Topline Results from FORTITUDE™, a Randomized Phase 1/2 Trial Evaluating AOC 1020 (*Del-brax*) in Adults with FSHD

32nd Annual FSHD Society International Research Conference

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DISCLOSURES:

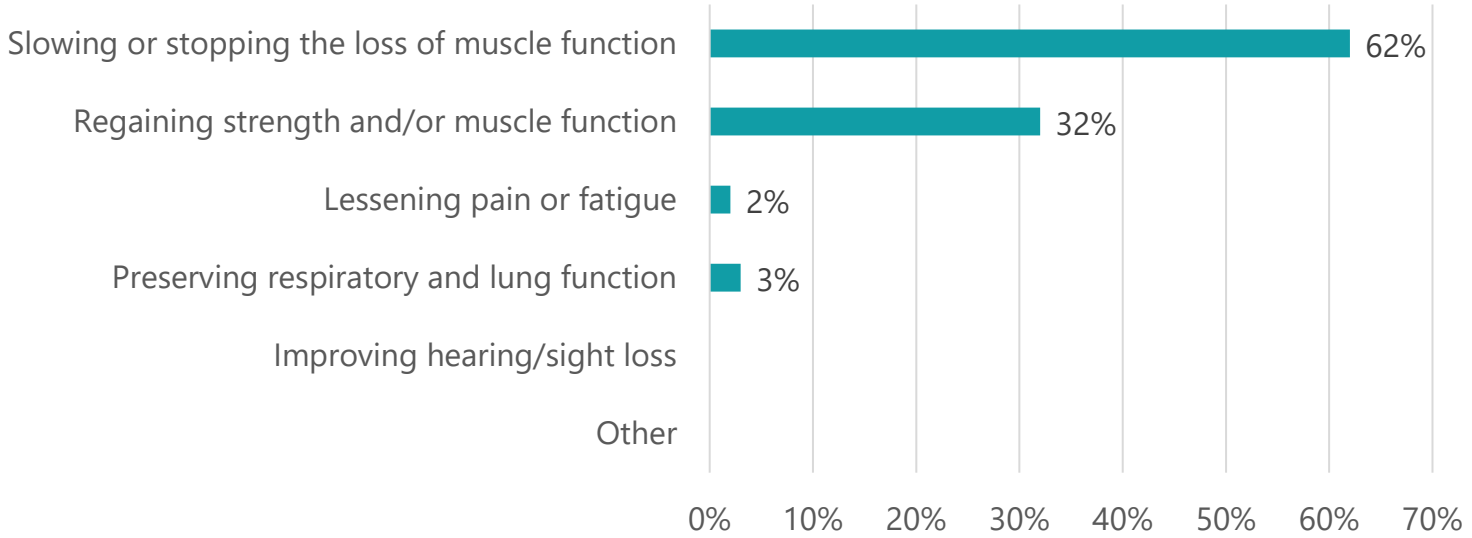
- Jeffrey M. Statland has received grants from the FSHD Society, Friends of FSH Research, MDA, FSHD Canada, NIH, CDC, Dyne Therapeutics, and Avidity Biosciences
- He has received consulting fees from Fulcrum Therapeutics, Avidity Biosciences, Dyne Therapeutics, Arrowhead Pharmaceuticals, Sarepta, Epic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

What Matters to Patients is to Have Their Disease Under Control

Over 60% of patients express that slowing or stopping the loss of muscle function would be the most meaningful outcome

- FSHD Voice of the Patient (June 2020) highlighted that the most meaningful outcome for patients is to slow or stop the loss of muscle function.
- People living with FSHD are most worried about:
  - the unknown of how the disease will progress
  - losing independence
  - losing mobility/ability to walk
  - becoming a burden to their family

Short of a cure, what outcome is the most meaningful to you in a future treatment? Select your top choice.



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FSHD Society. *Voice of the Patient Report: Externally Led Patient-Focused Drug Development Meeting*. Published November 2020. Accessed June 2025.

AOC 1020 *delpacibart braxlosiran (del-brax)* is an investigational Antibody Oligonucleotide Conjugate (AOC)

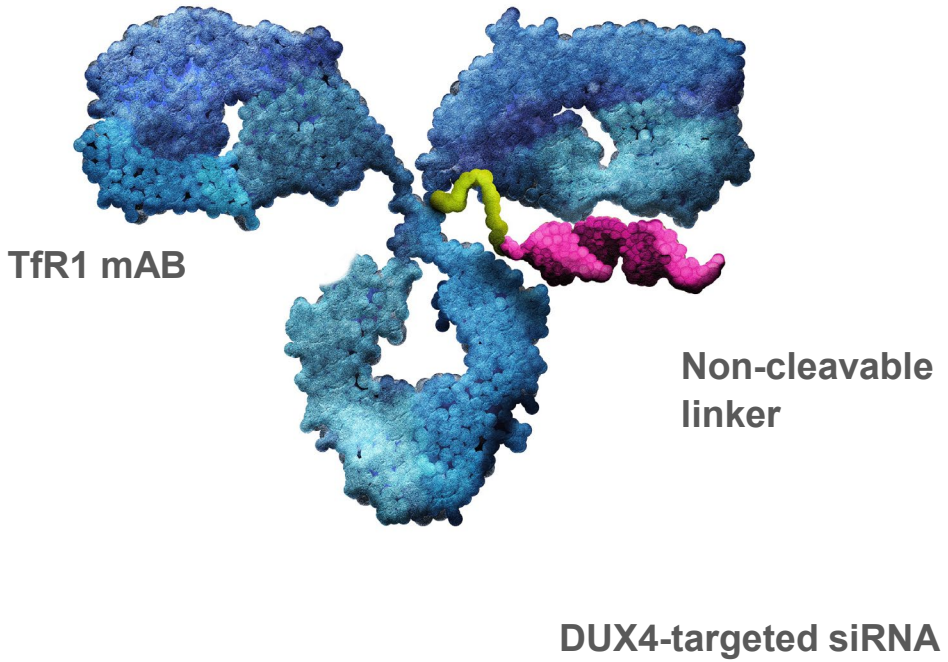
Del-brax targets DUX4, the Root Cause of FSHD

Three main components:

