

# Safety and efficacy of DYNE-101 in adults with DM1: Phase 1/2 ACHIEVE trial data

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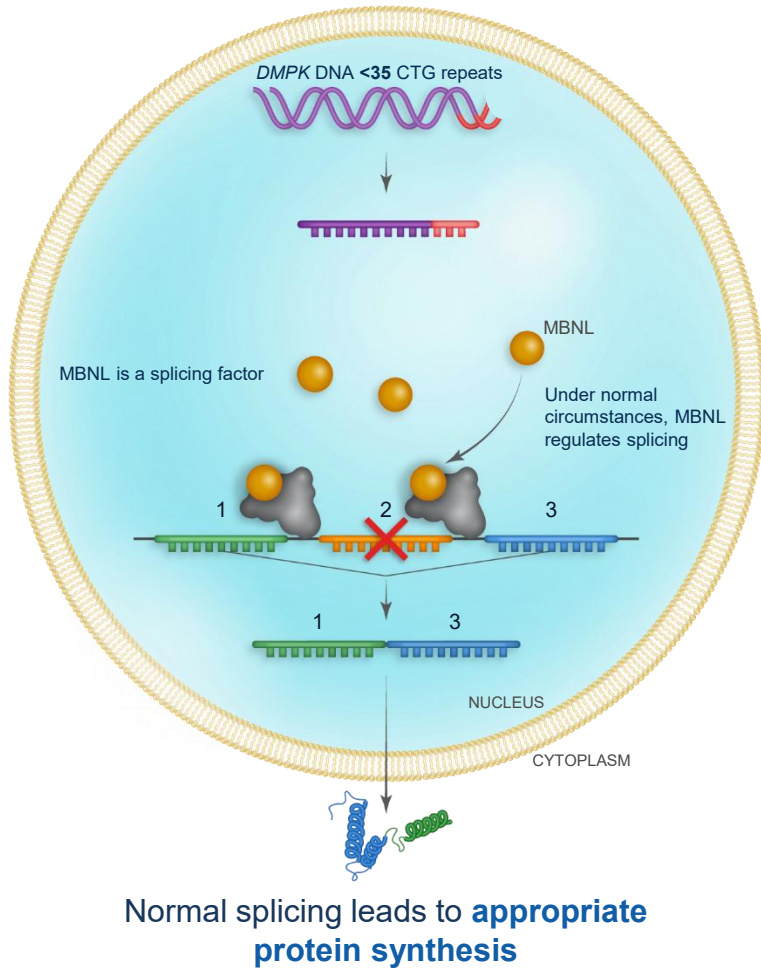
# Disclosures

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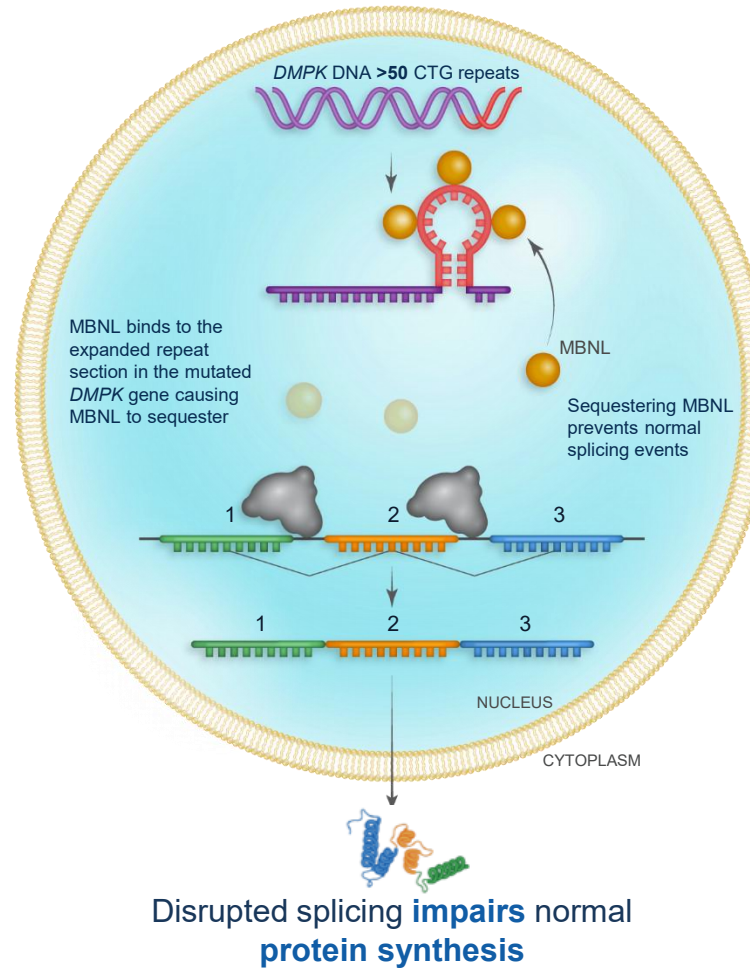
- I have received advisory board and/or conference presentation support from Dyne Therapeutics, Roche, and Sanofi
- DYNE-101 is an investigational medicine being evaluated in the ongoing ACHIEVE trial and has not received approval by the FDA, EMA, or any other regulatory authorities

