# Safety and Efficacy of DYNE-101 in Adults with DM1: Phase 1/2 ACHIEVE Trial Data

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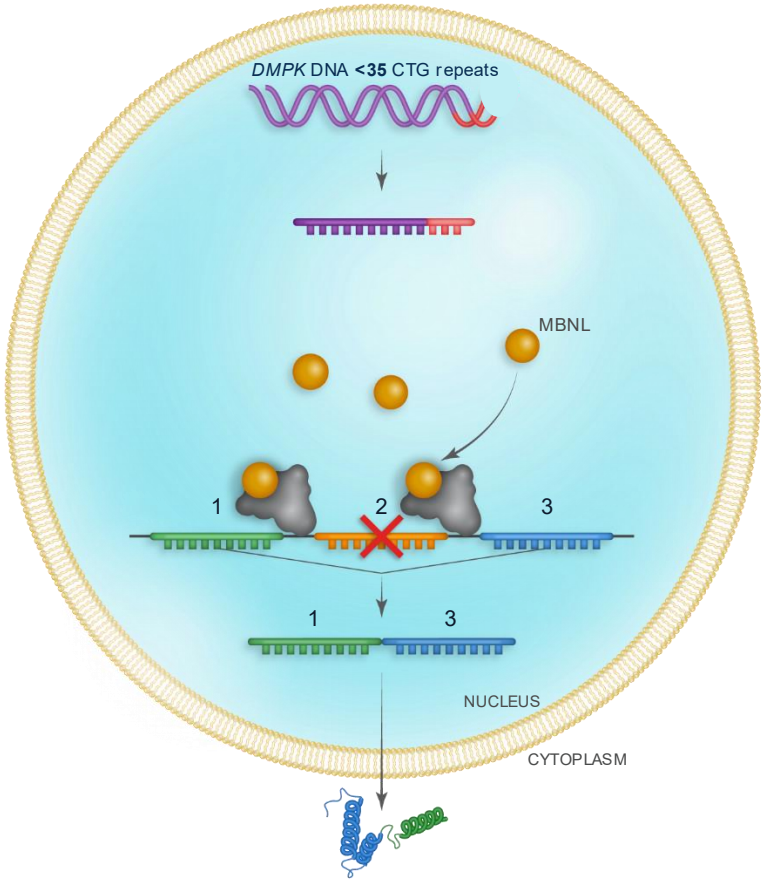
18th International Congress on Neuromuscular Diseases, October 26, 2024

# Disclosures

- I have received travel compensation from Dyne to attend this congress.
- DYNE-101 is an investigational medicine being evaluated in the ongoing ACHIEVE trial and has not received approval by FDA, EMA, or any other regulatory authorities

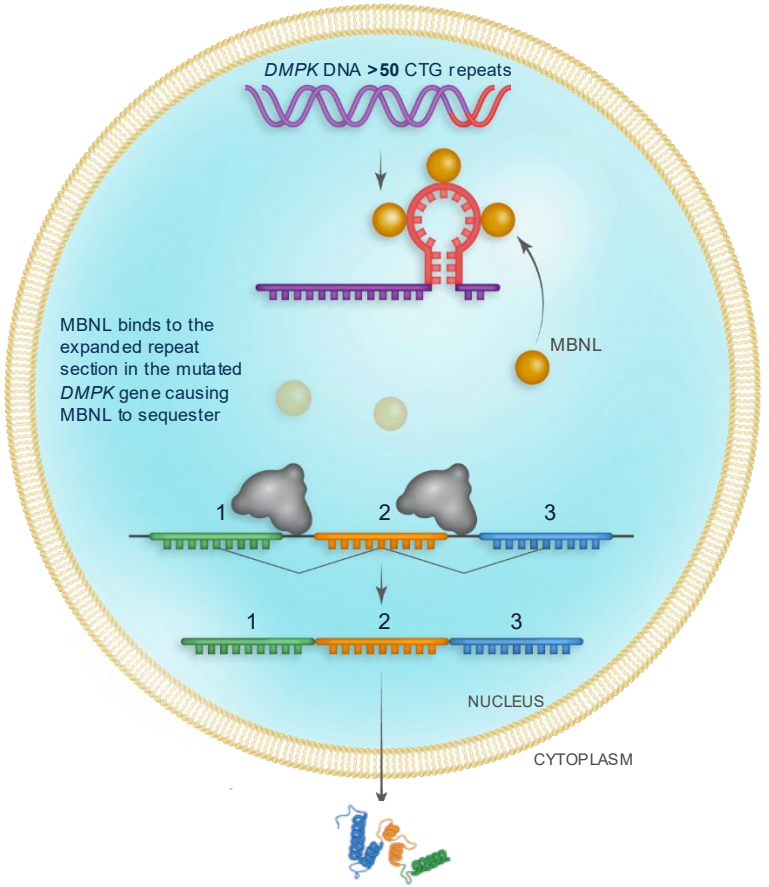
# Spliceopathy in DM1 Drives Multisystem Disease Manifestations

