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

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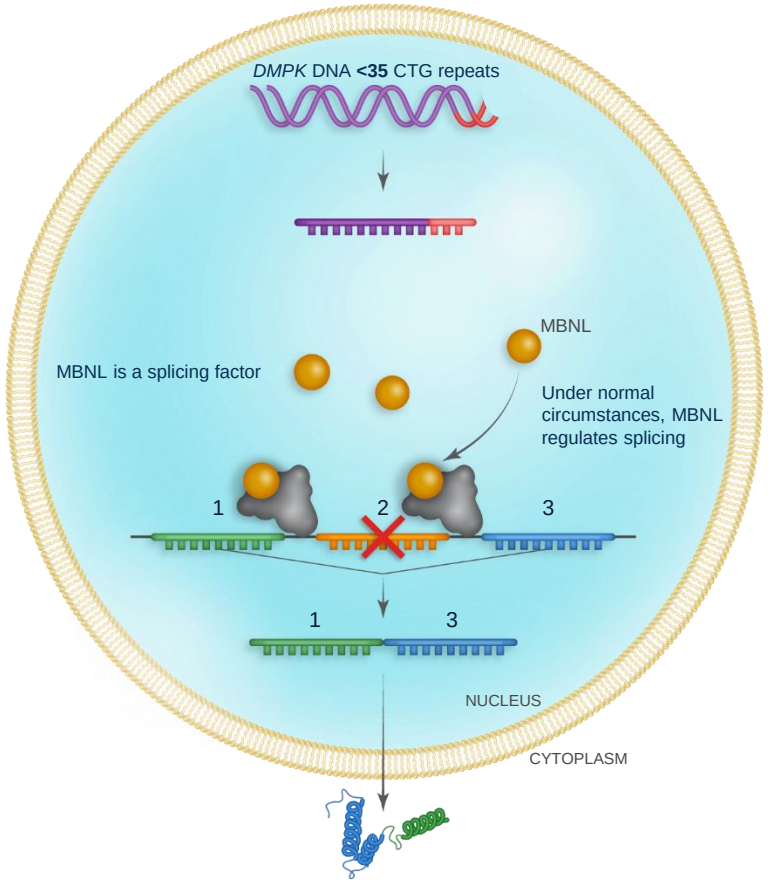
EMA, European Medicines Agency; FDA, Food and Drug Administration.

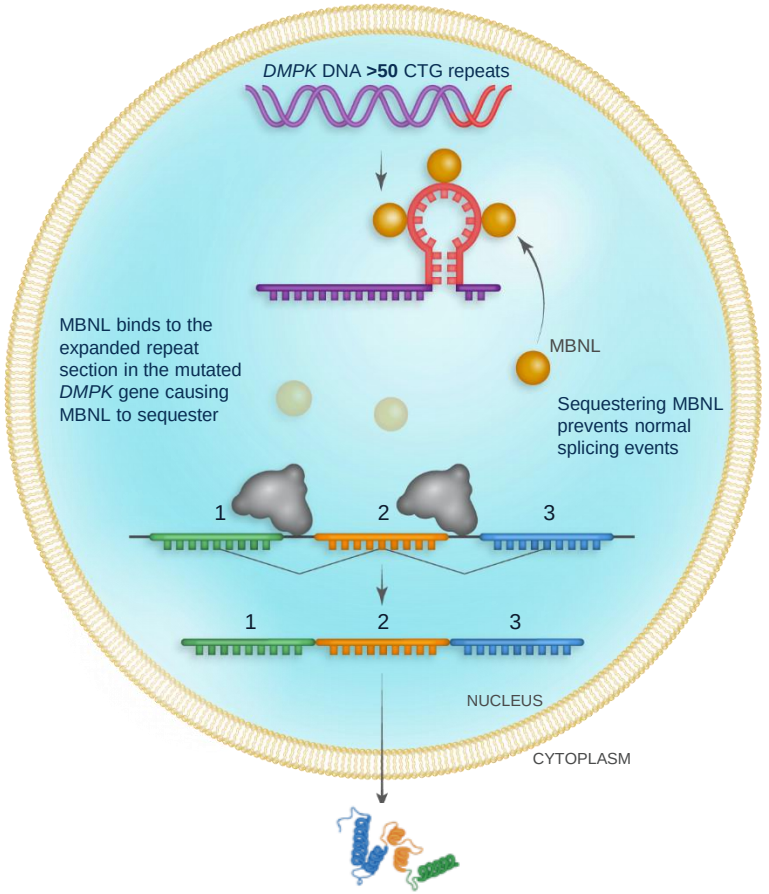
Spliceopathy in DM1 drives multi-system disease manifestations

