Effect of Long-Term Treatment of AOC 1001 in Adults with Myotonic Dystrophy Type 1: from MARINA® to MARINA-OLE™

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Disclosures

- Dr. Johnson has received personal compensation for serving as a consultant for Arthex Biotech, Avidity Biosciences, Dyne Therapeutics, Juvena Therapeutics, Kate Therapeutics, Pepgen, Rgenta Therapeutics, Sarepta Therapeutics, Takeda Pharmaceuticals, and Vertex Pharmaceuticals
- He has received personal compensation for serving on data safety monitoring board for Biogen
- He has stock or an ownership in Juvena Therapeutics
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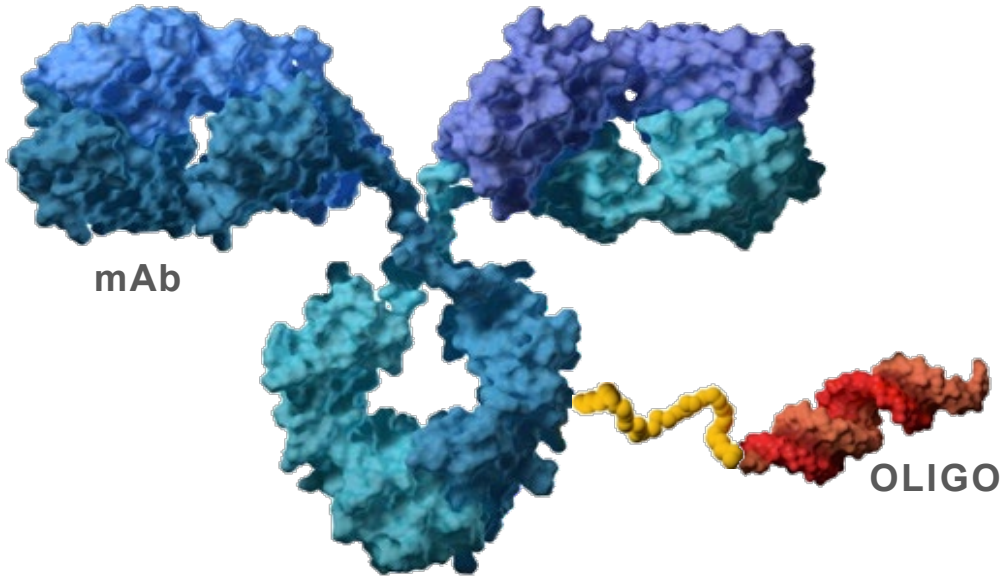
Evolution of AOC 1001: *Delpacibart Etedesiran* (*Del-desiran*)

- The main components of del-desiran are:
  - **Antibody:** human TfR1-targeting, effector function-null, humanized IgG1 antibody (TfR1 mAb)
  - **Non-cleavable linker**
  - **Oligonucleotide:** double-stranded siRNA oligonucleotide (siDMPK.19) that is complementary to a sequence in the 3' untranslated region (exon 15) of both wild-type and mutant-human DMPK mRNA
- The TfR1 mAb targets muscles for delivery of siDMPK.19 into the cytoplasm and nucleus where it mediates DMPK mRNA degradation



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MARINA OLE™

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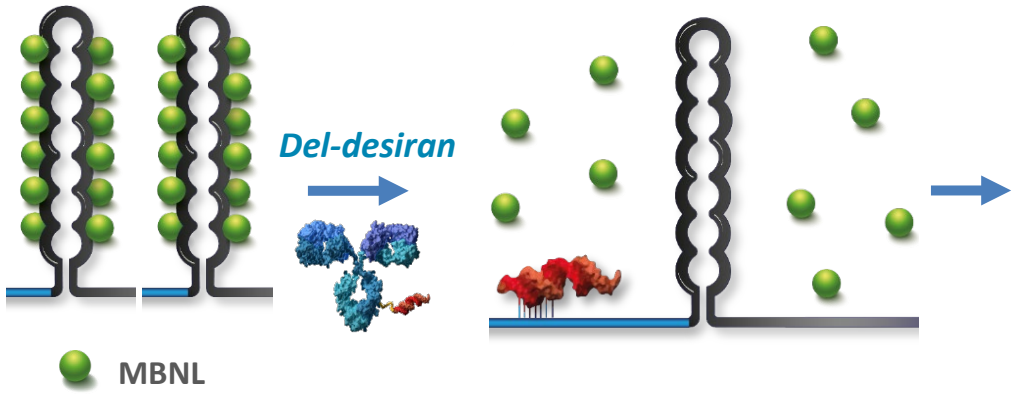
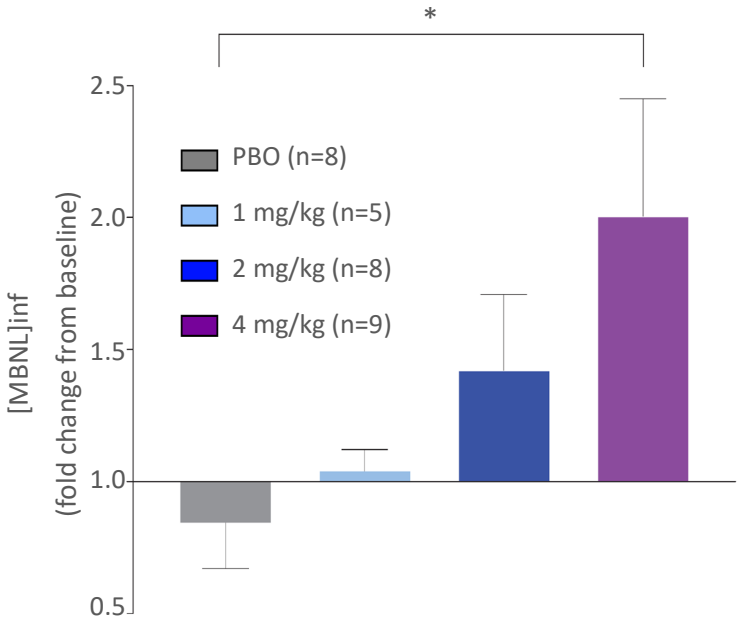
Del-desiran is Designed to Address Underlying Cause of Myotonic Dystrophy by Liberating Free Functional MBNL