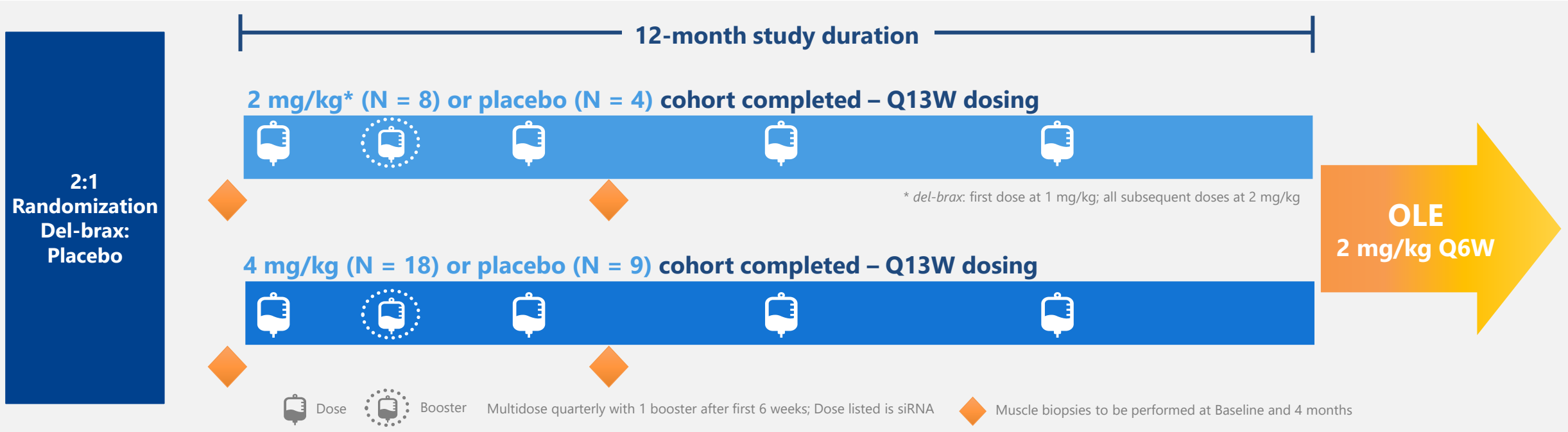
- **Antibody**: human transferrin receptor 1 (TfR1)-targeting, effector function-null, humanized IgG1 antibody
- **Non-cleavable linker**: MCC maleimide linker, enhanced for safety and durability
- **Oligonucleotide**: Stabilized siRNA targeting DUX4 mRNA; engineered and stabilized to withstand lysosomal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



FORTITUDE™ 12 Month Topline Readout



Study Design

- Randomized, double-blind, placebo-controlled study
- FSHD participants ages 18-65

Primary and Secondary Objectives

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

Key Exploratory Objectives

- Pharmacodynamics
  - Biomarkers
- Patient and Clinician reported outcomes
- Clinical measures
  - 10MWRT
  - TUG
  - QMT
  - RWS

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Participants received a first dose of 1mg/kg and then received the 2mg/kg dose for the remainder of the study
QMT = quantitative muscle testing; 10MWRT = 10-meter walk-run test; TUG = timed up-and-go; RWS = Reachable Workspace; OLE = Open Label Extension; OLE efficacy measures every 6 months

Baseline Demographics and Characteristics

	Placebo N=13 % or mean (SD)	*Del-brax* 2 mg/kg* N=8 % or mean (SD)	*Del-brax* 4 mg/kg N=18 % or mean (SD)
Sex, % Male	92.3	62.5	50.0
Age, years	52.1 (9.92)	51.6 (11.62)	45.2 (11.49)
Genetic Diagnosis, % FSHD 1	100	100	100
FSHD Clinical Score	9.2 (2.28)	9.3 (2.31)	8.5 (1.92)
D4Z4 Repeat Number	5.5 (2.03)	5.8 (2.60)	4.7 (1.53)
Age at First Symptom Onset (y)	22.2 (15.54)	28.6 (17.75)	20.7 (13.82)

*Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study; FSHD Clinical Score range: 0 - 15. 0 = no signs of muscle weakness are present; 15 = all muscle group tested are severely impaired.

Del-brax: Favorable Long-Term Safety and Tolerability including OLE

Subjects with ≥ 1 AE n (%)	Placebo N=13	2 mg/kg* N=8	4 mg/kg N=18	OLE** N=38
Any AE	12 (92.3%)	8 (100%)	18 (100%)	21 (55.3)
Related to study drug	3 (23.1%)	6 (75%)	11 (61.1%)	9 (23.7%)
Severe AE	0	0	0	2 (5.3%)
Serious AE (SAE)	0	0	0	1 (2.6%)
Severe or SAEs related to study drug	0	0	0	0
AE leading to study discontinuation	0	0	0	0
AE leading to death	0	0	0	0

*Participants receive a first dose of 1mg/kg and then receive the 2mg/kg dose for the remainder of the study
**38 out of 39 participants had begun treatment in OLE as of May 7th, 2025; Final participant began treatment in FORTITUDE-OLE™ after the data cut

All participants enrolled remain in study

- No discontinuations
- Most AEs mild or moderate
- No related severe or serious AEs
- Most common related AEs occurring in greater than 3 participants:
  - Fatigue
  - Hemoglobin decreased
- 1 unrelated severe, non-serious AE of herpes zoster occurred in one participant
- 3 unrelated severe, serious AEs of radius fracture, pelvic fracture, and fractured sacrum occurred in one participant

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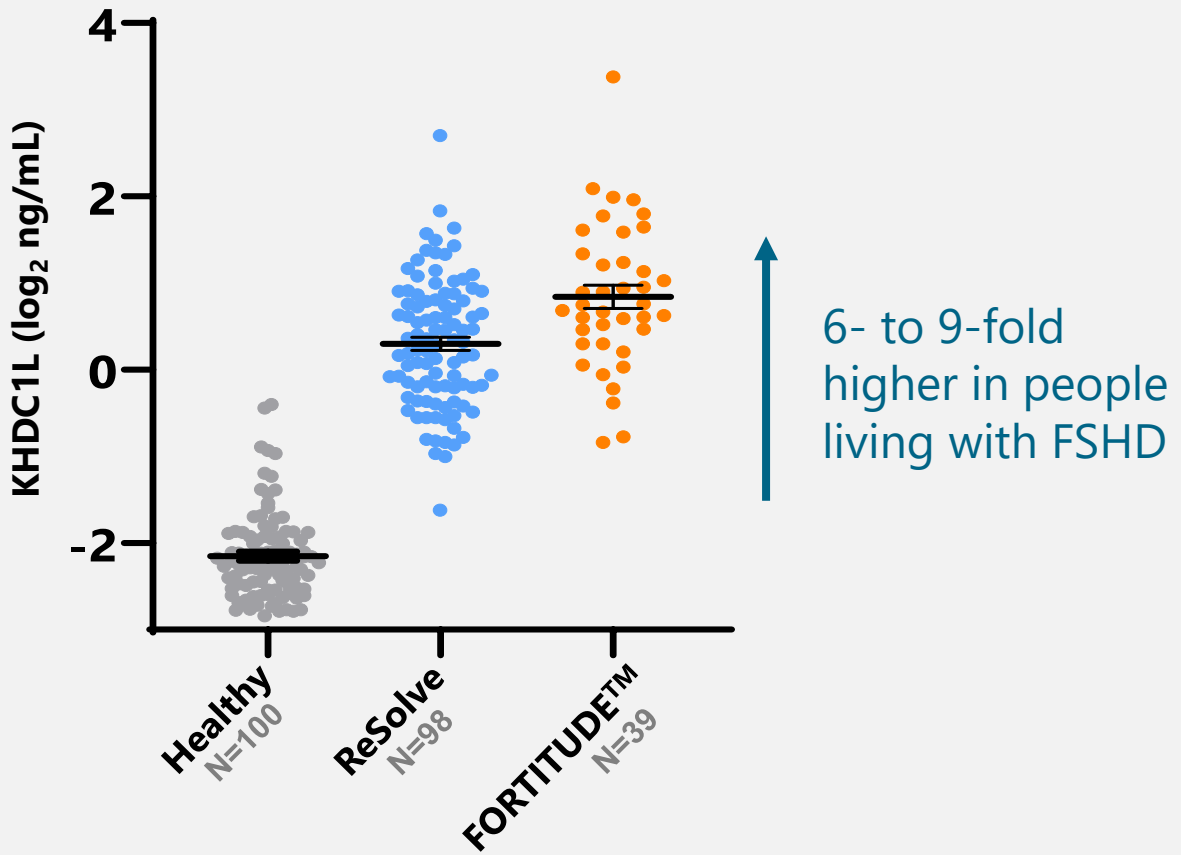
KHDC1L (cDUX™) Is Significantly Elevated in People Living with FSHD and Allows Continuous Monitoring During *del-brax* Treatment