Normal splicing



Normal splicing leads to **appropriate protein synthesis**

DM1 spliceopathy



Disrupted splicing **impairs** normal **protein synthesis**

Consequences of spliceopathy

Myotonia and muscle weakness

Cognitive impairment, fatigue, EDS

Cardiac conduction complications

Pulmonary abnormalities

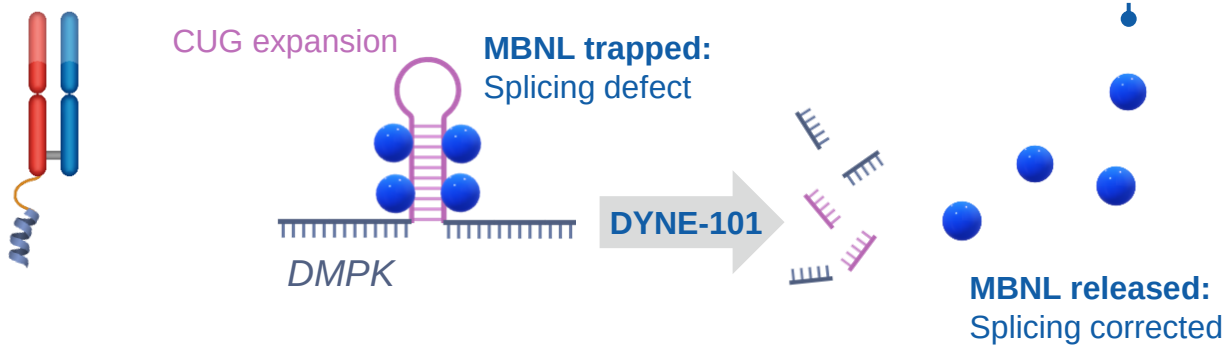
Abnormal splicing in **multiple tissues** causes symptoms of DM1

Goal of treatment: address the genetic cause of DM1 to correct splicing and enable functional improvement

CTG, cytosine, thymine and guanine; DM1, myotonic dystrophy type 1; DMPK dystrophia myotonica protein kinase; EDS, excessive daytime sleepiness; MBNL, muscleblind-like.

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**



DYNE-101

Differentiated MOA

Early effect on myotonia

Muscle strength:
Quantitative muscle testing

Functional outcomes:
10-meter walk/run;
5 times sit-to-stand

Patient-reported outcomes:
Myotonic Dystrophy Health Index (MDHI)

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Image depicts the intended DYNE-101 mechanism of action.
DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; MBNL, muscleblind-like; MOA, mechanism of action.

ACHIEVE trial of DYNE-101 in adults with DM1

Placebo-controlled period (MAD cohorts)

- **6.8 mg/kg** N=8 (3:1) Q8W with Booster, Placebo
- **5.4 mg/kg** N=8 (3:1) Q8W with Booster, Placebo
- **3.4 mg/kg** N=8 (3:1) Q8W with Booster, Placebo
- **3.4 mg/kg** N=16 (3:3:2) Q4W, Recovery, Placebo
- **1.8 mg/kg** N=16 (3:3:2) Q4W, Recovery, Placebo

Fully enrolled

Muscle biopsies at baseline, 12, and 24 weeks

Transition to 6.8 mg/kg[1]

Open-label extension (OLE)

Long-term extension (LTE)

Population

- Ages 18–49 years

Primary endpoints

- Safety and tolerability

Additional endpoints

- Pharmacokinetics
- Change from baseline of:
  - Splicing
  - *DMPK* RNA expression
  - Multiple assessments of muscle strength and function
  - Patient-reported outcomes, including MDHI

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, dystrophia myotonica protein kinase; MAD, multiple ascending dose; MDHI, Myotonic Dystrophy Health Index; Q4W, every 4 weeks; Q8W, every 8 weeks.

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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^2)	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)

BMI, body mass index; CASI, composite alternative splicing index; CTG, cytosine, thymine and guanine; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks; QMT, quantitative muscle testing; SD, standard deviation; sec, seconds; vHOT, video hand opening time.