Video Hand Opening Time (vHOT)

MYOTONIA

Hand Grip

Quantitative Muscle Testing

STRENGTH

DM1-Activ

ACTIVITIES OF DAILY LIVING

MBNL sequestered by CUG repeats of mutant DMPK

Del-desiran treatment reduced mutant DMPK

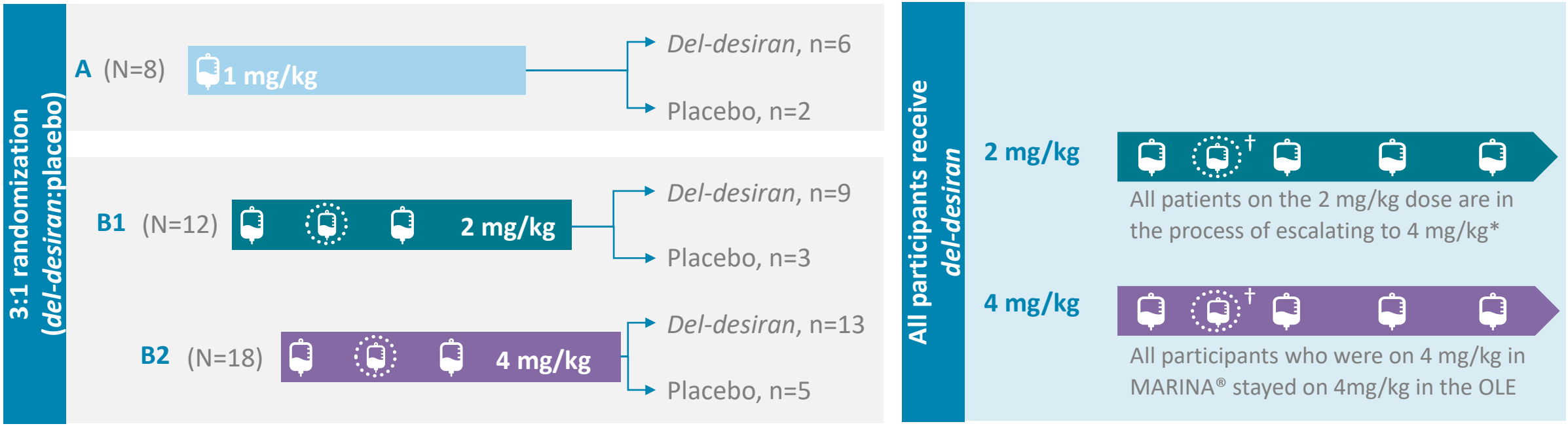
**Del-desiran* leads to dose-dependent increase in functional MBNL[#]

*P<0.05, unpaired t-test

[#]Data shown as mean and standard error. Fold change is calculated per subject as post-treatment relative to baseline;

Wagner, SD, et al. *PLOS Genet.* 2016;12(9):e1006316

MARINA® and MARINA-OLE™ Trials Designed to Evaluate Safety and Tolerability of *Del-desiran*



*Under the terms of the partial clinical hold, the first dose of *del-desiran* must be less than or equal to 2 mg/kg.
†Booster dose was only given to participants who were in Cohort A1 and placebo B1/B2.
Dose listed is siRNA.