KHDC1L is a Breakthrough in FSHD

- K-homology domain-containing 1 like (KHDC1L) is an RNA-binding protein implicated in germ-cell biology and apoptosis
- Directly regulated by DUX4, the root cause of FSHD
- Significantly elevated in people with FSHD compared to healthy volunteer plasma

KHDC1L Significantly* Elevated in People Living with FSHD at Baseline



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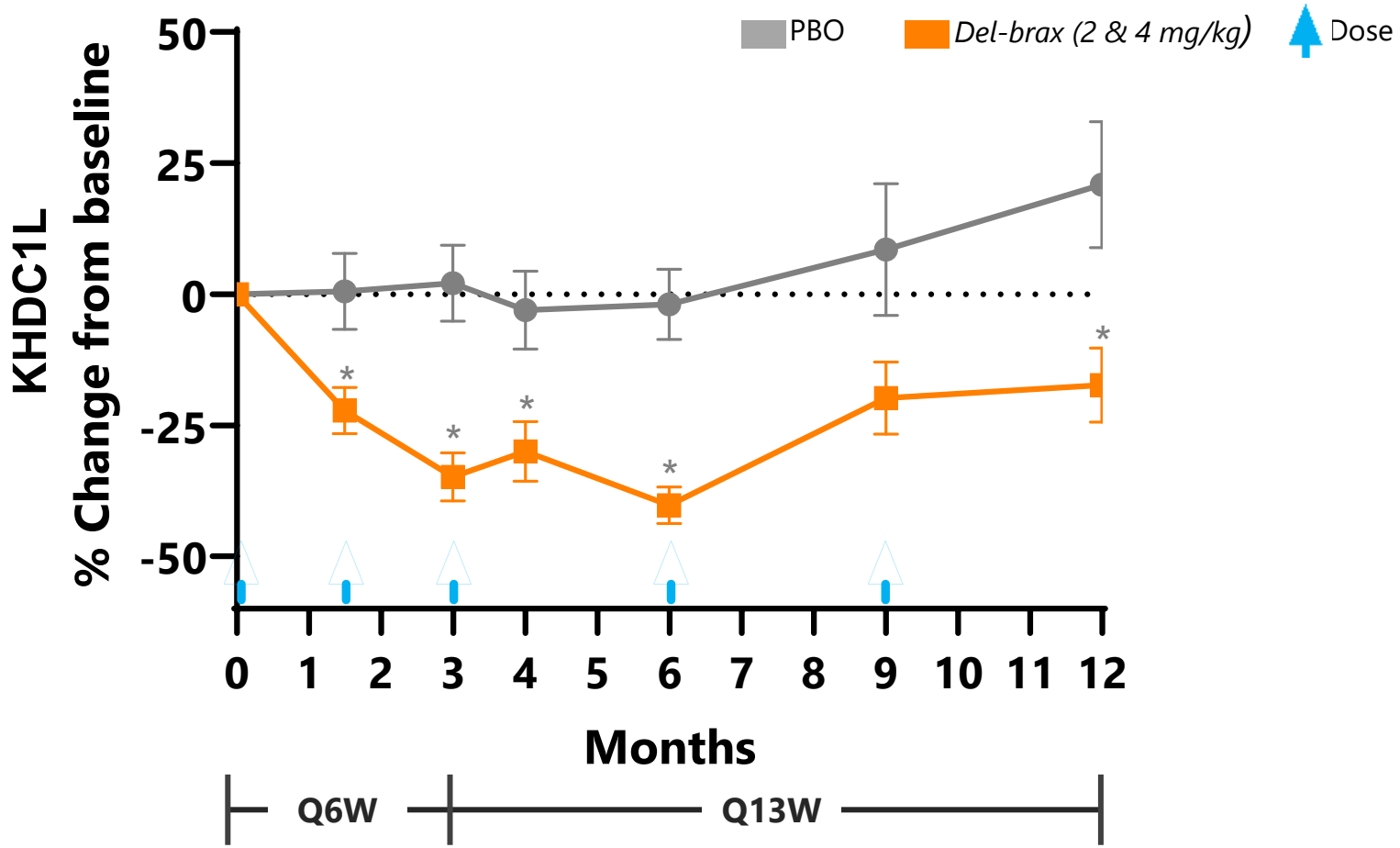
Analysis of plasma KHDC1L levels in healthy volunteers (n=100), ReSolve participants (n=98), and FORTITUDE™ participants (n=39) at baseline. Data shown as log2 of mean concentration ± SEM. [1]Yao, Z. et al. Hum Mol Genet 23:5342 (2014); Jagannathan, S et al. Hum Mol Genet 25:4419 (2016); Van den Heuvel *et al*, Sci Reports 12:1426 (2022); Tawil, R. et al., Lancet Neurol 23:477 (2024); *p < 0.0001 for ReSolve vs healthy and FORTITUDE vs healthy

Rapid and Significant Decrease in KHDC1L (cDUX™) following *del-brax* Treatment

Reduction of KHDC1L was highly statistically significant compared to placebo following *del-brax* treatment

