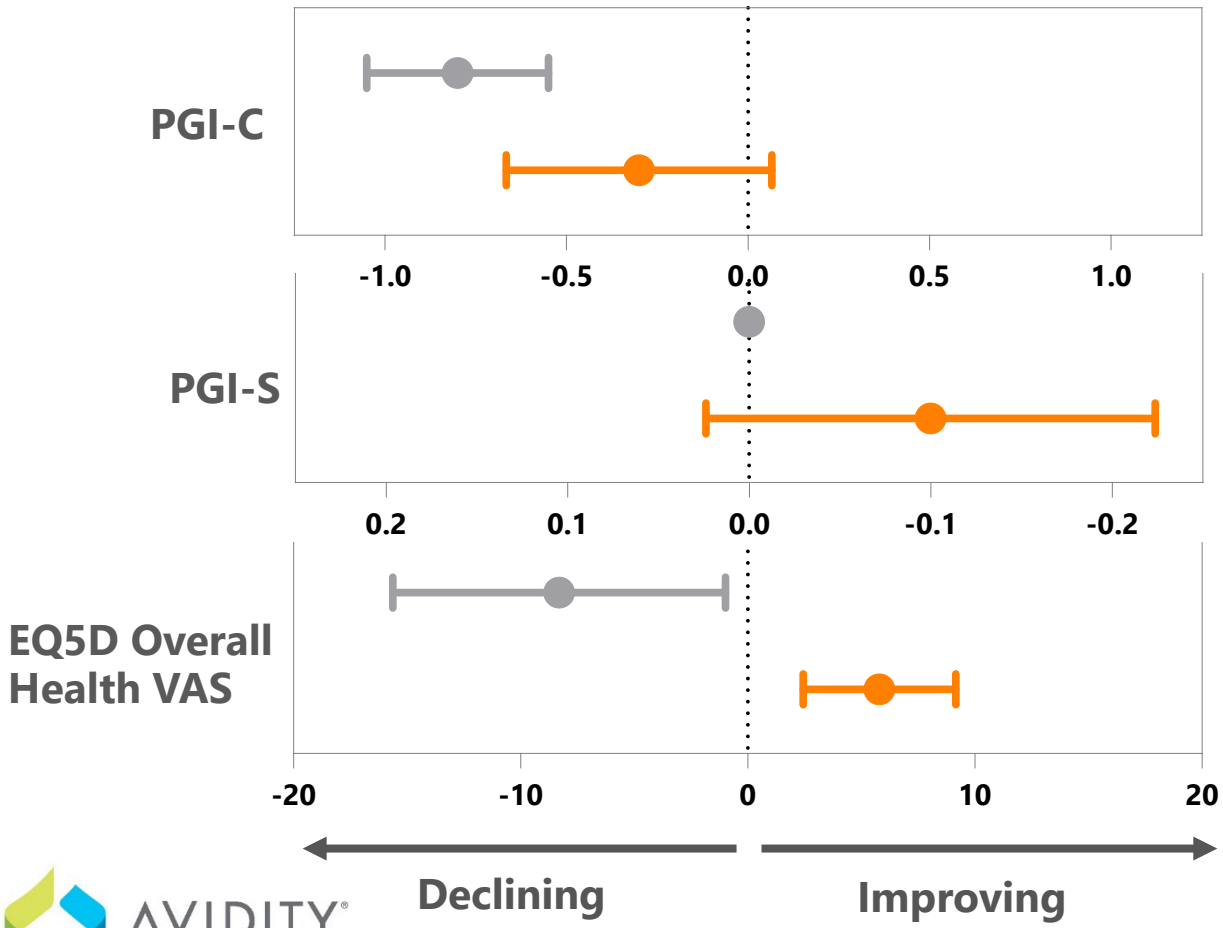
Del-brax: Positive Trends Toward Improvement in Both Patient and Clinician Reported Outcome Measures