- All participants that completed MARINA® enrolled in the MARINA-OLE™
- All participants remain in the MARINA-OLE™

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Del-desiran Demonstrates Favorable Long-Term Safety and Tolerability

As of January 2024, over 265 infusions of *del-desiran* have totaled 61.1 patient-years of exposure

	MARINA®				MARINA-OLE™
Subjects with ≥1 AE, n (%)	Placebo (N=10)	1 mg/kg (N=6)	2 mg/kg (N=9)	4 mg/kg (N=13)	All (N=37)
Any AE	8 (80%)	6 (100%)	9 (100%)	13 (100%)	35 (95%)
AE related to study drug	2 (20%)	1 (17%)	3 (33%)	10 (77%)	9 (24%)
Any Serious AE (SAE)	0	0	1 (11%)	1 (8%)	4 (11%)
SAE related to study drug	0	0	0	1 (8%)	0
AE leading to study discontinuation	0	0	0	1 (8%)	0
AE leading to death	0	0	0	0	0

Safety/Tolerability in MARINA-OLE

- **All 37 participants enrolled remain on study**
- **All related AEs were mild or moderate**
  - Most common related AEs reported in 2 or more participants include:
    - Nausea
    - Headache
  - No discontinuations
  - No related SAEs; unrelated SAEs are consistent with DM1*

*SAEs considered unrelated to treatment included nausea/vomiting, worsening of atrial fibrillation, and chest pain. One participant had acute cholelithiasis and biliary pancreatitis.

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END-DM1 Natural History Study: Understanding DM1 Disease Progression

- Non-interventional natural history study aimed to advance the understanding of disease progression in DM1 patients
- Focuses on clinical outcome assessments to support development of therapies for DM1
- 700 patient, 2-year study, ~20 centers
- Designed and run by the Myotonic Dystrophy Clinical Research Network (DMCRN)
- Supported by FDA, MDA, MDF; Avidity is one of several sponsoring organizations

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END-DM1 Data Informed Design of the MARINA® & Phase 3 HARBOR™ Trials

Same endpoints measured

Clinical trial sites overlap with MARINA® & HARBOR

Contemporary data set based upon standard of care

Hundreds of patients with at least one-year of follow-up in END-DM1 natural history study