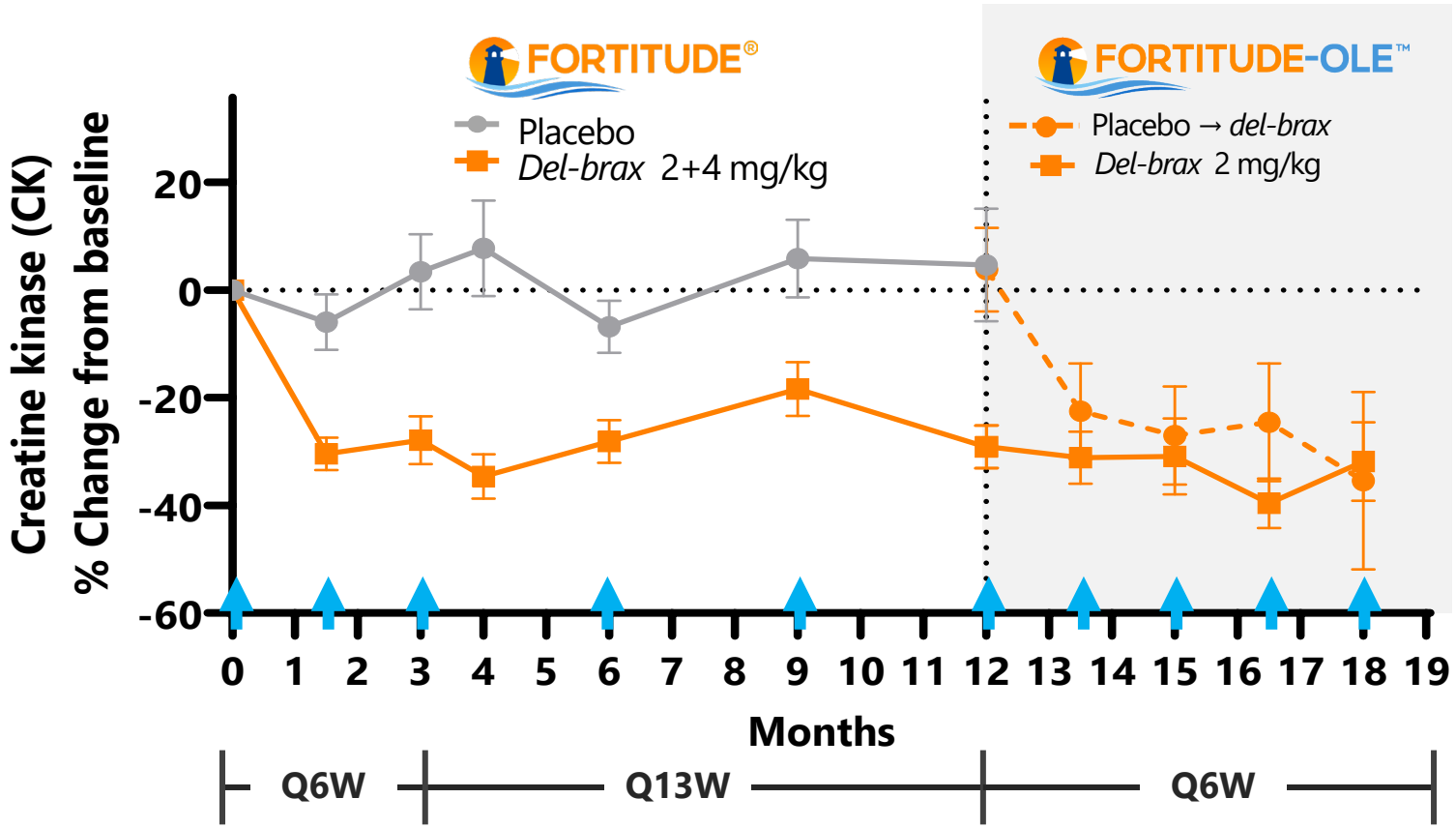


Informing *del-brax* dosing interval

- The FORTITUDE™ Phase 1/2 dose escalation study data support selection of the dosing regimen ***del-brax 2mg/kg* Q6 weeks**
- This dose has been selected for registrational studies to ensure continuous suppression of DUX4

Mean percent change from baseline (averaged screen + day 1 pre-dose) ± SEM. Placebo (n = 13) and *del-brax* (n = 26); Placebo (n = 13) and pooled *del-brax* 2mg/kg and 4mg/kg treatment arms (n = 26). In post-hoc analyses, nominal statistical significance reached ($p<0.005$) for *del-brax* compared to placebo for cDUX except at the 9-month timepoint.

Placebo Participants Transitioning to *del-brax* Showed Rapid and Consistent Reductions in Creatine Kinase



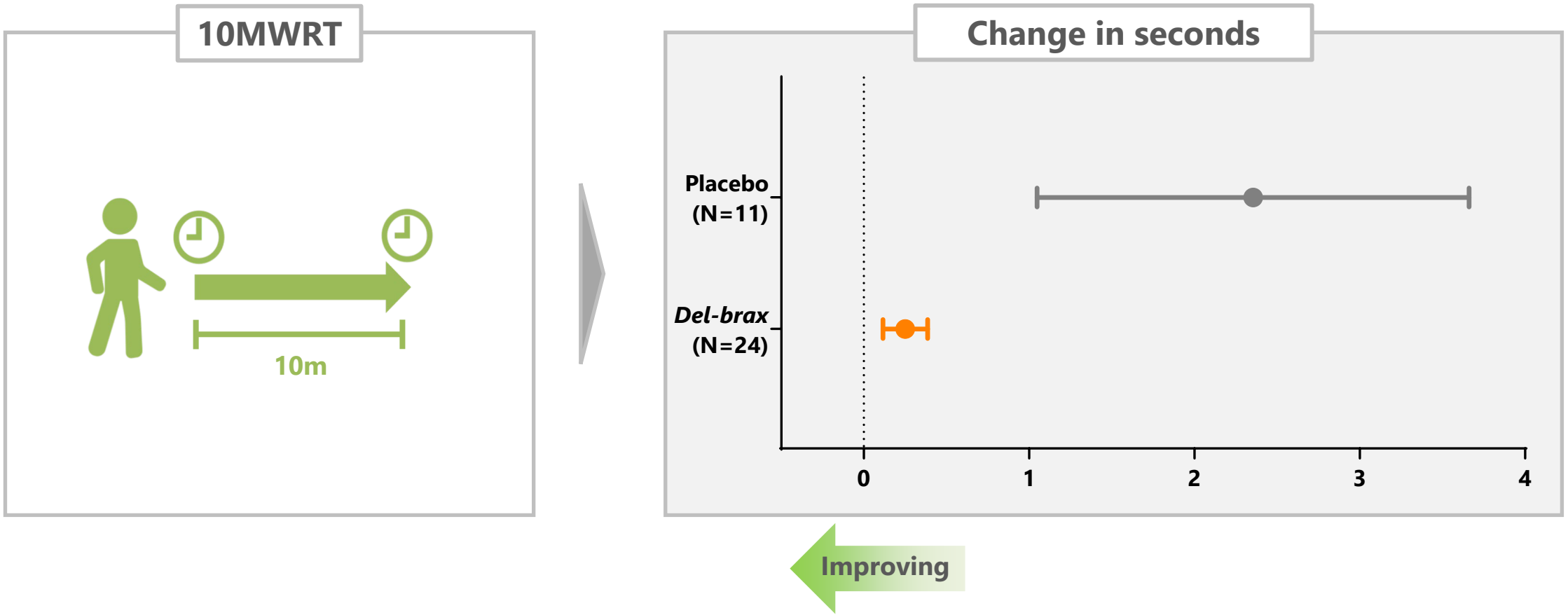
Dose

Mean percent change from baseline (averaged screen + day 1 pre-dose) ± SEM; FORTITUDE: pooled *del-brax* 2mg/kg and 4mg/kg treatment arms (n = 26) or placebo (PBO; n = 13); FORTITUDE-OLE *del-brax* treatment (n = 24) or placebo transitioned to *del-brax* (n = 12); OLE data as of May 7th, 2025

Exploratory Endpoints: Muscle Strength and Function, Patient Reported Outcomes

Improved Functional Mobility in *del-brax* Treated Participants Compared to Placebo