## NORMAL SPLICING



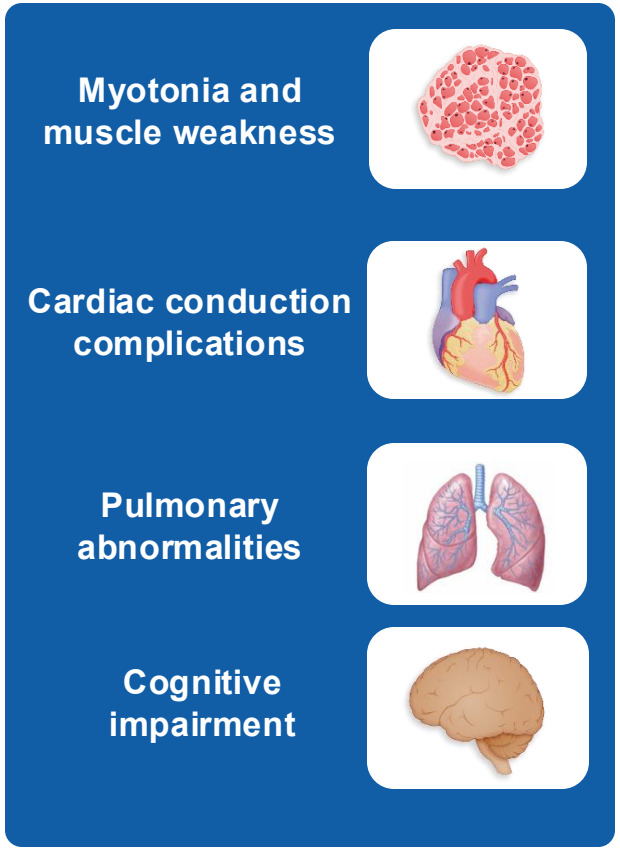

Normal splicing leads to **appropriate protein synthesis**

## DM1 SPLICEOPATHY




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

## CONSEQUENCES OF SPLICEOPATHY




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

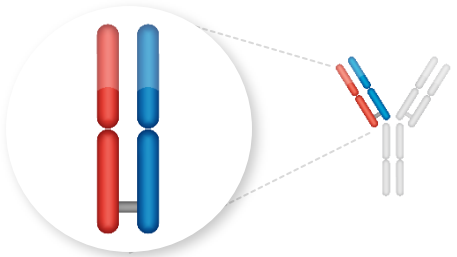
CTG, cytosine-thymine-guanine; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; MBNL, muscleblind-like.

Lopez-Martinez A, et al. *Genes (Basel)*. 2020;11:1109.