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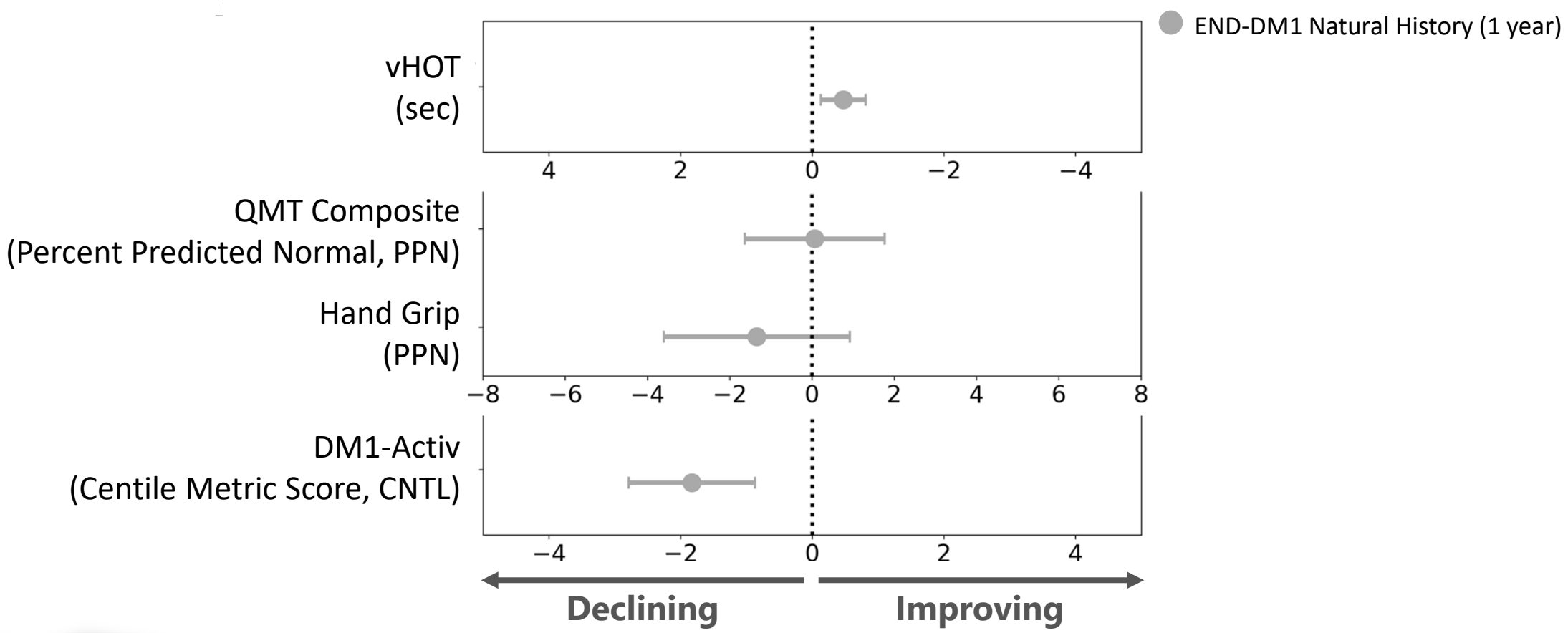
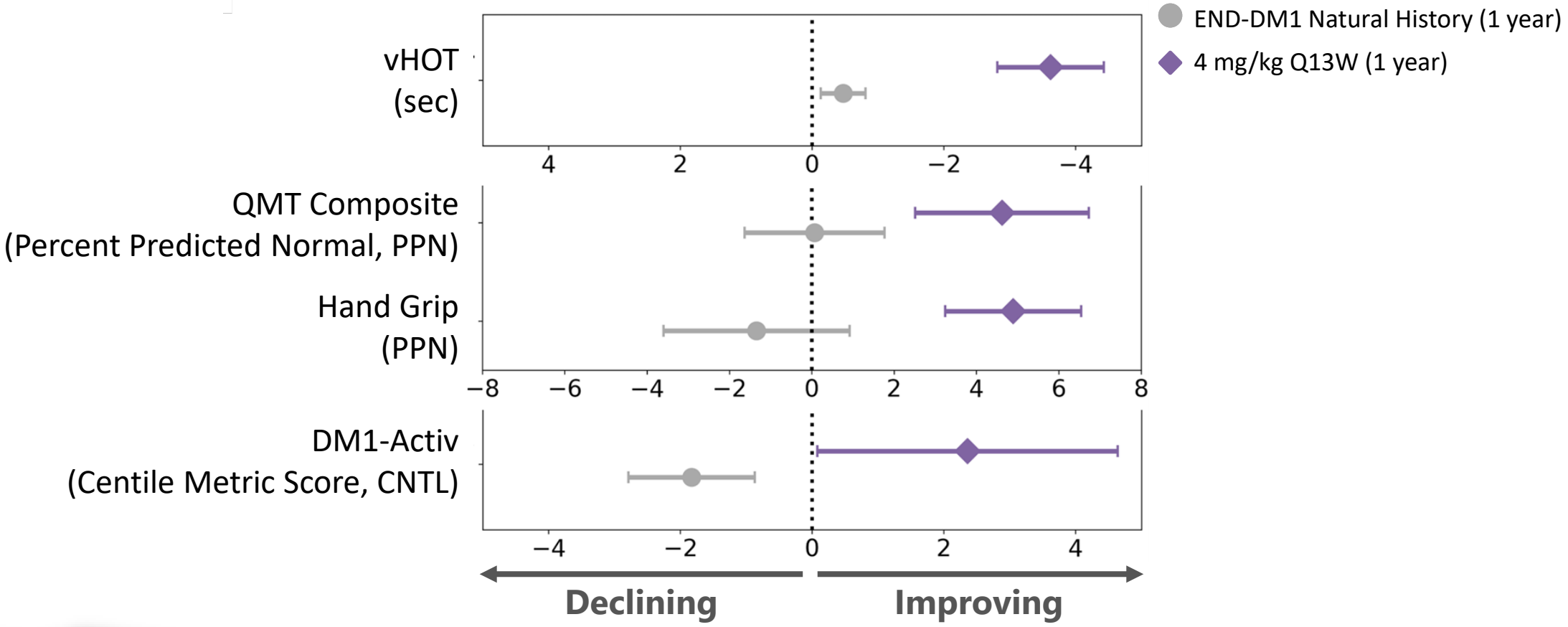
END-DM1: Disease Progression Over 1 Year



Thanks to END-DM1 physicians for reviewing and approving use of this Avidity analysis. END-DM1 subpopulation based on MARINA® (n ~ 60; MIRS≥2 and 3.8<10MWRT<14 secs)
CNTL, centile metric score; PPN, percent predicted normal.
Error bars represent standard error of the mean.

Del-desiran: Reversal of Disease Progression in MARINA-OLE™ Compared to Natural History

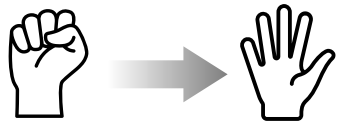
Key endpoints to be used in HARBOR study