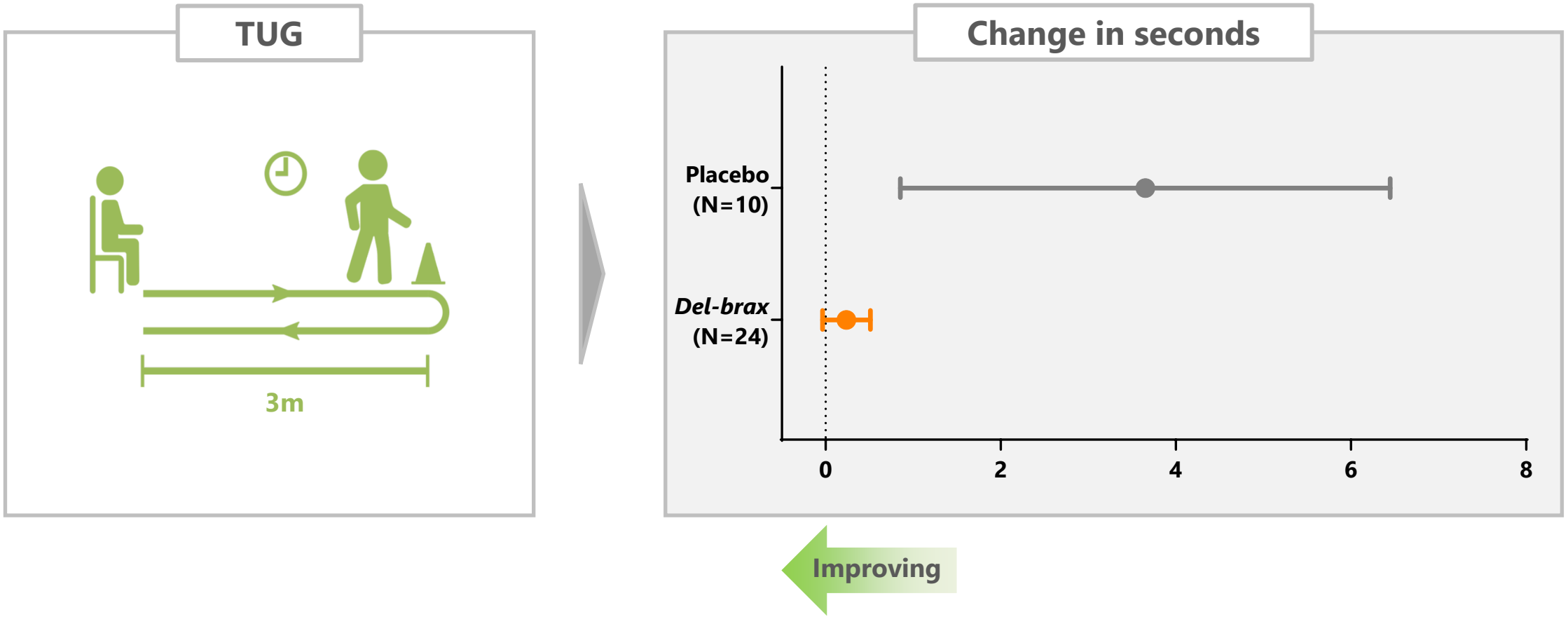
Data at 12 months with Q13W dosing



All del-brax data shown in this presentation is as of the May 2025 data cutoff date. All data shown are mean change (± SEM) from Baseline to Month 12. 2mg/kg and 4mg/kg treatment arms pooled. 10MWRT = 10-meter walk-run test. One placebo participant had an unreliable baseline measurement and was removed from all efficacy analyses. One placebo and two *del-brax* participants did not complete the assessment.

Improved Functional Mobility in *del-brax* Treated Participants Compared to Placebo

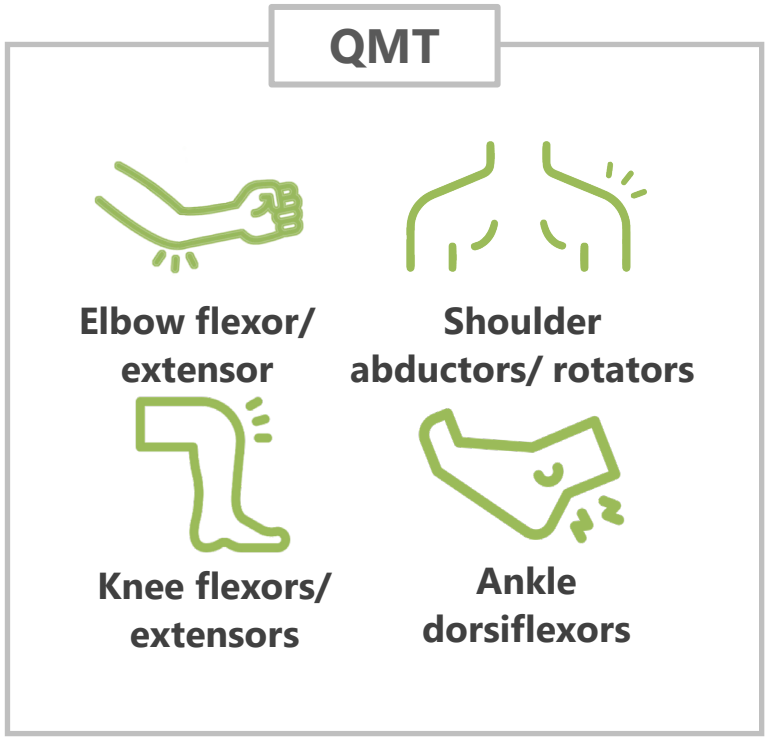
Data at 12 months with Q13W dosing

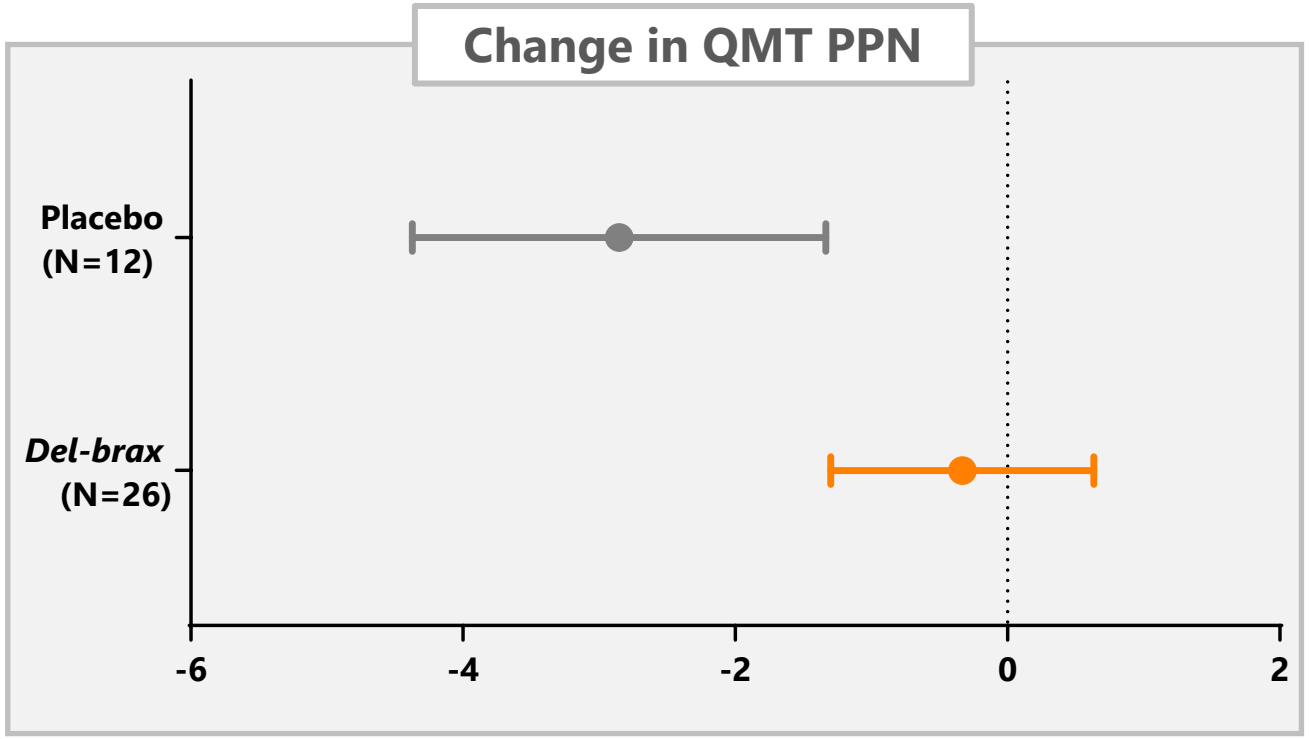


All data shown are mean change (± SEM) from Baseline to Month 12. 2mg/kg and 4mg/kg treatment arms pooled. TUG = timed up-and-go; maximal effort. One placebo participant had an unreliable baseline measurement and was removed from all efficacy analyses. Two placebo and two *del-brax* participants did not complete the assessment.