# Spliceopathy in DM1 drives multisystem disease manifestations

## Normal splicing

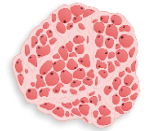


## DM1 spliceopathy



## Consequences of spliceopathy

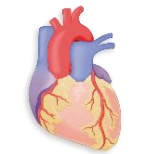
Myotonia and muscle weakness



Cognitive impairment, fatigue, EDS



Cardiac conduction complications



Pulmonary abnormalities



Abnormal splicing in **multiple tissues** causes symptoms of DM1

**Goal of treatment: address the genetic cause of DM1 to correct splicing and improve function**

# DYNE-101 addresses the central pathobiology of DM1 to enable broad functional improvement

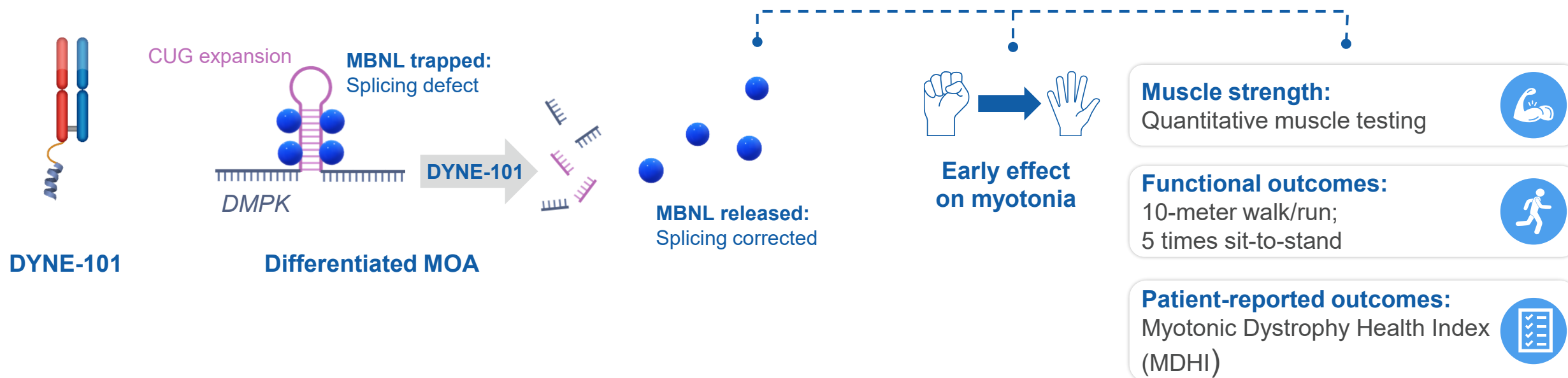
Robust and widespread delivery

DMPK degradation in the nucleus

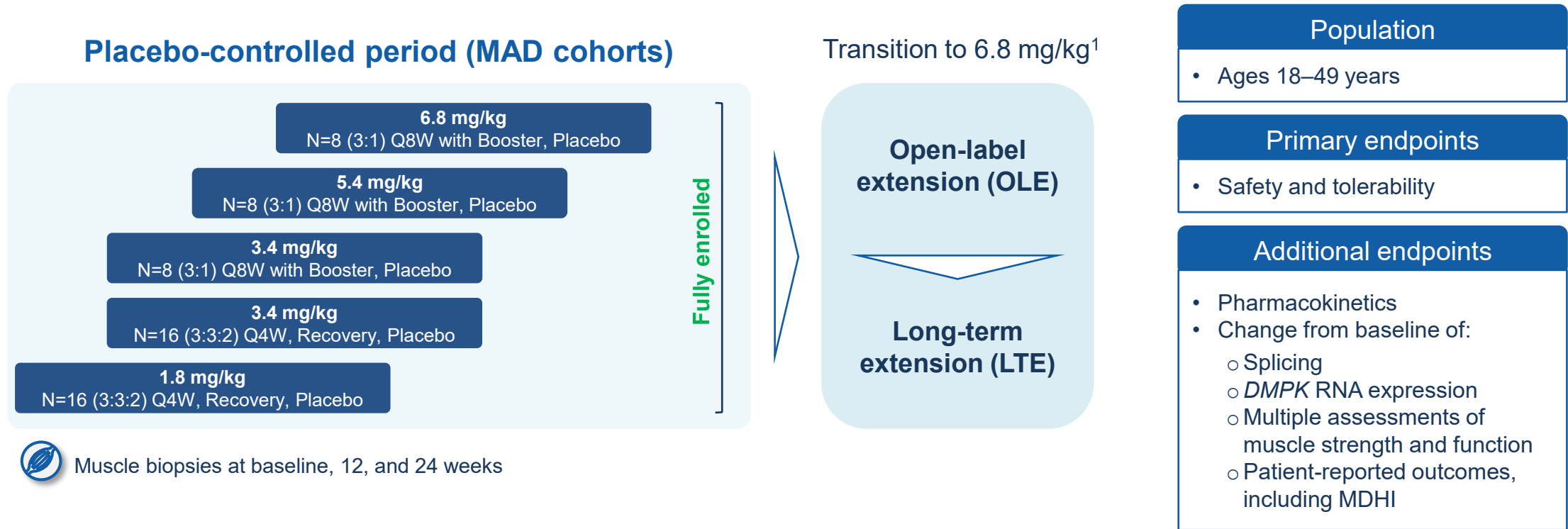
MBNL release and splicing correction

Early clinical effect

Broad functional improvement



# ACHIEVE trial of DYNE-101 in adults with DM1



Muscle biopsies at baseline, 12, and 24 weeks

**Registrational dose and dose regimen selected at 6.8 mg/kg Q8W; Registrational expansion cohort planned (N=32–48, 3:1 randomization)**

Doses provided refer to antisense oligonucleotide component of DYNE-101. Recovery cohort Q4W x 2 doses then placebo for the remainder of the 24W placebo-controlled period. Q8W with booster includes Q4W x 3 doses then Q8W dosing. Additional endpoints include select secondary and exploratory endpoints.

1. Transition to 6.8 mg/kg dose occurs at non-uniform times during OLE or LTE.

DM1, myotonic dystrophy type 1; *DMPK*, dystrophin myotonia protein kinase; MAD, multiple ascending dose; MDHI, Myotonic Dystrophy Health Index; Q4W, every 4 weeks; Q8W, every 8 weeks.

# Baseline participant characteristics in 6.8 mg/kg Q8W cohort

| Mean (SD) or n (%)         | Placebo (N=14) | 6.8 mg/kg Q8W (N=6) |
|----------------------------|----------------|---------------------|
| Age (years)                | 32.6 (9.6)     | 37.2 (9.7)          |
| BMI (kg/m <sup>2</sup> )   | 24.4 (4.7)     | 23.4 (5.6)          |
| CASI-22                    | 0.68 (0.20)    | 0.74 (0.25)         |
| CTG repeats                | 597 (246)      | 542 (191)           |
| vHOT (middle finger) (sec) | 7.5 (3.0)      | 7.8 (3.8)           |
| QMT total (% predicted)    | 51.5 (14.3)    | 51.3 (10.4)         |
| 10-meter walk/run (sec)    | 3.34 (0.48)    | 3.94 (1.56)         |
| 5 times sit-to-stand (sec) | 9.24 (2.03)    | 9.98 (3.33)         |
| MDHI total                 | 18.7 (13.8)    | 26.5 (13.7)         |