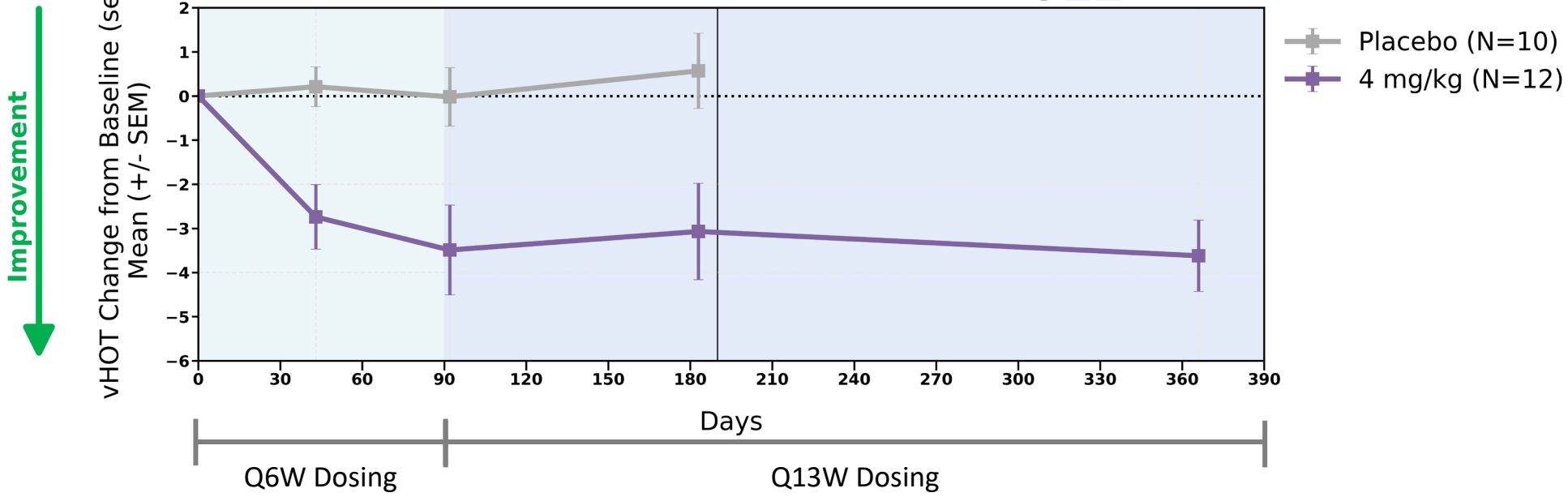
Thanks to END-DM1 physicians for reviewing and approving use of this Avidity analysis. END-DM1 subpopulation based on MARINA® (n ~ 60; MIRS≥2 and 3.8<10MWRT<14 secs). In MARINA-OLE™ data 4 mg/kg, n=12 for vHOT, QMT composite, hand grip; n=11 for DM1-Activ.
CNTL, centile metric score; PPN, percent predicted normal.
Error bars represent standard error of the mean.

Del-desiran (4 mg/kg): Long-Term Improvement in Myotonia as Measured by vHOT at 1 Year on Treatment

Video Hand Opening Time (vHOT)



Independently adjudicated



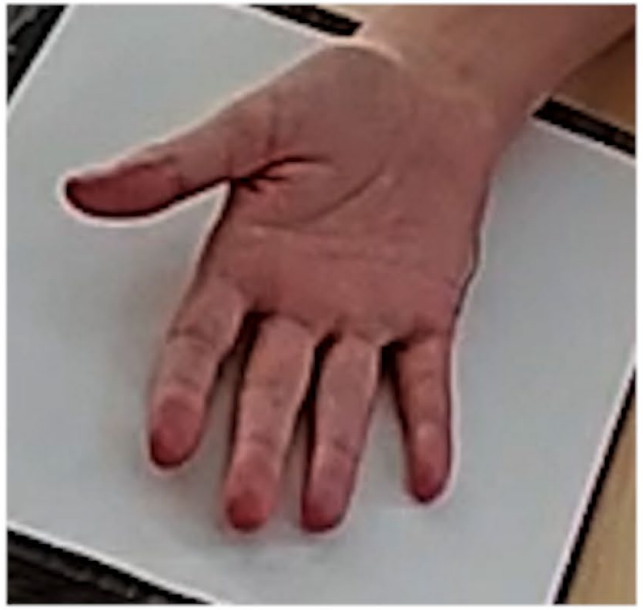
MARINA® data statistically significant at all assessment time points*

SEM, standard error of the mean.
*Based on a post-hoc analysis

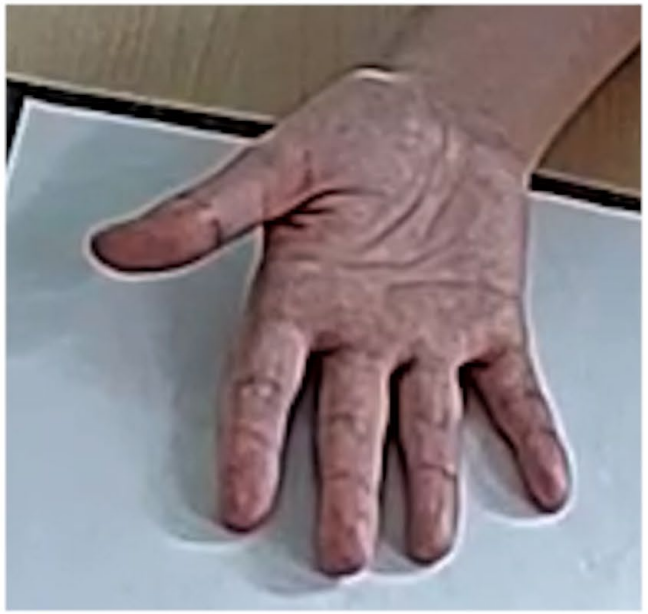
Del-desiran (4 mg/kg): Long-Term Improvement in Myotonia as Measured by vHOT at 1 Year on Treatment