Improved Strength in *del-brax* Treated Participants Compared to Placebo

Data at 12 months with Q13W dosing





All data shown are mean change (± SEM) from Baseline to Month 12. QMT = quantitative muscle testing, PPN = percent predicted normal. One placebo participant had an unreliable baseline measurement and was removed from all efficacy analyses. 2mg/kg and 4mg/kg treatment arms pooled

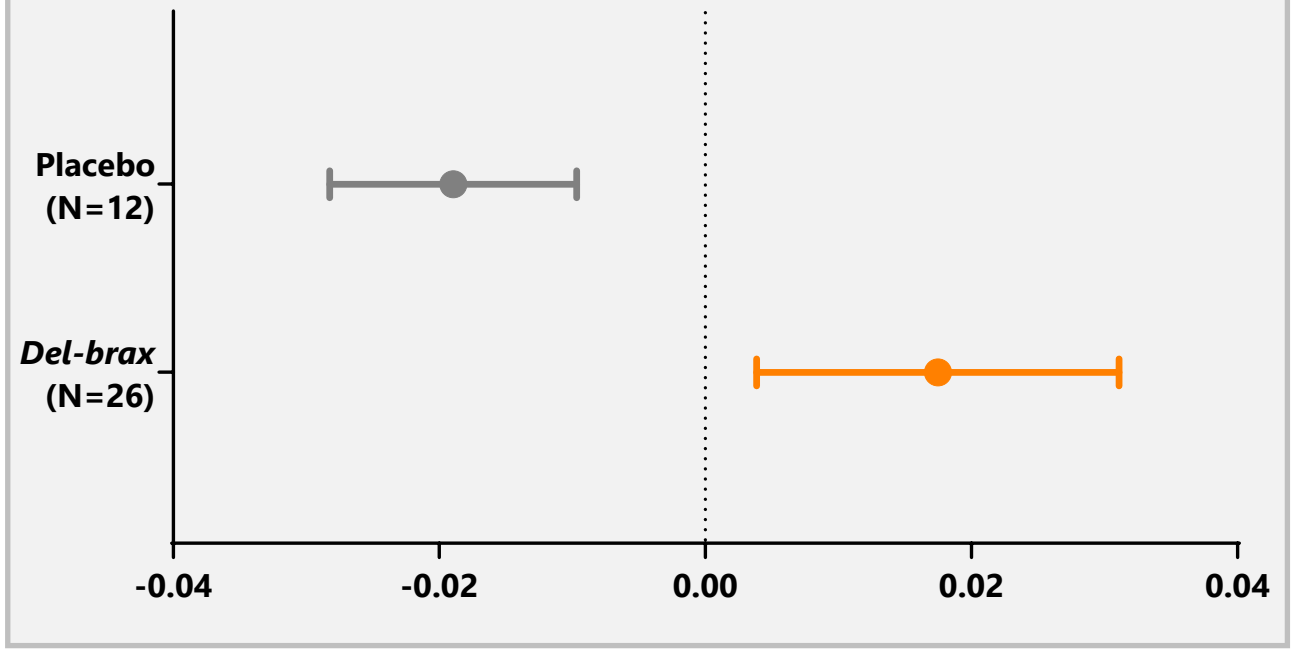
Improved Upper Limb Function in *del-brax* Treated Participants Compared to Placebo

Data at 12 months with Q13W dosing

RWS

Average of Q1 and Q3 in both arms with weight

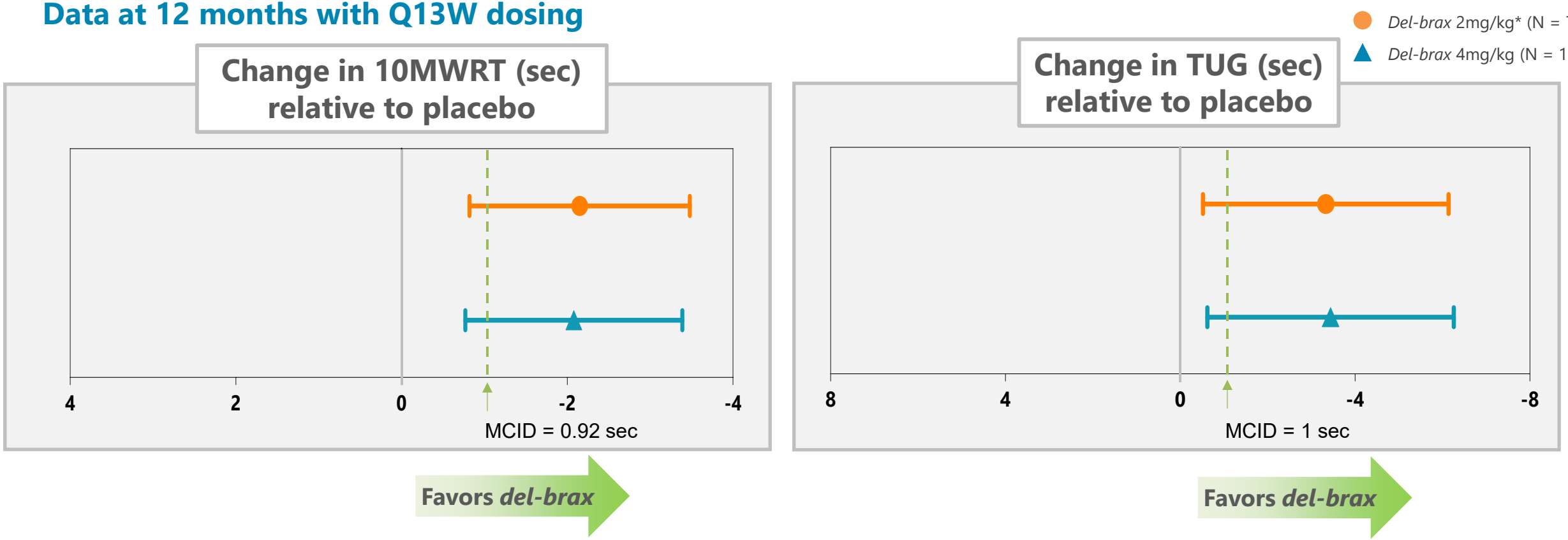
Change in RSA



All data shown are mean change (± SEM) from Baseline to Month 12. RWS = Reachable Workspace; RSA = Relative Surface Area. One placebo participant had an unreliable baseline measurement and was removed from all efficacy analyses. 2mg/kg and 4mg/kg treatment arms pooled