# FORCE™ Platform-based Oligonucleotide Therapeutics for Muscle Diseases

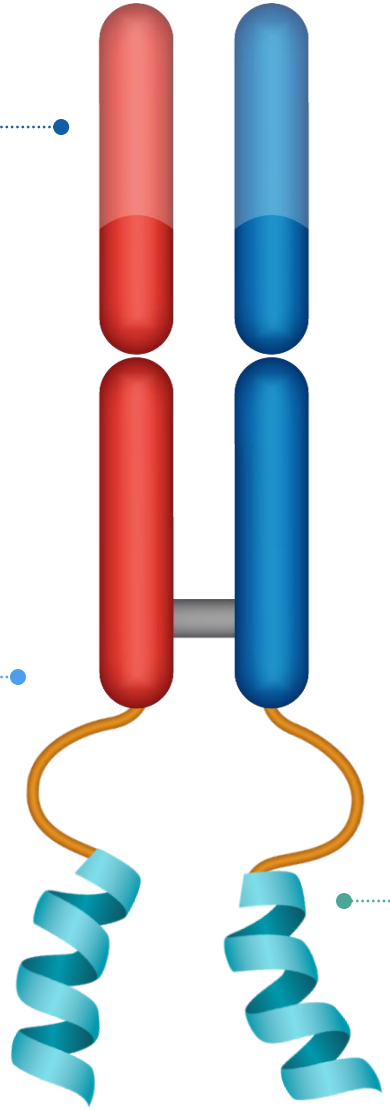
## ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



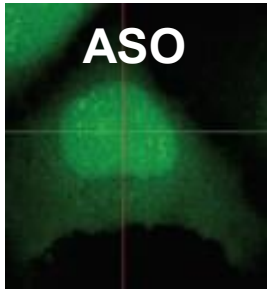
## LINKER

Enables precise conjugation of multiple payloads to a single Fab



## PAYLOAD

Modularity enables rational selection of payload to target the genetic basis of disease




Nuclear localization


Cytoplasmic localization

ASO, antisense oligonucleotide; Fab, antigen-binding fragment; siRNA, small interfering RNA; TfR1, transferrin receptor 1.
Adapted from Desjardins CA, et al. *Nucleic Acids Res* 2022;50(20):11401–11414 and Ohrt T, et al. *Nucleic Acids Res* 2006;34(5):1369.

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# DYNE-101 Targets Mutant Nuclear *DMPK* RNA