# Favorable safety profile with no serious related TEAEs

## Summary of treatment-emergent adverse events (TEAEs)<sup>1</sup>

| TEAE category                             | Participants with ≥1 TEAE – n (%) |                         |                   |                   |                   | Overall (N=56) |
|-------------------------------------------|-----------------------------------|-------------------------|-------------------|-------------------|-------------------|----------------|
|                                           | 1.8 mg/kg Q4W+Rec. N=16           | 3.4 mg/kg Q4W+Rec. N=16 | 3.4 mg/kg Q8W N=8 | 5.4 mg/kg Q8W N=8 | 6.8 mg/kg Q8W N=8 |                |
| Any TEAE                                  | 16 (100)                          | 16 (100)                | 8 (100)           | 8 (100)           | 8 (100)           | 56 (100)       |
| Any related TEAE                          | 9 (56)                            | 9 (56)                  | 2 (25)            | 3 (38)            | 6 (75)            | 29 (52)        |
| Any serious TEAE                          | 4 (25)                            | 0                       | 1 (13)            | 0                 | 0                 | 5 (9)          |
| Any serious related TEAE                  | 0                                 | 0                       | 0                 | 0                 | 0                 | 0              |
| Any TEAE leading to withdrawal from study | 0                                 | 0                       | 0                 | 0                 | 0                 | 0              |
| Any TEAE leading to death                 | 0                                 | 0                       | 0                 | 0                 | 0                 | 0              |

## Most TEAEs were mild or moderate in intensity<sup>1</sup>

- **6 serious TEAEs unrelated to study drug**
  - Atrioventricular block first degree (1)<sup>2</sup>
  - Pneumonia (2 events in same participant)
  - Pulmonary embolism (1)<sup>3</sup>
  - Hyponatremia (1)
  - Influenza (1)
- **Most common TEAEs (≥20% participant incidence)<sup>4</sup>**
  - Nasopharyngitis (38%)
  - Procedural pain (30%)
  - Influenza (27%)
  - Infusion-related reaction (25%)
  - Diarrhea; headache (each 21%)

## Additional safety data

- **Liver enzyme elevations have been observed in a minority of participants**
  - No impact on liver function (bilirubin or coagulation)
  - Interpretation is complicated by underlying disease and elevated baseline values up to ~2.5x greater than the upper limit of normal
- **No participants have demonstrated persistent related anemia or thrombocytopenia**

~855 doses administered to date representing over 72 patient-years of follow-up<sup>1</sup>

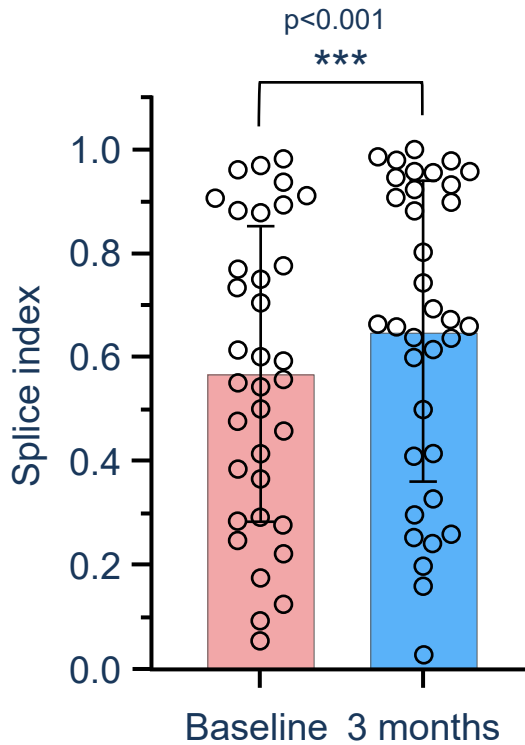
Q4W, every 4 weeks; Q8W, every 8 weeks; TEAE, treatment-emergent adverse event.

1. Data as of December 6, 2024; 2. Transient worsening of atrioventricular (AV) block in a participant with ongoing medical history of first-degree AV block;

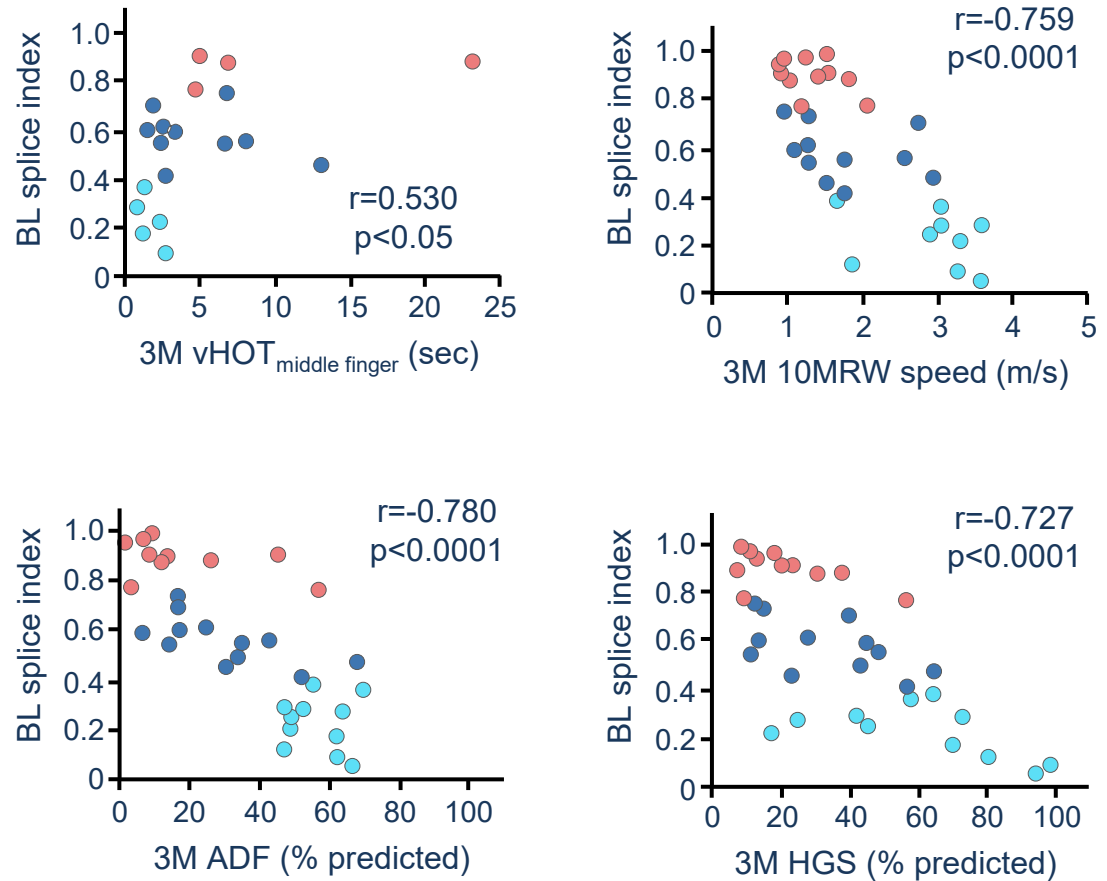
3. Attributed to risk factors for pulmonary embolism; 4. All cohorts combined; preferred terms are reported.