Improved Functional Mobility in *del-brax* Treated Participants Relative to Placebo Exceeding MCID at Both Doses

Data at 12 months with Q13W dosing



Dose regimen selected for registrational studies is 2mg/kg Q6W

All data shown are mean difference (± SEM) between *del-brax* and placebo for change from baseline at Month 12. TUG, maximal effort One placebo participant had an unreliable baseline measurement and was removed from all efficacy analyses. One *del-brax* participant was removed from the 10MWRT results as they transitioned to using a walker due to a hamstring injury during the study. MCID = Minimal Clinically Important Difference from ReSolve Study anchored to Current Abilities Scale. *Participants received a first dose of 1mg/kg and then received the 2mg/kg dose for the remainder of the study

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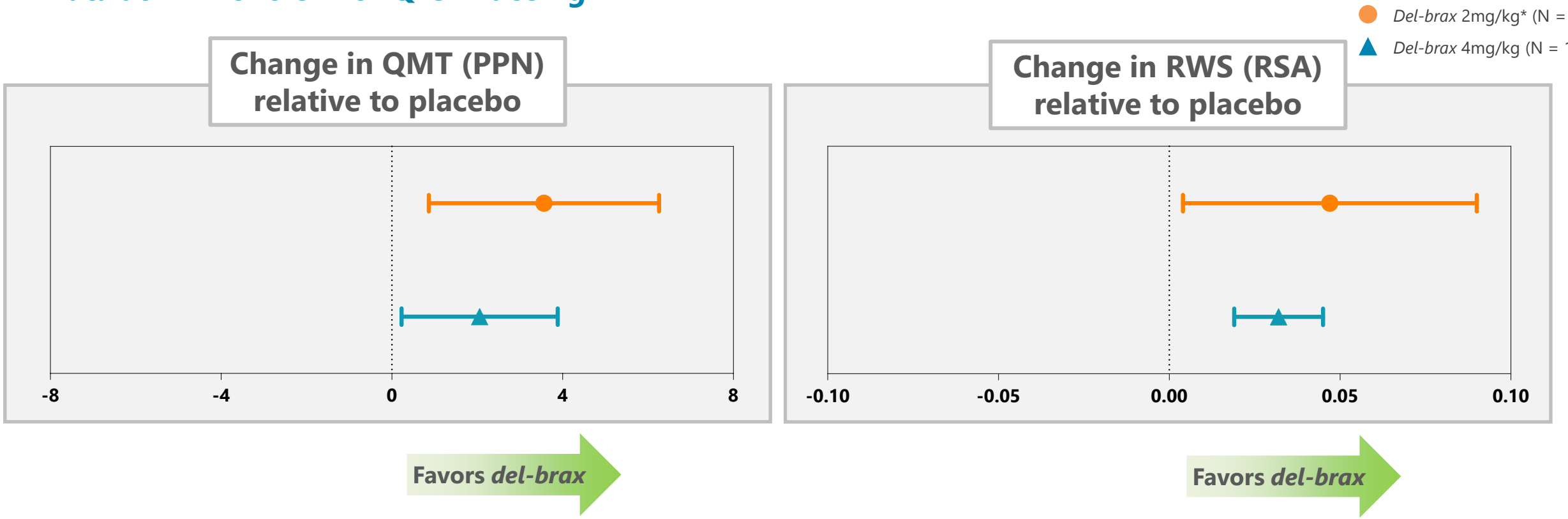
Improved Strength and Upper Limb Mobility in *del-brax* Treated Participants Relative to Placebo

Data at 12 months with Q13W dosing

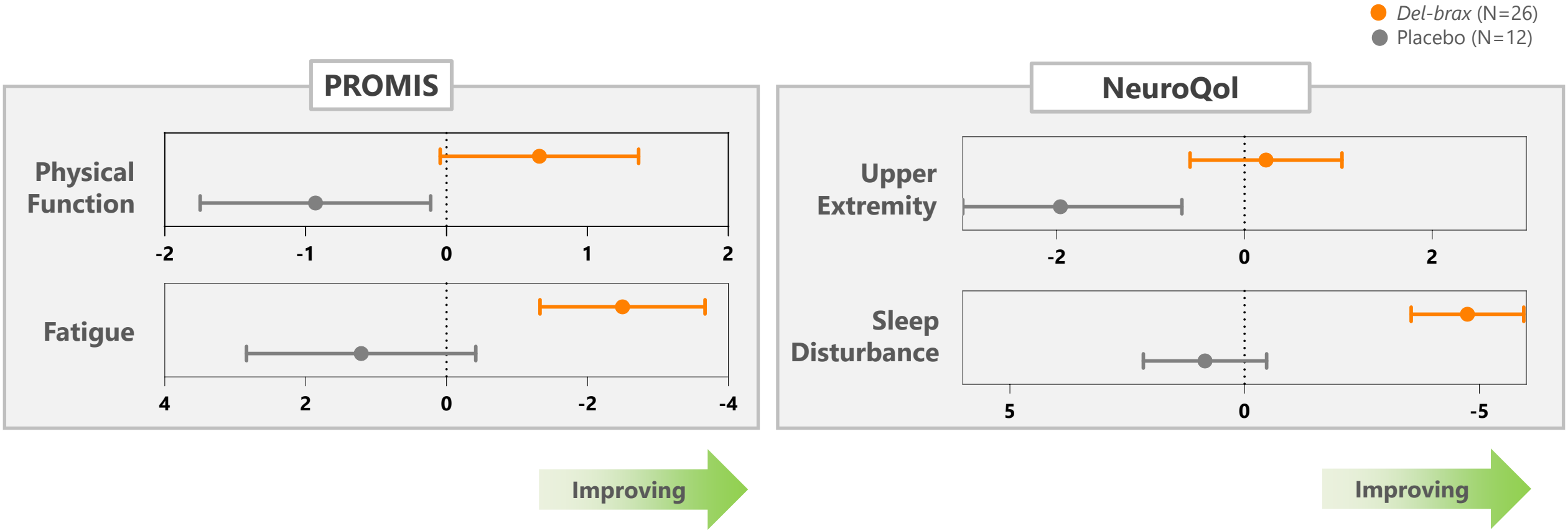


Dose regimen selected for registrational studies is 2mg/kg Q6W

All data shown are mean difference (± SEM) between *del-brax* and placebo for change from baseline at Month 12. One placebo participant had an unreliable baseline measurement and was removed from all efficacy analyses. *Participants received a first dose of 1mg/kg and then received the 2mg/kg dose for the remainder of the study.