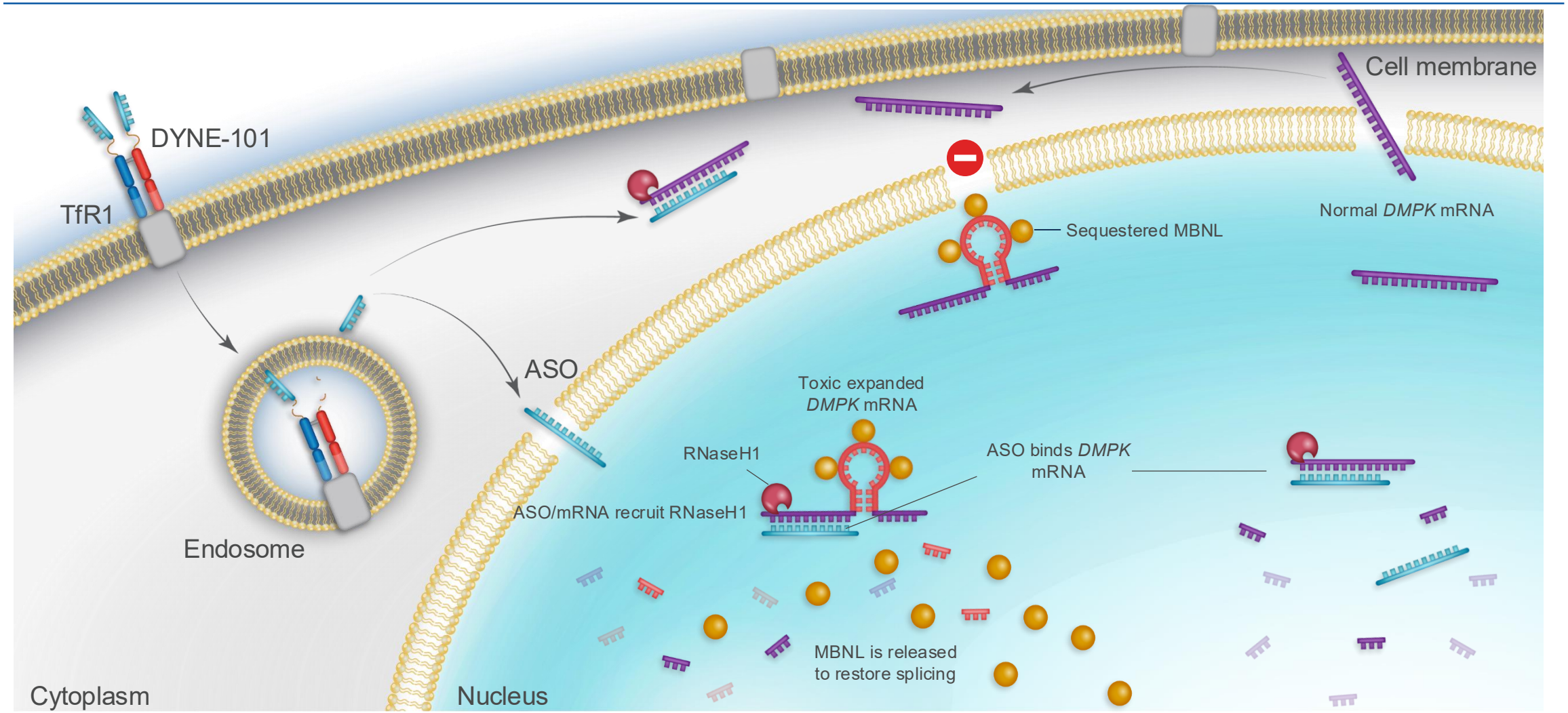


Image depicts intended mechanism of action of DYNE-101.

# Phase 1/2 Clinical Trial to Evaluate DYNE-101 in Patients with DM1

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## Population

- Adult patients living with DM1
- Ages 18 to 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 DM1-ACTIV$^{c}$ and MDHI