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Favorable safety profile with no serious related TEAEs

Summary of treatment-emergent adverse events (TEAEs)[1]

TEAE category	Participants with ≥1 TEAE – n (%)					
	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	Overall (N=56)
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[1]

- **6 serious TEAEs unrelated to study drug**
  - Atrioventricular block first degree (1)[2]
  - Pneumonia (2 events in same participant)
  - Pulmonary embolism (1)[3]
  - Hyponatremia (1)
  - Influenza (1)
- **Most common TEAEs (≥20% participant incidence)[4]**
  - 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[1]

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.

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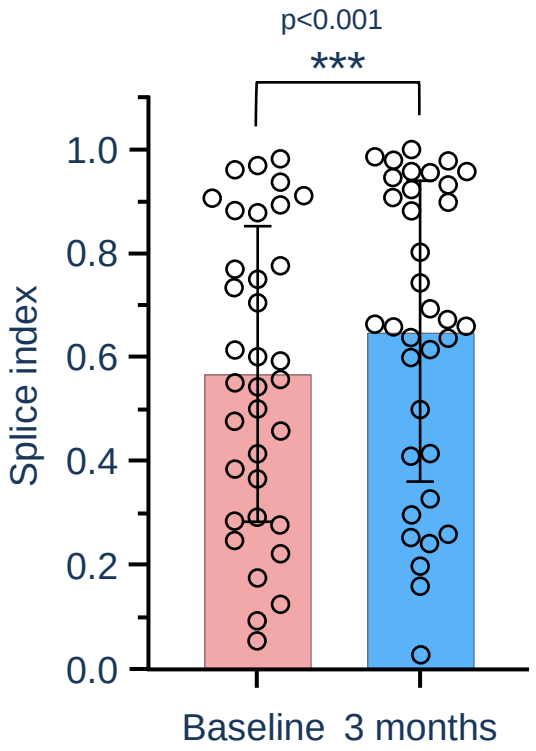
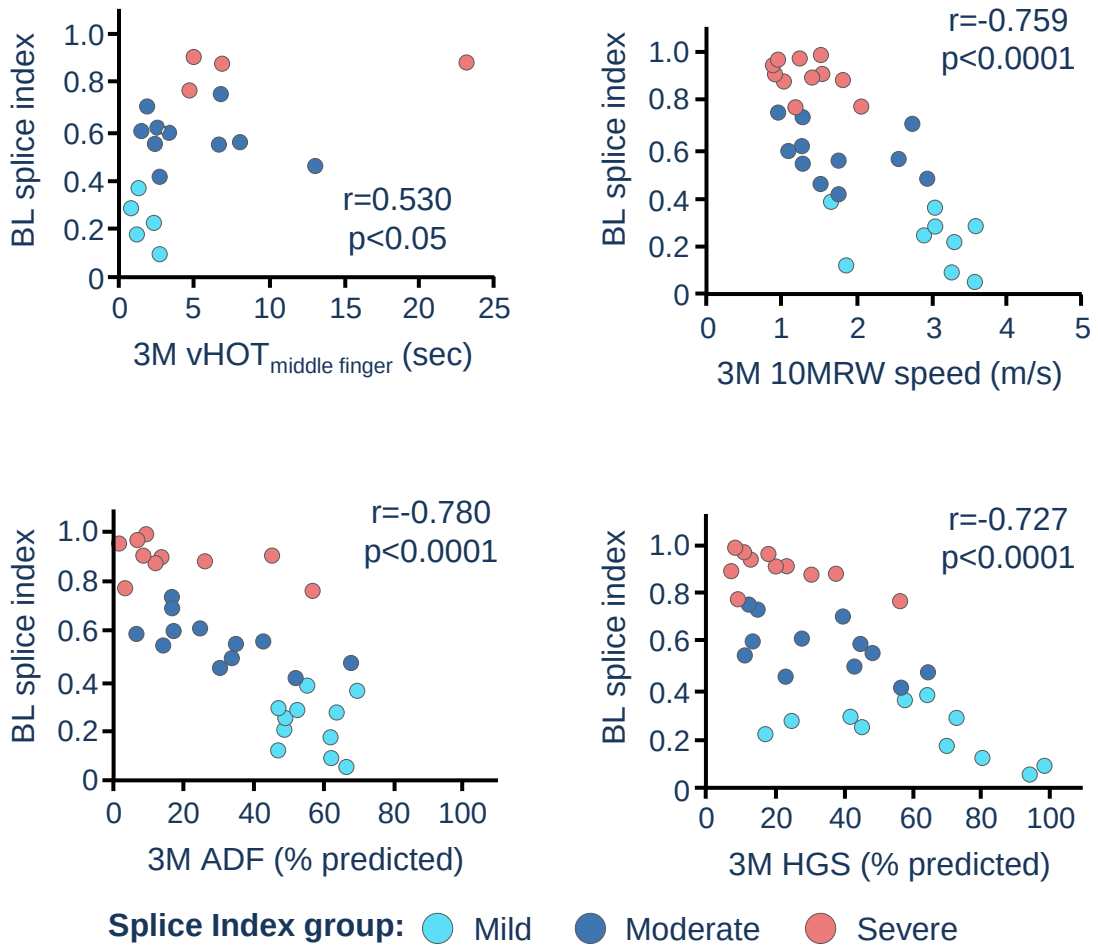
The Splice Index quantifies RNA splicing and is a prognostic biomarker that predicts clinical benefit in DM1