# The Splice Index quantifies RNA splicing and is a prognostic biomarker that predicts clinical benefit in DM1

**Worsening in Splice Index is observed in as little as 3 months in the NH cohort (N=35)\***



**The Splice Index is predictive of function**



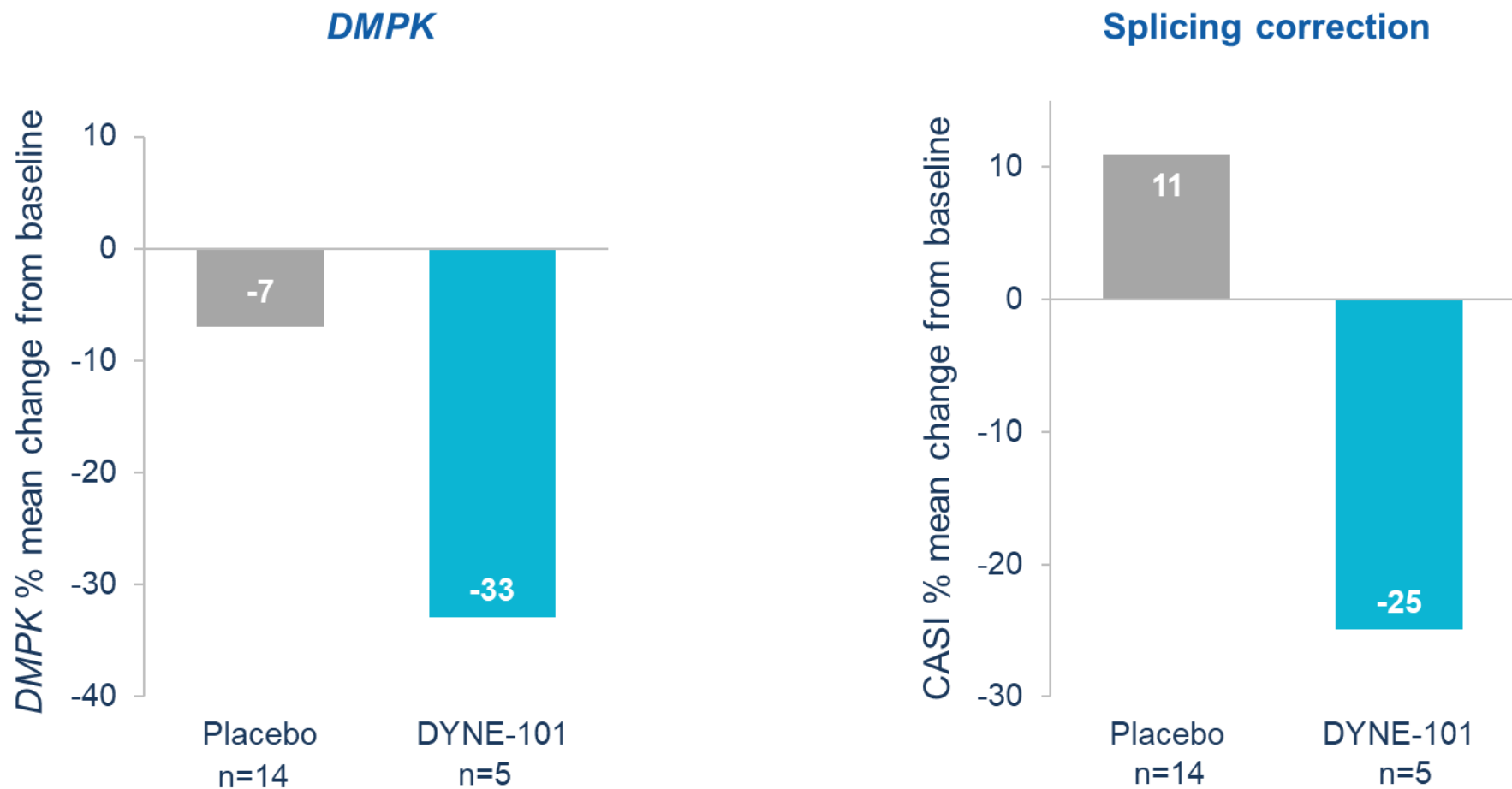
**Splice Index group:** ● Mild ● Moderate ● Severe

\*Data represent mean  $\pm$  standard deviation.