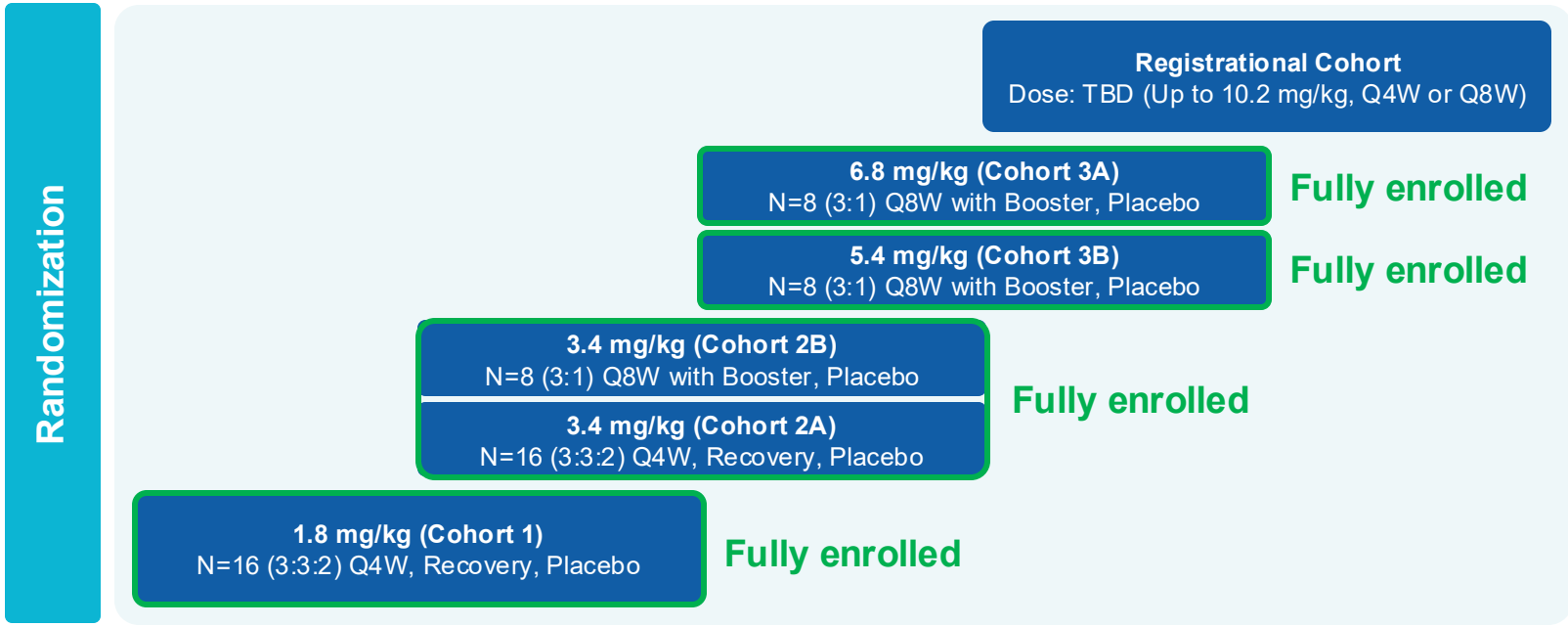
## Stages of ACHIEVE

- Multiple ascending dose (MAD): 24 weeks
- Open-label extension (OLE): 24 weeks
- Long-term extension (LTE): 96 weeks

Additional endpoints include select secondary and exploratory endpoints.
DM1-ACTIV$^{c}$, Myotonic Dystrophy type 1 Activity and participation scale; MDHI, Myotonic Dystrophy Health Index.
For more information visit the ACHIEVE clinical trial posting on ClinicalTrials.gov Identifier:NCT05481879 or clinicaltrialsregister.eu EudraCT Number:2022-000889-18.
Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P.

# ACHIEVE Trial Design – Multiple Ascending Dose (MAD)

Global, randomized, placebo-controlled study evaluating once monthly or less frequent administration of DYNE-101 in adult patients living with DM1




## MAD Study Details

- IV administration of DYNE-101 or placebo every 4 weeks or every 8 weeks
- Muscle biopsies: Baseline, 12 weeks, 24 weeks
- Patients in MAD study escalated to highest tolerable dose in OLE and LTE

MAD, multiple ascending dose; Q4W, every 4 weeks dosing; Q8W, every 8 weeks dosing; TBD, to be determined.
Doses provided refer to ASO component of DYNE-101. Recovery cohort Q4W × 2 doses then placebo for the remainder of the 24W placebo-controlled period. Q8W with booster includes Q4W × 3 doses then Q8W dosing. Study protocol allows for dosing up to 10.2 mg/kg.
Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P.

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# Baseline Participant Characteristics

| Mean (SD) or n (%)[1] | 1.8 mg/kg Q4W (N=16)* | 3.4 mg/kg Q4W (N=16)* | 5.4 mg/kg Q8W (N=8)† |
|---|---|---|---|
| Age (years) | 34.6 (10.4) | 34.3 (7.6) | 39.6 (7.0) |
| Female n (%) | 7 (43.8) | 3 (18.8) | 5 (62.5) |
| BMI (kg/m$^2$) | 22.4 (5.3) | 23.8 (3.8) | 21.7 (2.7) |
| CASI | 0.62 (0.26) | 0.67 (0.20) | 0.79 (0.14) |
| CTG Repeats | 375 (217) | 527 (241) | 586 (294) |
| Video Hand Opening Time (sec) (middle finger) | 11.2 (4.3) | 8.0 (5.7) | 10.1 (6.2) |
| Quantitative Muscle Testing Total (% predicted) | 49.6 (10.9) | 47.8 (10.6) | 45.8 (16.1) |
| 10-Meter Run/Walk Test (sec)[2] | 3.5 (0.8) | 3.6 (0.7) | 4.7 (2.1) |
| 5 Times Sit to Stand (sec) | 9.33 (2.02) | 10.05 (3.03) | 12.28 (5.96) |
| DM1-ACTIV$^c$ Total | 43 (7) | 42 (7) | 44 (6) |
| MDHI Total | 25 (20) | 25 (20) | 16 (9) |

*Q4W, recovery, and placebo arms are reported together for baseline characteristics. †Q8W and placebo arms are reported together for baseline characteristics.
BMI, body mass index; CASI, composite alternative splicing index; MDHI, Myotonic Dystrophy Health Index; SD, standard deviation; sec, seconds.
1. Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P; 2. Dyne Corporate presentation. September 2024.