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



*Data represent mean ±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.

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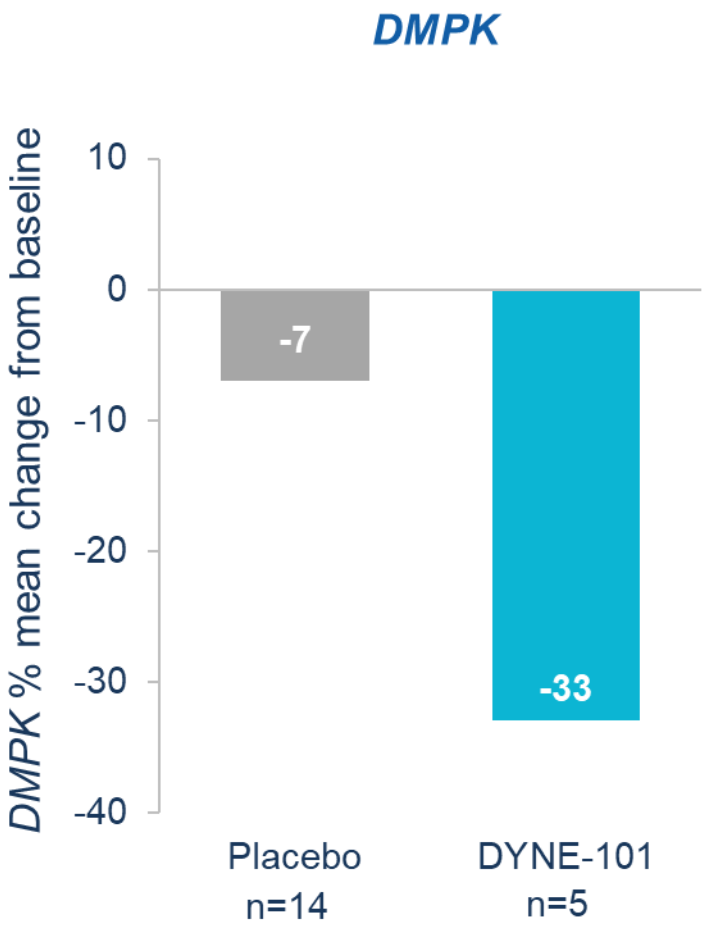
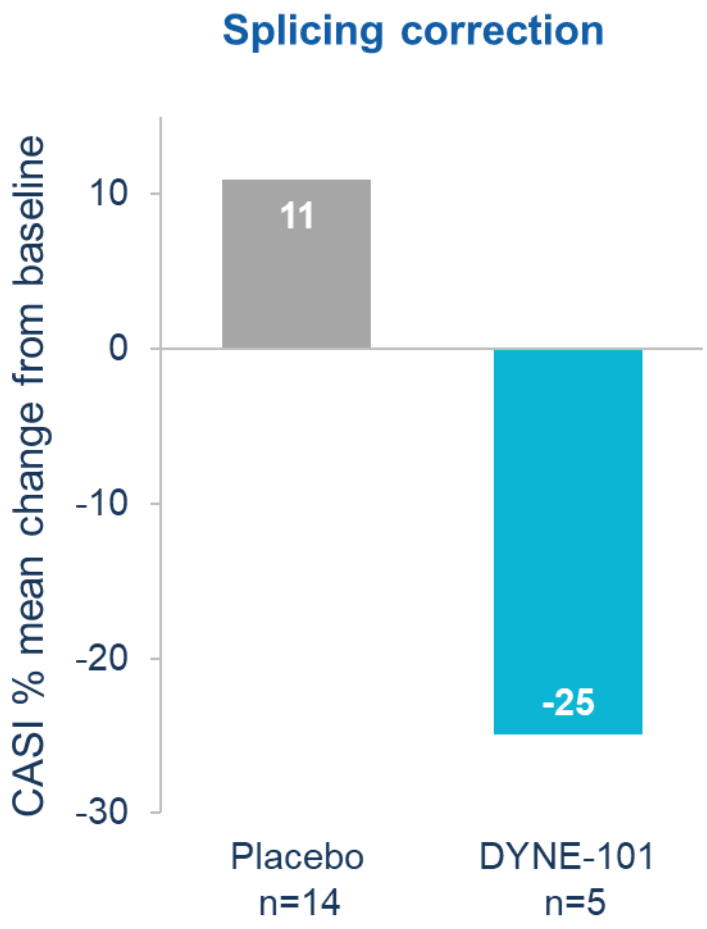
DYNE-101 at 6.8 mg/kg Q8W improved the foundational pathobiology of DM1 at 3 months