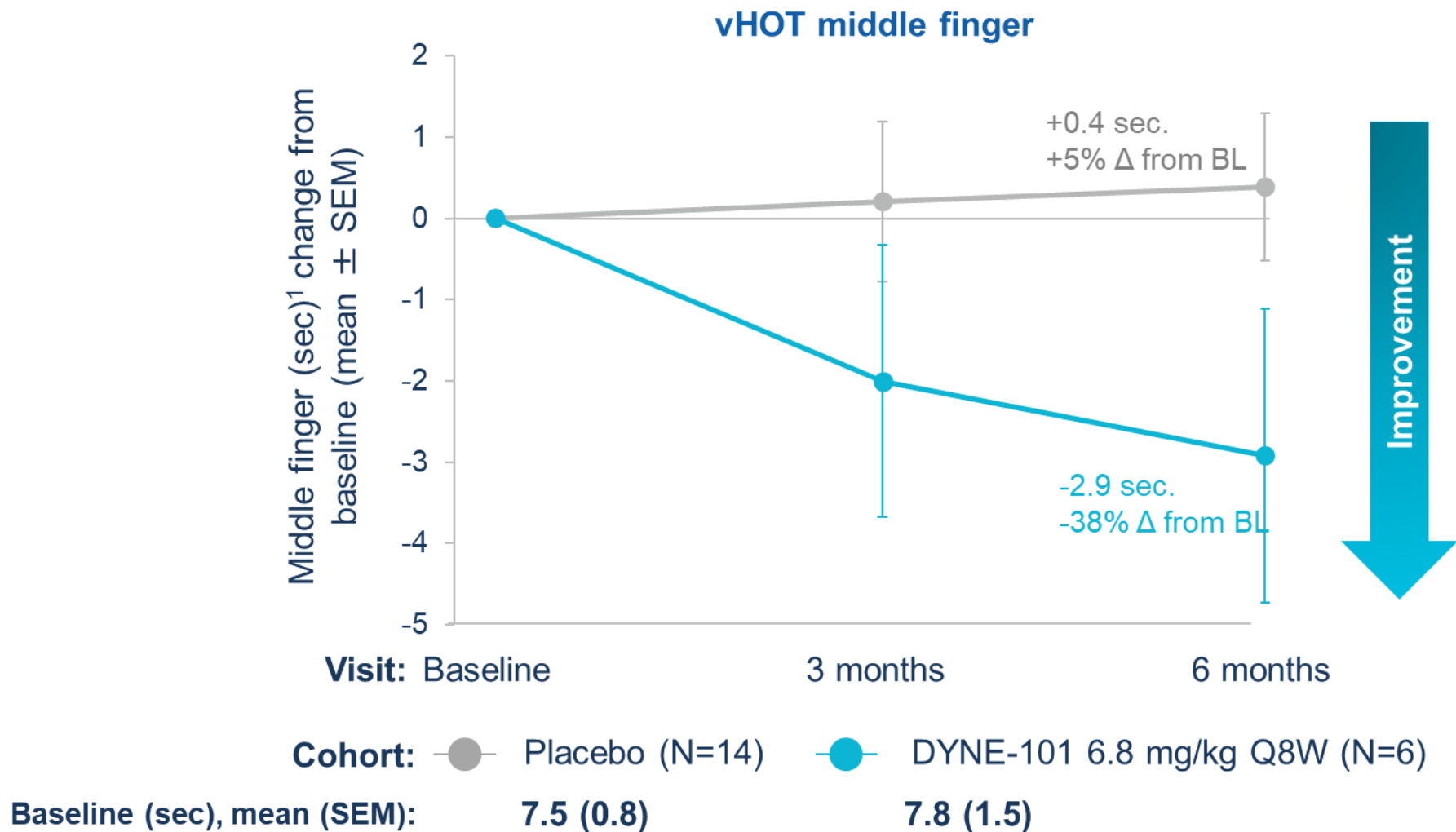
3M, 3 month; 10MWR, 10-meter walk/run; ADF, ankle dorsiflexion; BL, baseline; DM1, myotonic dystrophy type 1; HGS, hand grip strength; NH, natural history; vHOT, video hand opening time.

Provenzano M, et al. *J Clin Invest.* 2025:e185426.

# DYNE-101 at 6.8 mg/kg Q8W improved the foundational pathobiology of DM1 at 3 months



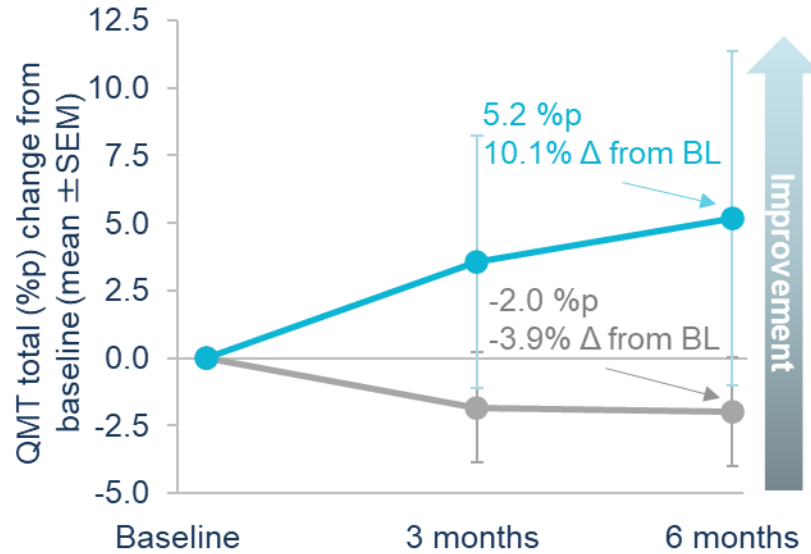
# Treatment with 6.8 mg/kg Q8W DYNE-101 resulted in early and robust improvement in functional myotonia at 6 months



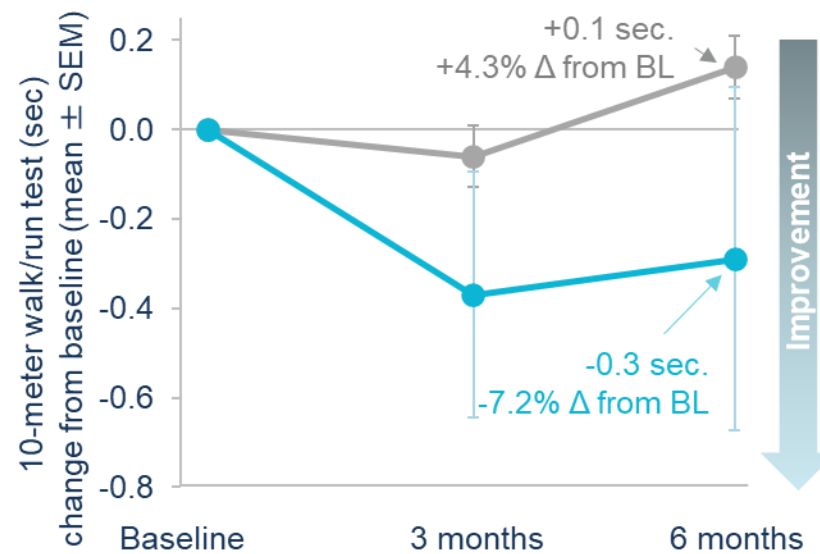
1. vHOT middle finger (sec) is the average of all myotonia trials for an individual participant in ACHIEVE. 3 months = 85 days; 6 months = 169 days.  
BL, baseline; Q8W, every 8 weeks; SEM, standard error of mean; vHOT, video hand opening time.