Improved Quality of Life in *del-brax* Treated Participants Compared to Placebo

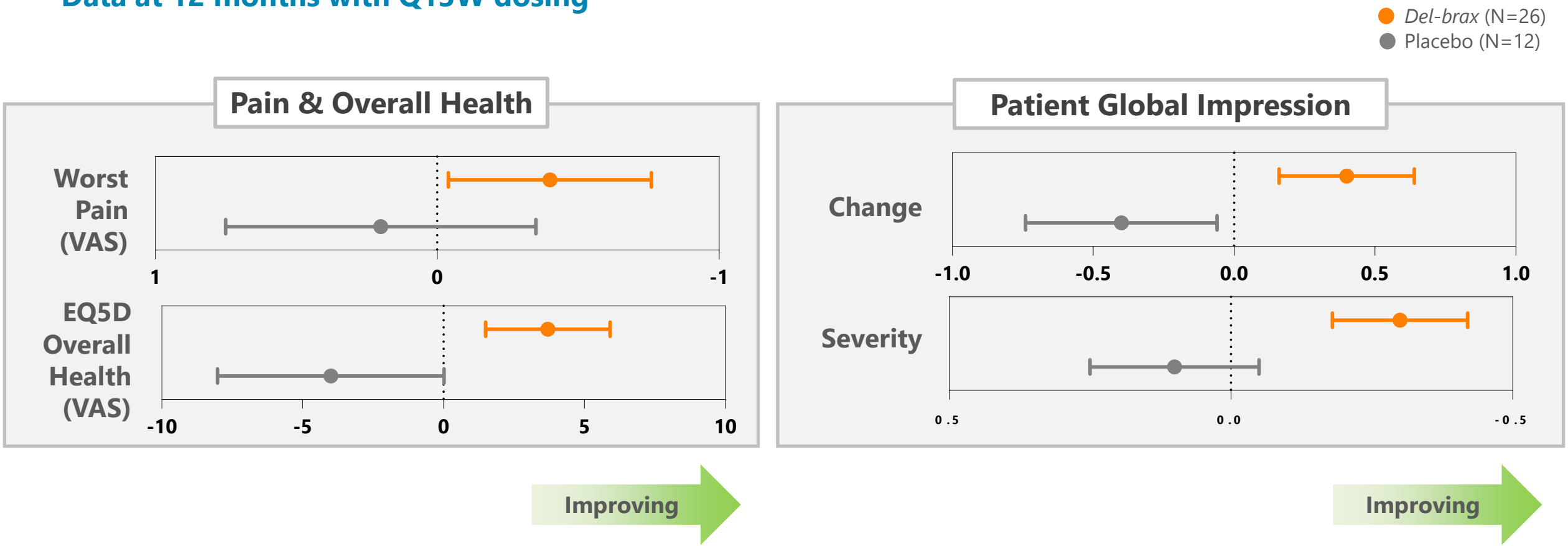
Data at 12 months with Q13W dosing



All data shown are mean change (± SEM) from Baseline to Month 12. One placebo participant had an unreliable baseline measurement and was removed from all efficacy analyses. 2mg/kg and 4mg/kg treatment arms pooled

Improved Quality of Life in *del-brax* Treated Participants Compared to Placebo

Data at 12 months with Q13W dosing

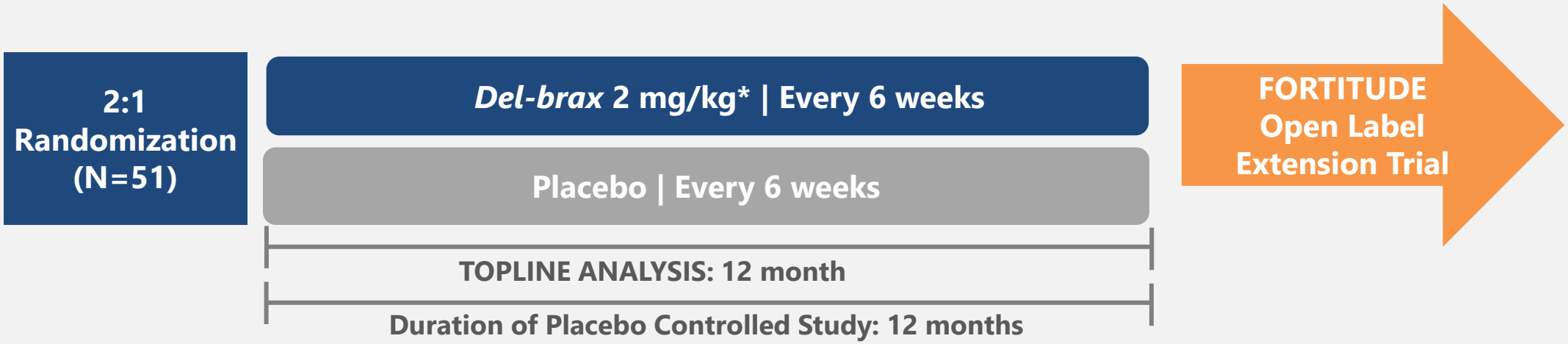


All data shown are mean change (± SEM) from Baseline to Month 12. VAS = Visual Assessment Score. One placebo participant had an unreliable baseline measurement and was removed from all efficacy analyses. EQ5D overall VAS is 100 point scale; Worst Pain VAS is 10 point scale. 2mg/kg and 4mg/kg treatment arms pooled

Ongoing *Del-brax* Registrational Studies

FORTITUDE™ Biomarker Cohort

Biomarker cohort enrollment completed



Study Design

- Size: N=51, randomized 2:1
- Treatment Period: 12 months
- Dose and Regimen: 2 mg/kg or placebo, IV Q6W
- Population: Male or Female, FSHD1 & FSHD2, 16-70 yr

Endpoints

- Primary: Change from baseline in KHDC1L
- Secondary: Change from baseline in Creatine Kinase

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*Dose listed is siRNA

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FORWARD™ Global Confirmatory Phase 3 Study Underway

Study Design

- Treatment Period: 18 months
- Dose: 2 mg/kg or placebo, IV Q6W
- Population: Male or Female, FSHD1 & FSHD2, 16-70 yr

Number of Participants, Sites and Regions

- Size: N=200, randomized 1:1
- Sites: ~45 sites
- North America, Europe, and Japan

Functional Endpoints*

- 10MWRT
- TUG
- QMT

* Final hierarchy will be selected prior to data base lock, based on evaluation of latest natural history data and efficacy data from FORTITUDE biomarker cohort. Currently, QMT is assigned as the primary endpoint.

On Track to be First Disease-Modifying Treatment for People with FSHD

- Reduction in KHDC1L (cDUX™), a DUX4-regulated circulating biomarker, and CK
- 12-month data for *del-brax* treated participants compared to placebo:
  - Improved functional mobility measured by 10MWRT and TUG
  - Improved muscle strength measured by QMT
  - Improved quality of life as measured by patient reported outcomes
- Favorable long-term safety and tolerability
- Rapidly advancing FORTITUDE™ biomarker trial and global confirmatory Phase 3 FORWARD™ trial with selected 2mg/kg Q6W dose and interval

Thank you to the study participants, families, investigators, and research teams.

- *Jeffery Statland*, MD*
- *Leo Wang, MD, PhD*
- *Katherine Mathews, MD*
- *Han Phan, MD*
- *Hanns Lochmuller* MD, PhD*
- *Johanna Hamel, MD*
- *Bakri Elsheikh, MD*
- *John Day, MD, PhD*
- *Dianna Quan*, MD*
- *Perry Shieh, MD, PhD*
- *Enrico Bugiardini*, MD*
- *Nicholas Johnson*, MD*
- *Rabi Tawil*, MD*
- *Colin Quinn*, MD*
- *Jaya Trivedi, MD*
- *Lisa Hobson-Webb*, MD*
- *Chamindra Laverty, MD*
- *Channa Hewamadduma*, MD, MSc, PhD*
- *Sankarasubramon Subramony, MD*

** Author group for the IRC 2025 FORTITUDE publication*