One baseline sample in 6.8 mg/kg treatment group not included as the sample did not meet quality control criteria. 3 months = 85 days.
CASI, composite alternative splicing index; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; Q8W, every 8 weeks.

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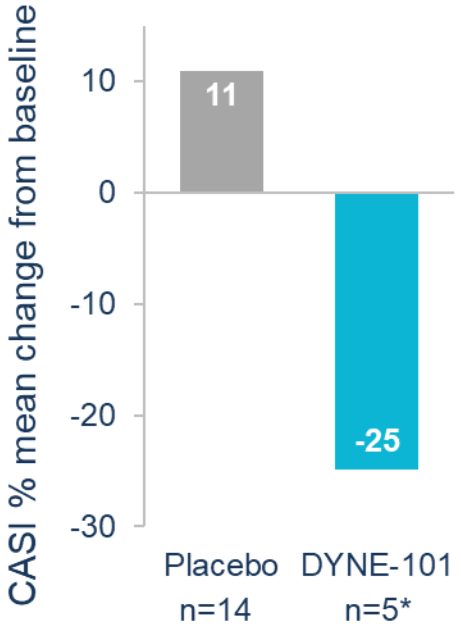
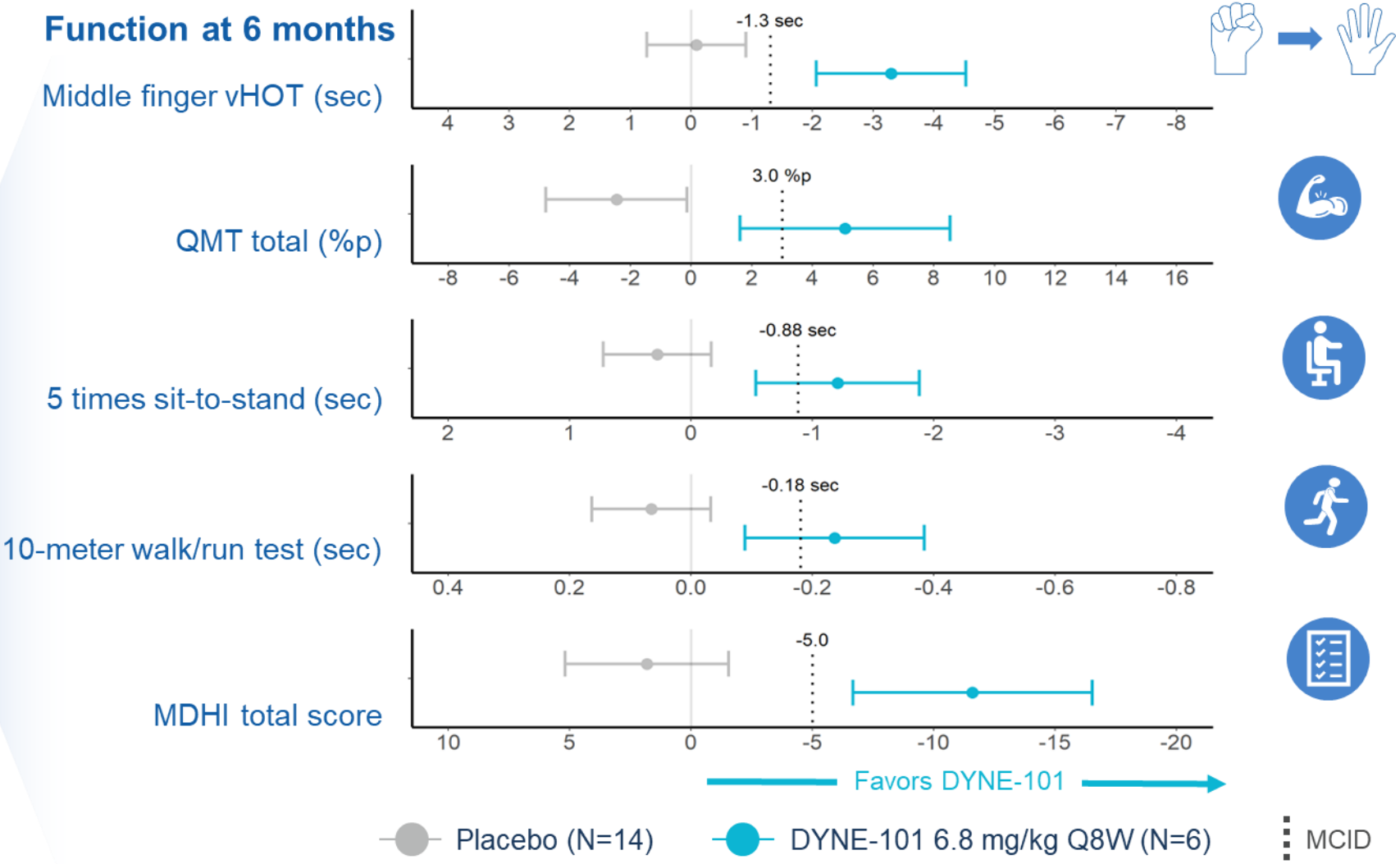
DYNE-101 demonstrates functional improvement in areas that are most impactful for patients[1]