# Early and robust benefit also noted across multiple measures of muscle strength and function

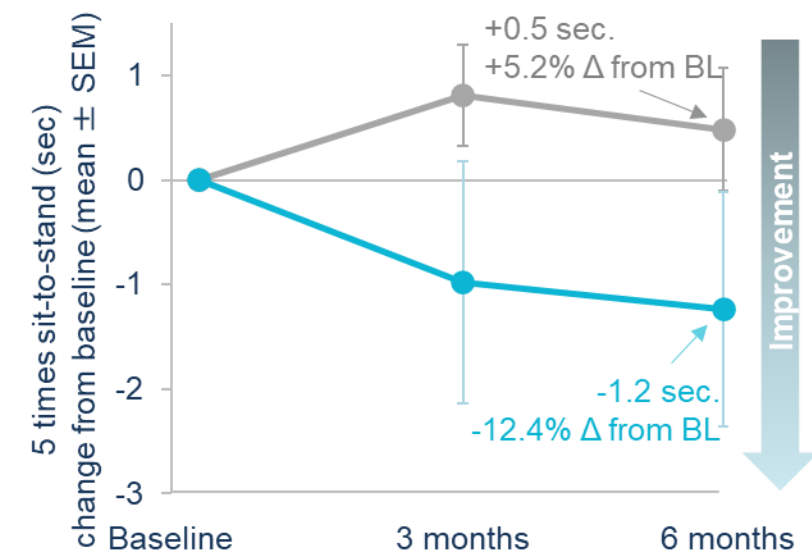
## QMT total



## 10-meter walk/run test



## 5 times sit-to-stand



Baseline score, mean (SEM):  
Placebo: 51.5 (3.8)  
DYNE-101: 51.3 (4.2)

Baseline (sec), mean (SEM):  
Placebo: 3.3 (0.1)  
DYNE-101: 3.9 (0.6)

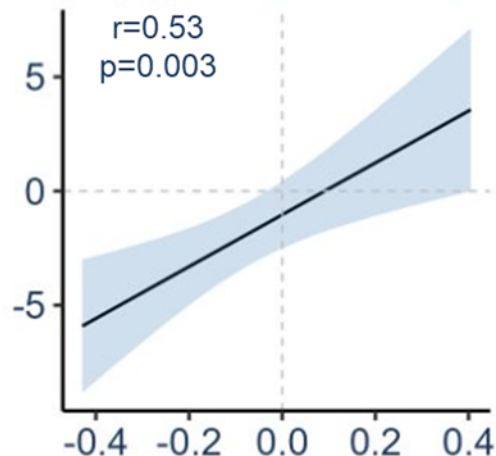
Baseline (sec), mean (SEM):  
Placebo: 9.2 (0.5)  
DYNE-101: 10.0 (1.4)

● Placebo (N=14) ● DYNE-101 6.8 mg/kg Q8W (N=6)

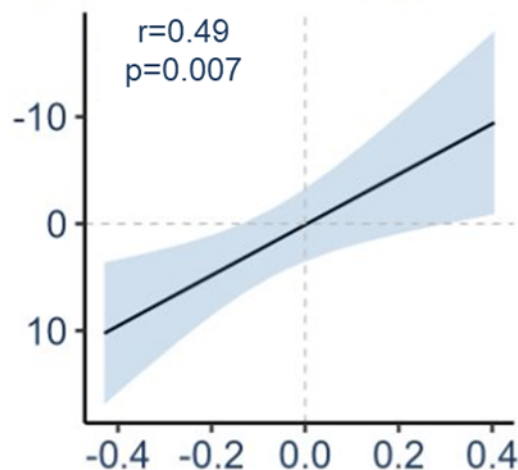
# In ACHIEVE, splicing correction at 3 months predicted functional benefit at 6 months