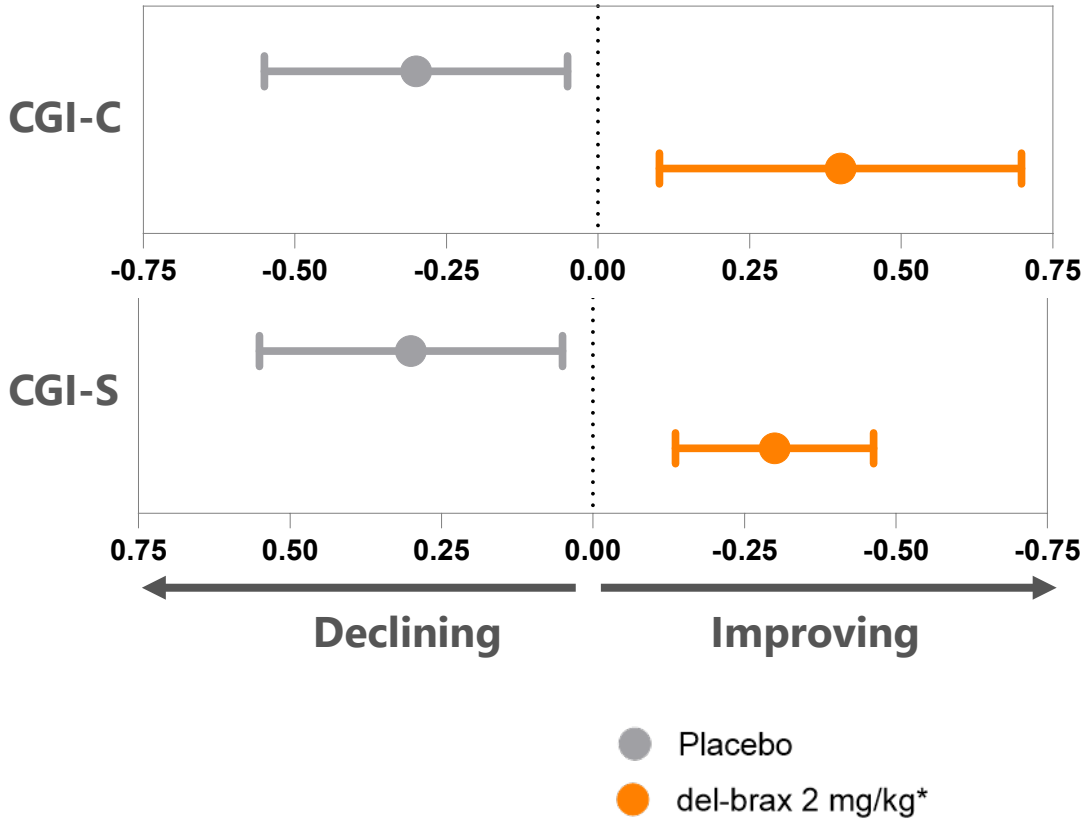
Patient Reported Outcome Measures

Change from Baseline at Month 4 (SEM)



Clinician Reported Outcome Measures

Change from Baseline at Month 4 (SEM)



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CGI-C; CGI-S (Clinician Global Impression of Change; Severity)
PGI-C; PGI-S (Patient Global Impression of Change; Severity)
*first dose 1 mg/kg

Del-brax: Promising New Potential Treatment for Patients with FSHD

First therapy to directly target DUX4 has potential to change course of disease

- Favorable safety and tolerability with no serious adverse (AE) events or patient discontinuation.
  - All observed AEs were mild or moderate.
- Effective muscle delivery with unprecedented and consistent >50% reduction in DUX4 regulated gene panels – impacting underlying FSHD disease biology
- Decrease in circulating biomarkers (novel and creatine kinase) indicate whole-body response
- Improvements in clinical measures of disease:
  - Muscle strength
  - Function: Reachable workspace compared to both placebo and natural history data
  - Patient and clinician reported outcomes
- These data support rapidly advancing the clinical evaluation of del-brax in registrational cohorts within FORTITUDE (biomarker and functional cohorts), in patients with FSHD

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Authors and Acknowledgements

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