Participant from *del-desiran* 4 mg/kg

Baseline vHOT



MARINA-OLE™ (1 year of 4 mg/kg)



Timepoint at Day 183 in MARINA-OLE™

Del-desiran (4 mg/kg): Long-Term Improvement in Muscle Strength as Measured by Hand Grip and QMT at 1 Year on Treatment

Hand Grip Strength

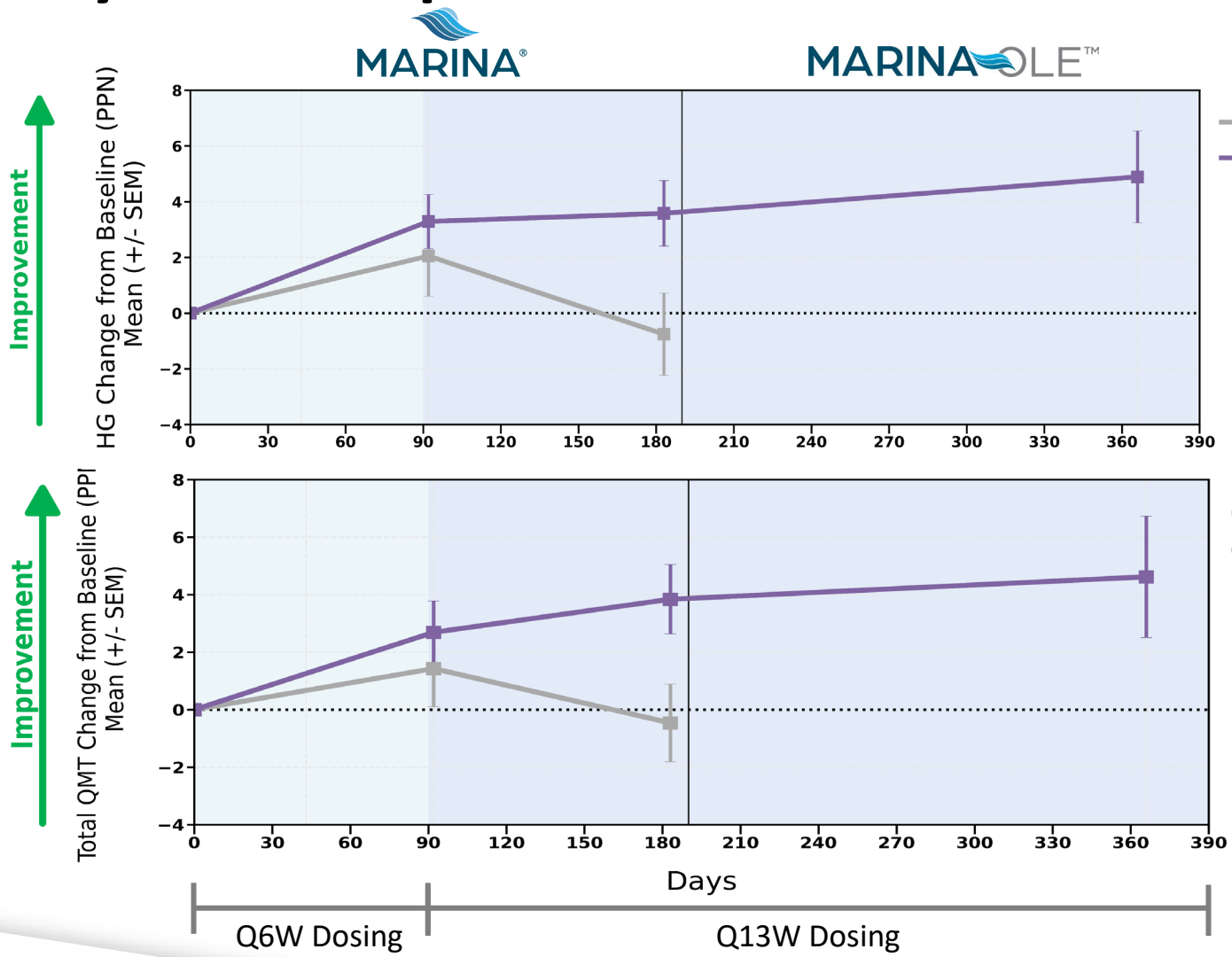
Quantitative Muscle Testing (QMT) Total Score