Function change from baseline at Month 6

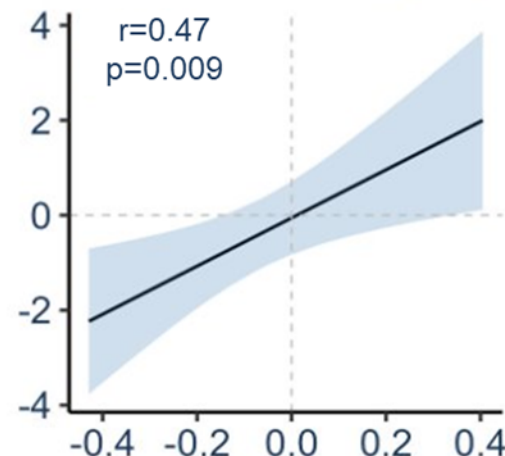
**vHOT middle finger average (sec)**



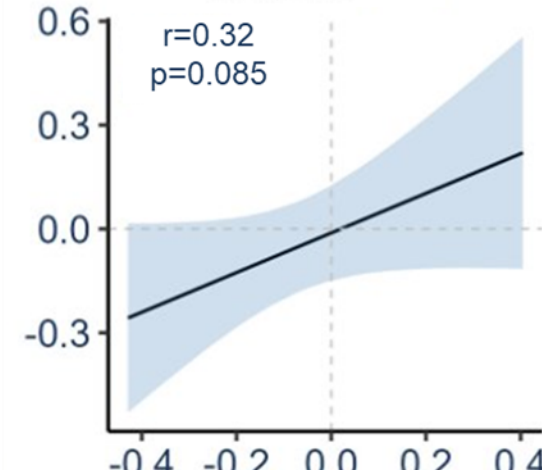
**QMT total (%p)**



**5 times sit-to-stand (sec)**



**10-meter walk/run (sec)**



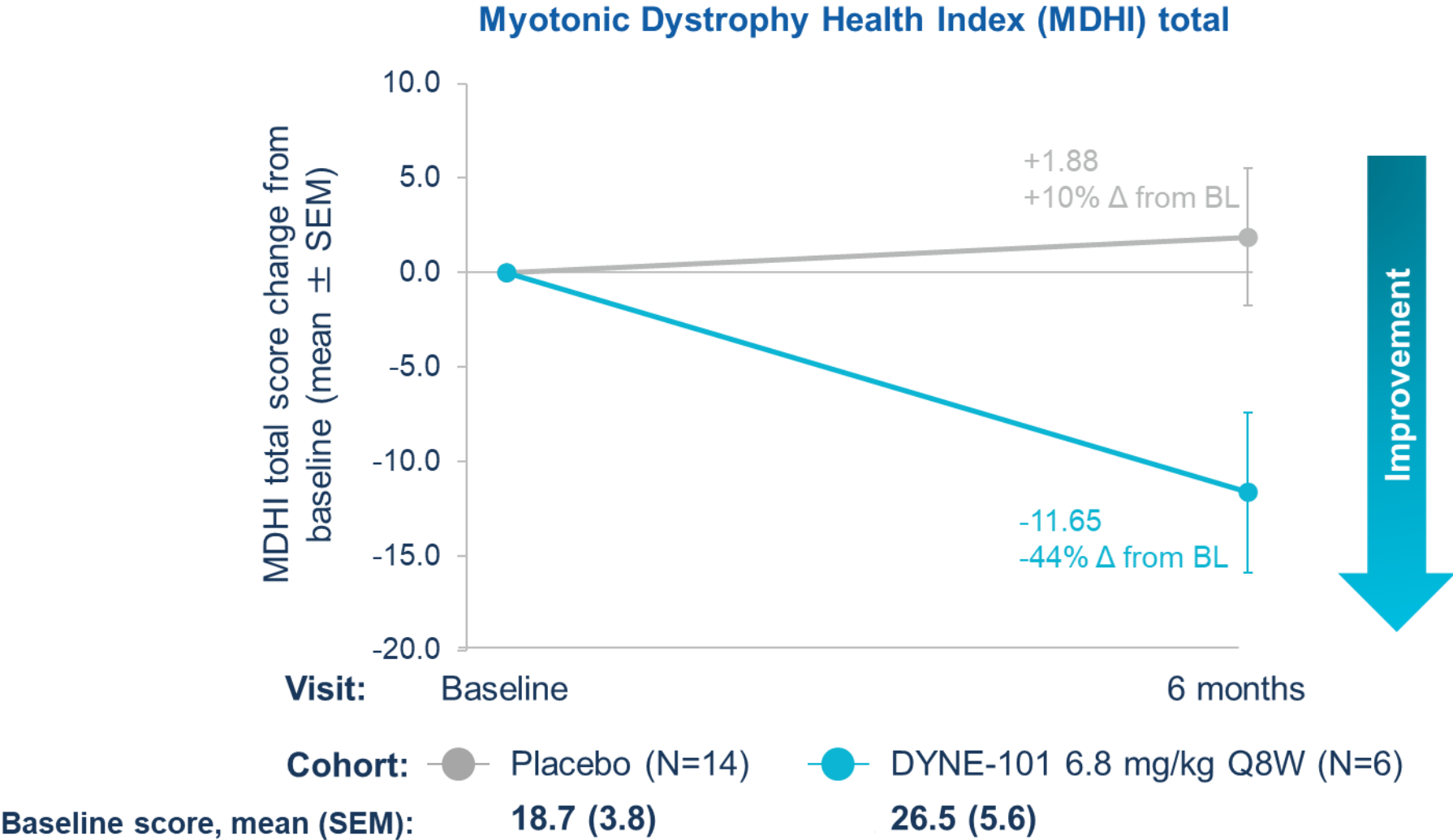
CASI change from baseline at 3 months

Shown are linear regression lines and correlation analysis for pooled 3.4 mg/kg Q4W, 5.4 mg/kg Q8W and 6.8 mg/kg Q8W and Placebo (N=24). Band for model predicted mean with 95% CI.

3 months = 85 days; 6 months = 169 days.

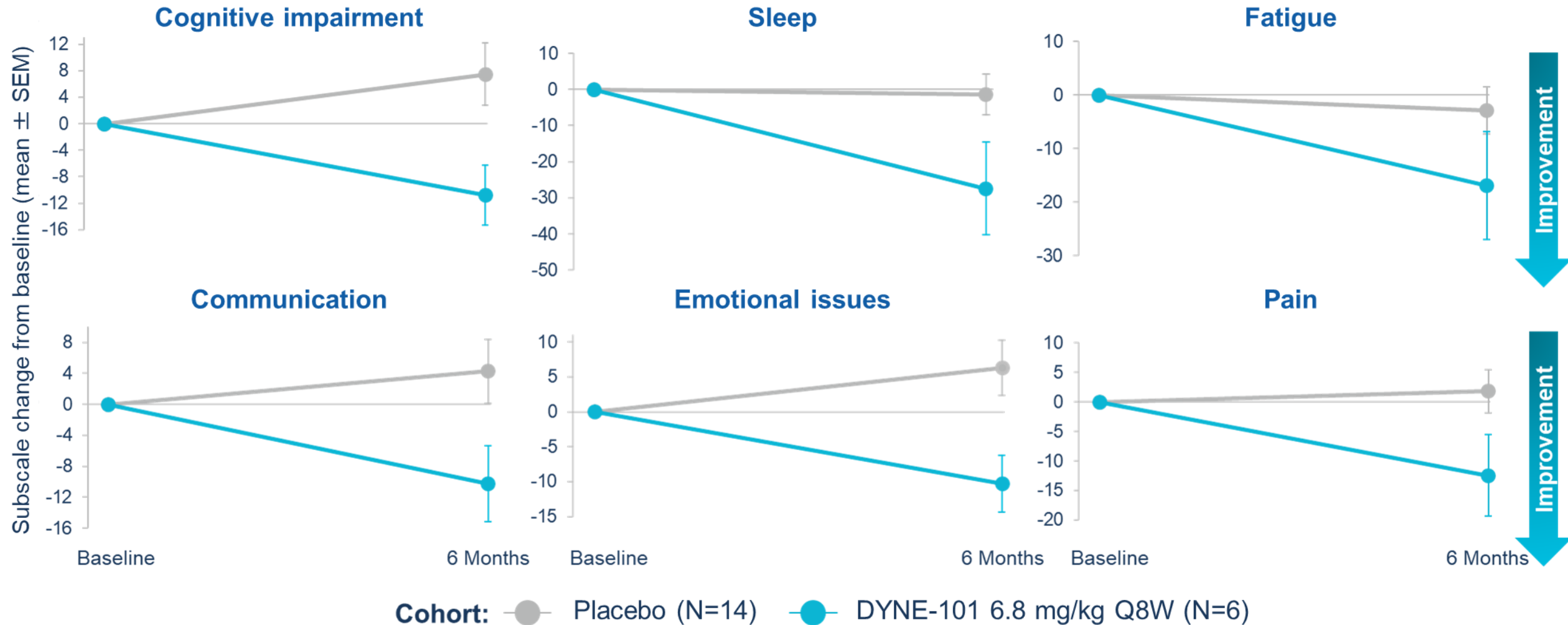
CASI, composite alternative splicing index; Q4W, every 4 weeks; Q8W, every 8 weeks; QMT, quantitative muscle testing; sec, seconds; vHOT, video hand opening time.