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# DYNE-101 Safety Profile is Favorable to Date

## 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%) | 7 (88%) | 55 (98%) |
| Any related TEAE | 8 (50%) | 8 (50%) | 2 (25%) | 3 (38%) | 5 (63%) | 26 (46%) |
| Any serious TEAE | 4 (25%) | 0 | 1 (13%) | 0 | 0 | 5 (9%) |

## Most TEAEs Were Mild or Moderate in Intensity[1]

- **6 serious TEAEs unrelated to study drug**
  - Atrioventricular block first degree (1)†
  - Pneumonia (2 events in same participant)
  - Pulmonary embolism (1)‡
  - Hyponatremia (1)
  - Influenza (1)
- **Most common TEAEs (≥20% participant incidence)** §
  - Nasopharyngitis (32%)
  - Procedural pain (29%)
  - Infusion-related reaction (21%)

## Additional Safety Data[1]

- **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 ~2.5 × greater than the upper limit of normal
- **No participants have demonstrated persistent related anemia or thrombocytopenia**
- **There have been no serious related TEAEs, and no TEAEs leading to withdrawal or death**

**~680 doses administered to date representing over 55 patient-years of follow-up*[2]**

*Data as of August 20, 2024. †Transient worsening of atrioventricular (AV) block in a participant with ongoing medical history of first-degree AV block;
‡Attributed to risk factors for pulmonary embolism; § All cohorts combined, preferred terms are reported. Rec, recovery.
1. Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P; 2. Dyne Corporate presentation. September 2024.

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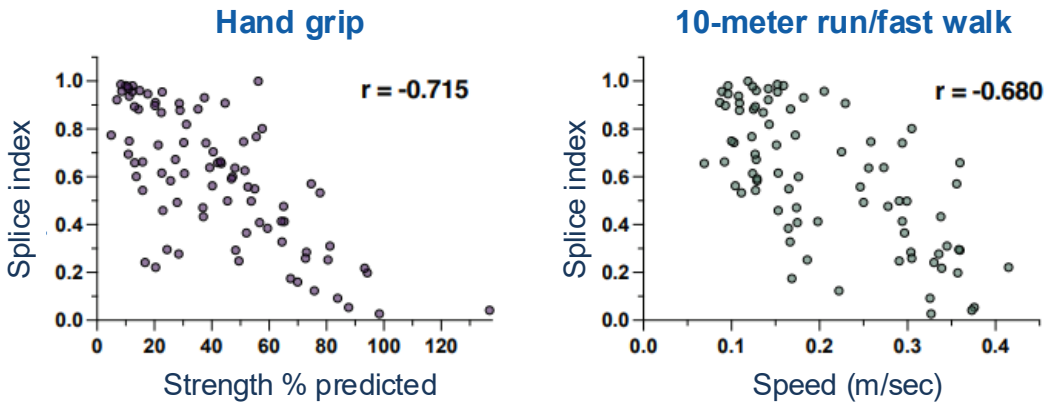
# Composite Alternative Splicing Index is a Prognostic Biomarker of Functional Outcomes in DM1

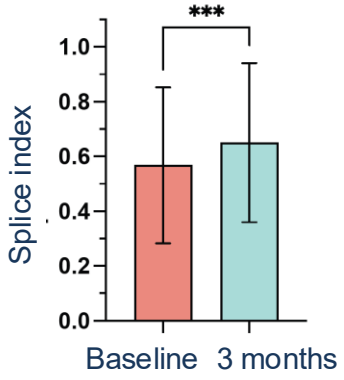
## CASI quantifies RNA missplicing across a panel of 22 genes implicated in the pathophysiology of DM1[1–4]

| Role in DM1 | Number of Genes |
|---|---|
| Muscle weakness and/or altered contraction and relaxation[1,2] | 8 |
| Aberrant mRNA splicing[1,2] | 2 |
| Insulin resistance[1,2] | 1 |
| Undefined, regulated by MBNL[1,5] | 11 |

## Natural history data support a strong correlation between CASI and muscle function (N=95)[4]




## Worsening in CASI is observed in as little as 3 months in the natural history cohort (N=35)*[4]




*Data represent mean ± standard deviation; ***p<0.001 by paired t-test.