CASI correction at 3 months



Function at 6 months



*One baseline sample in 6.8 mg/kg treatment group not included within splicing assay 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 ±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.

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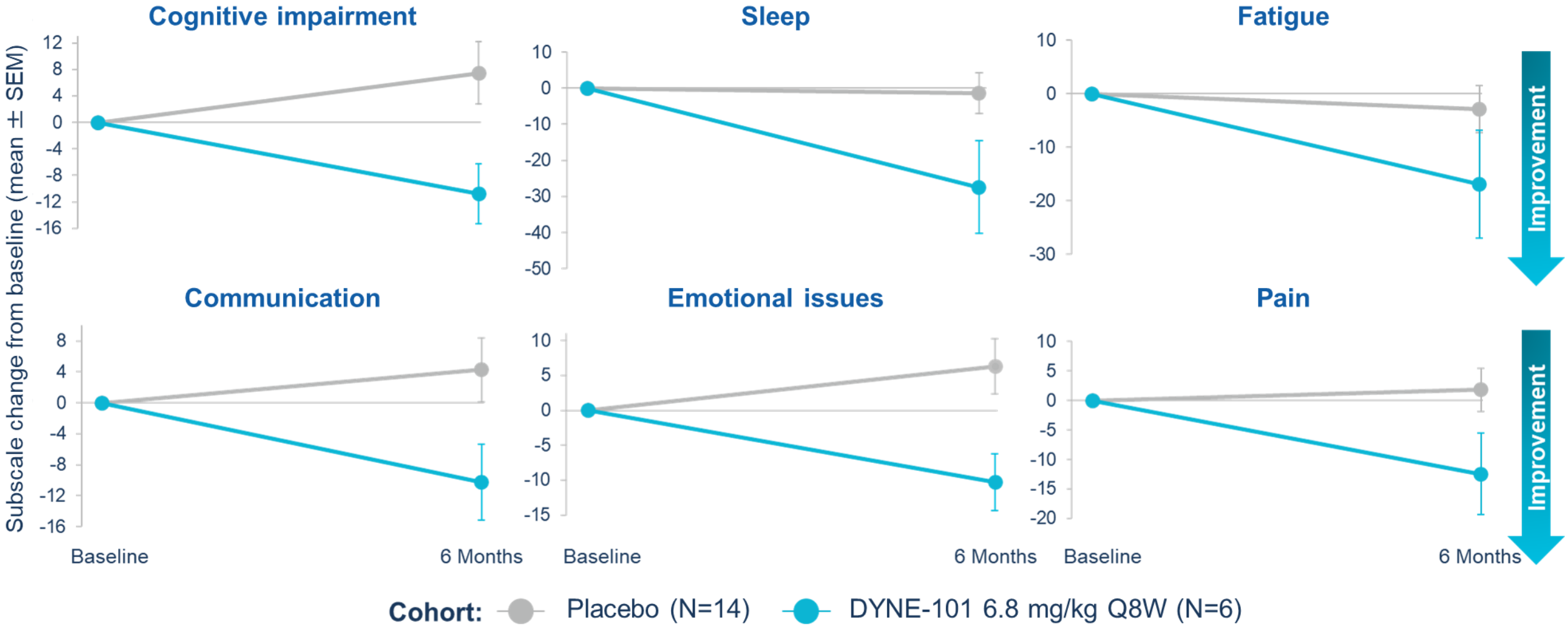
Improvement in CNS-related MDHI subscales