# Improvement in MDHI total score indicates encouraging patient-reported outcome trends

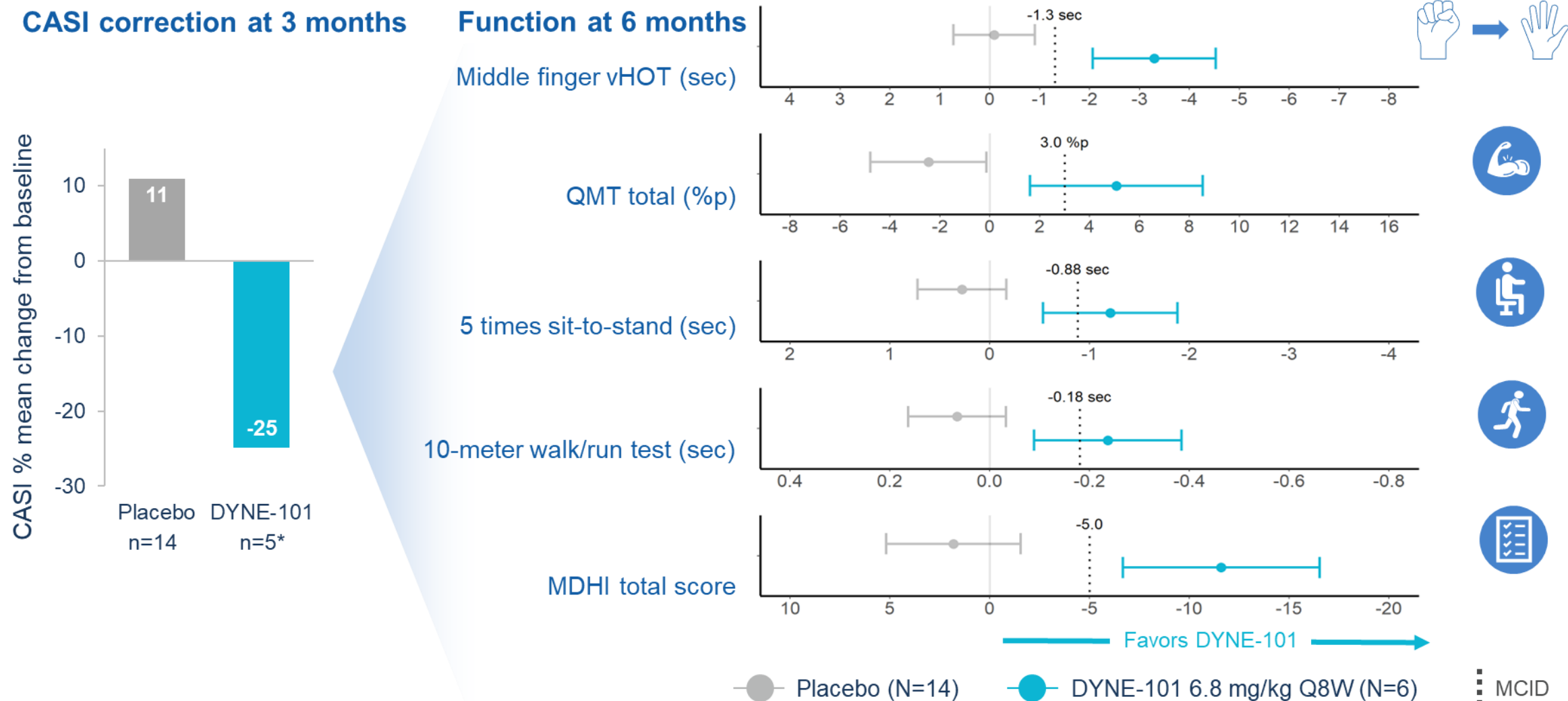


Patient-reported outcomes (PRO) including MDHI collected at baseline and 6 months (169 days).  
BL, baseline; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks; SEM, standard error of mean.

# Improvement in CNS-related MDHI subscales



# DYNE-101 demonstrates improvements in areas that patients find most impactful: muscle function and CNS-related manifestations<sup>1</sup>



\*One baseline sample in 6.8 mg/kg treatment group not included within splicing analysis as the sample did not meet quality control criteria.

Mixed model for repeated measures (MMRM): fixed effects: dose, visit, baseline, dose by visit interaction, baseline by visit interaction. Data: all dose groups except recovery group; excluding placebo data after 6 months; Data presented are least squares (LS) mean change from baseline  $\pm$  SE. MCID estimate is calculated as the average of 2 distribution-based methods using ACHIEVE data (0.2 SD of baseline [N=56] and 0.5 SD placebo change from baseline at 6 months [n=14]). 3 months = 85 days; 6 months = 169 days.

Q8W, every 8 weeks; CASI, composite alternative splicing index; CNS, central nervous system; MCID, minimal clinically important difference; MDHI, Myotonic Dystrophy Health Index; QMT, quantitative muscle testing; SD, standard deviation; SE, standard error; vHOT, video hand opening time. 1. Hagerman KA, et al. *Muscle Nerve* 2019;59(4):457-64.

# Summary

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- DYNE-101 is designed to target mutant nuclear *DMPK* RNA with the goal of correcting the abnormal splicing to improve the multisystem disease manifestations of DM1<sup>1,2</sup>
- DYNE-101 shows a continued favorable safety profile\*, with no serious related TEAEs
- DYNE-101 addresses the underlying pathobiology (dysregulated splicing) of DM1 and at 6.8 mg/kg Q8W has demonstrated clinically meaningful improvements on measures of strength, mobility and quality of life, including CNS manifestations
  - Splicing correction at 3 months with DYNE-101 was predictive of functional benefit at 6 months
- The MAD portion of ACHIEVE is completed; **6.8 mg/kg Q8W** has been selected as the **registrational dose/dose regimen** of DYNE-101

\*Data as of December 6, 2024.

CNS, central nervous system; MAD, multiple ascending dose; Q8W, every 8 weeks; TEAE, treatment-emergent adverse event.

1. López-Martínez A, et al. *Genes (Basel)*. 2020;11(9):1109; 2. Zanotti S. Presentation at the 26th American Society of Gene and Cell Therapy Annual Meeting. May 17, 2023. Los Angeles, USA. Abstract 82.

# Acknowledgements



## ACHIEVE participants and their families