Hand Grip

Elbow Extension & Elbow Flexion

Knee Extension & Knee Flexion

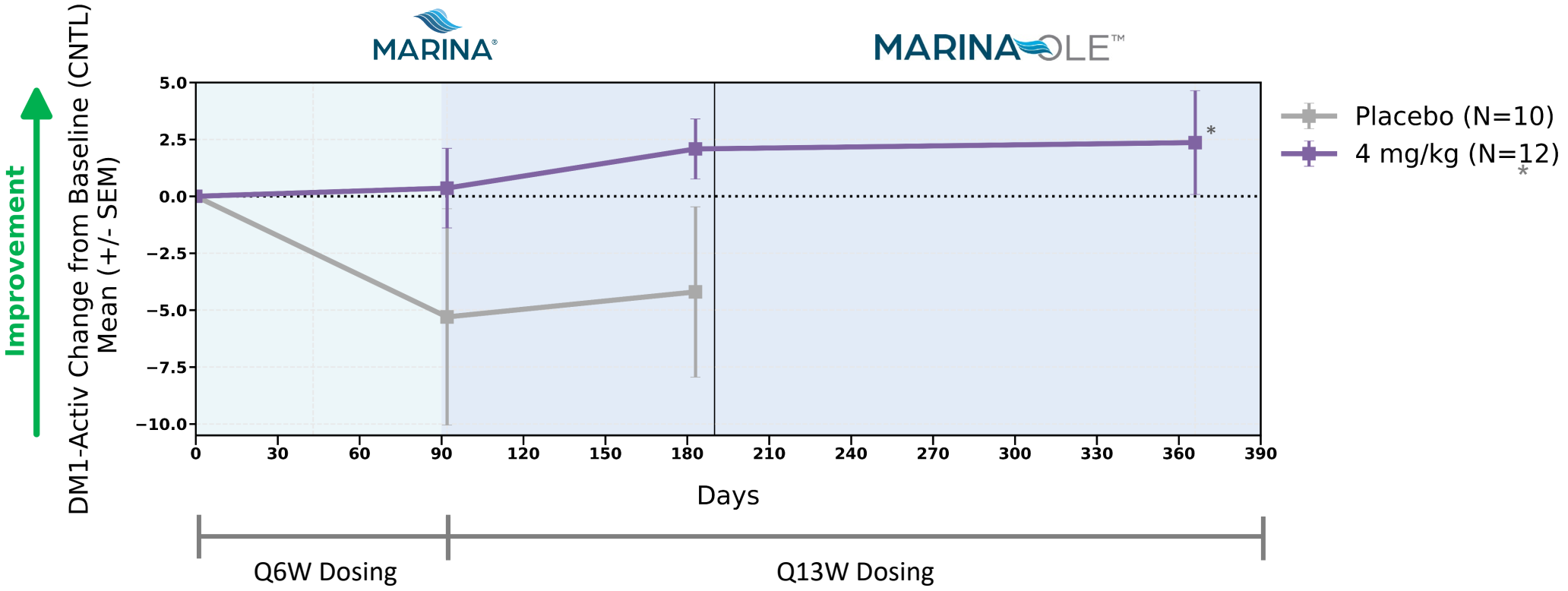
Ankle Dorsiflexion



HG, hand grip; PPN, percent predicted normal; QMT, quantitative muscle testing; SEM, standard error of the mean.

Del-desiran (4 mg/kg): Maintains Improvement in Activities of Daily Living as Measured by DM1-Activ at 1 Year on Treatment

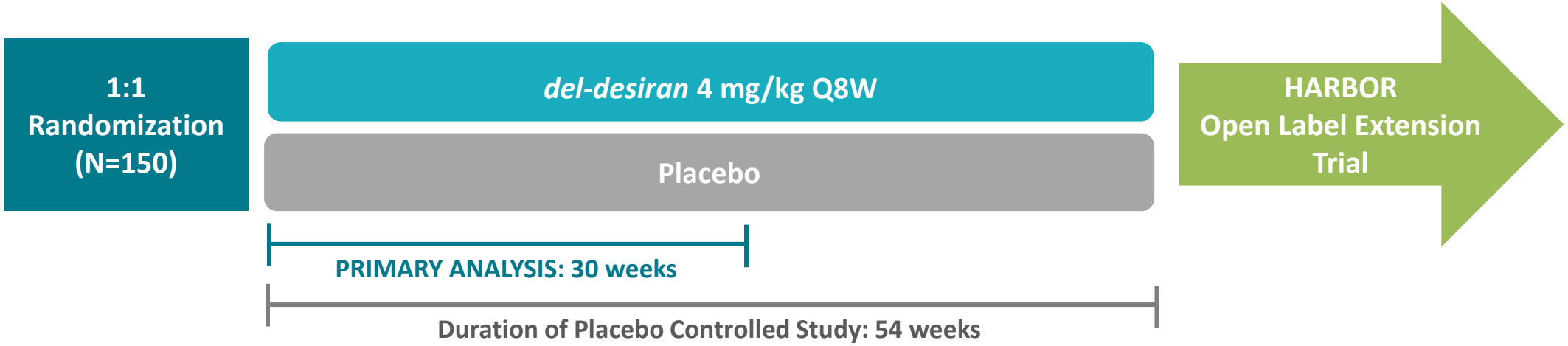
DM1-Activ



*Day 360 excludes one participant who experienced an injury impairing their ability to perform mobility measures.
CNTL, centile metric score; SEM, standard error of the mean