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

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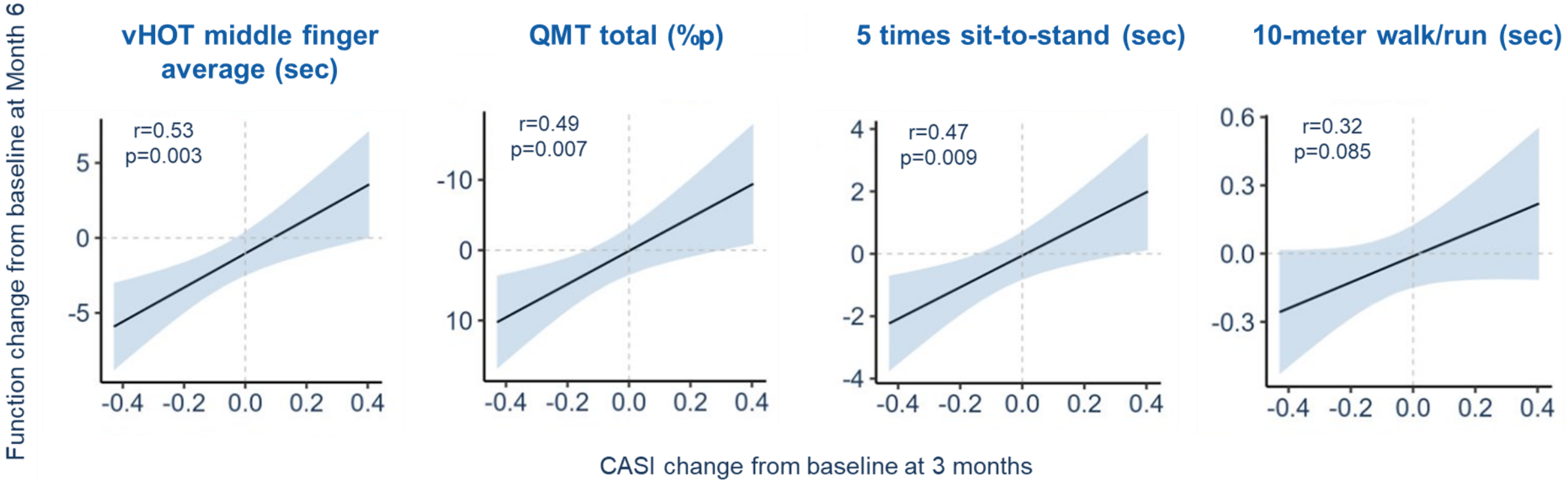
In ACHIEVE, splicing correction at 3 months predicted functional improvement at 6 months



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.

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Summary

- DYNE-101 is designed to target mutant nuclear *DMPK* RNA with the goal of correcting the abnormal splicing and enabling functional improvement in DM1[1,2]
- 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 functional improvement on measures of strength, mobility and quality of life, including CNS manifestations
  - Splicing correction at 3 months with DYNE-101 was predictive of functional improvement 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.

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Acknowledgements

ACHIEVE participants and their families

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