HARBOR™ Initiating Global Phase 3 Pivotal Trial

- Regulatory agreement on study design
- HARBOR™ study designed for efficiency and speed of execution
- On track to initiate in Q2 2024



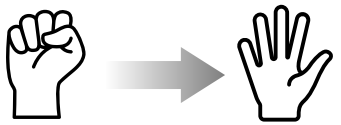
HARBOR™ Phase 3 Trial: Design and Objectives

Pivotal Study Design

- 4 mg/kg every 8 weeks; first dose of 2 mg/kg
- N=150; Ages 16+
- 1:1 randomization
- Primary analysis at Week 30; Placebo-control out to week 54
- Participants eligible to roll-over into an open label extension
- ~40 global sites

Primary Endpoint

Video Hand Opening Time (vHOT)



MYOTONIA

Key Secondary Endpoints

Hand Grip

STRENGTH

Quantitative Muscle Testing

DM1-Activ

ACTIVITIES OF DAILY LIVING

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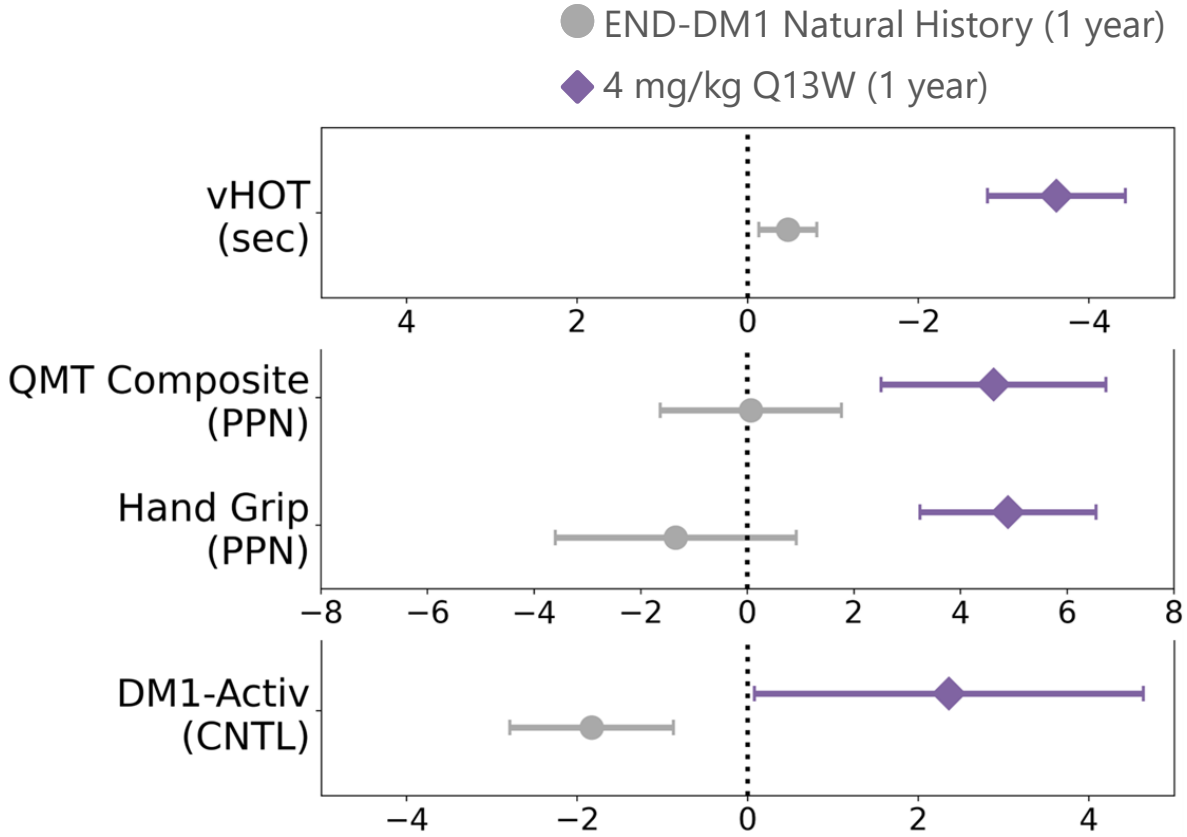
MARINA-OLE™ Long-Term Data Demonstrate the Potential of *Del-desiran* to be a Transformation Therapy for DM1 Patients

Del-desiran 4 mg/kg

- Demonstrated favorable long-term safety and tolerability
- Showed reversal of disease progression in MARINA® and MARINA-OLE™ compared to END-DM1 natural history data
- Provided consistent and durable improvements in multiple clinical endpoints

Global HARBOR™ trial initiation Q2 2024



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