1. Wang W. 2017. University of Rochester School of Medicine and Dentistry PhD thesis. Available at http://hdl.handle.net/1802/32572 (accessed August 2024); 2. López-Martínez A, et al. *Genes (Basel)*. 2020;11:1109; 3. Mikhail AI, et al. *Trends Mol Med* 2023;29:512–529; 4. Provenzano M, et al. *bioRxiv*. 2024. Available at: https://www.biorxiv.org/content/10.1101/2024.07.10.602610v1 (accessed August 2024); 5. Gene functions from AmiGO 2. Available at: https://amigo.geneontology.org/amigo (accessed August 2024).

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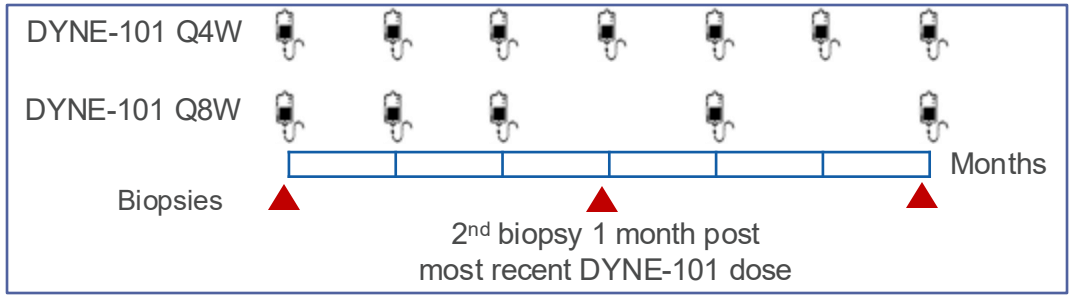
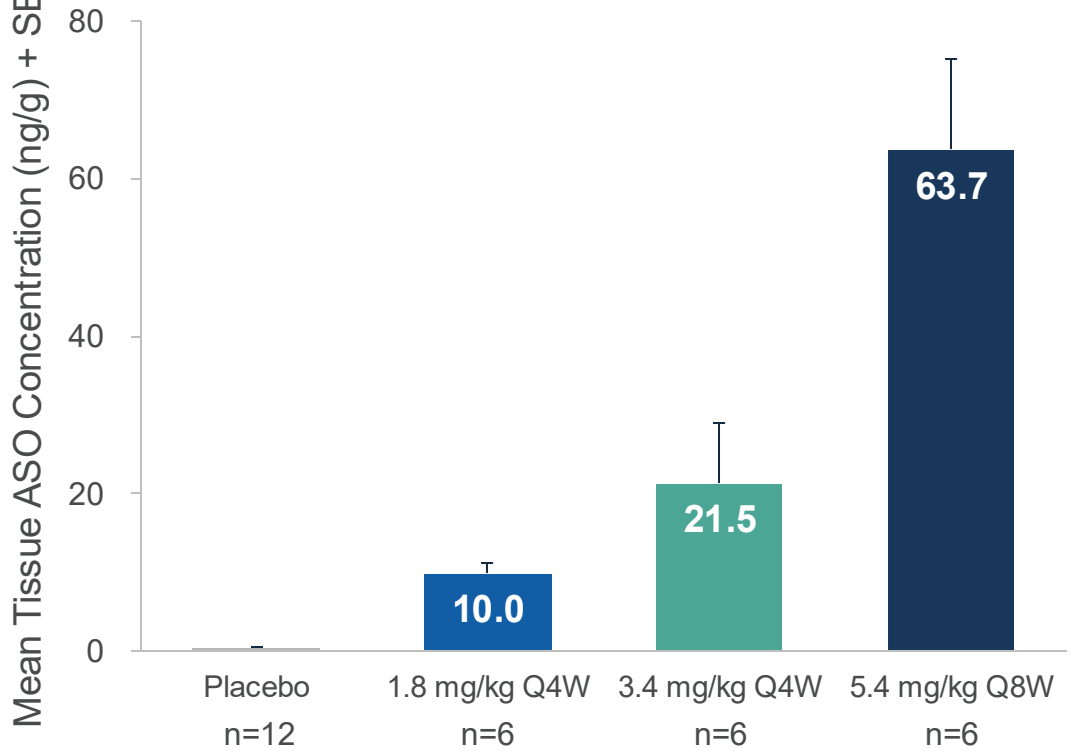
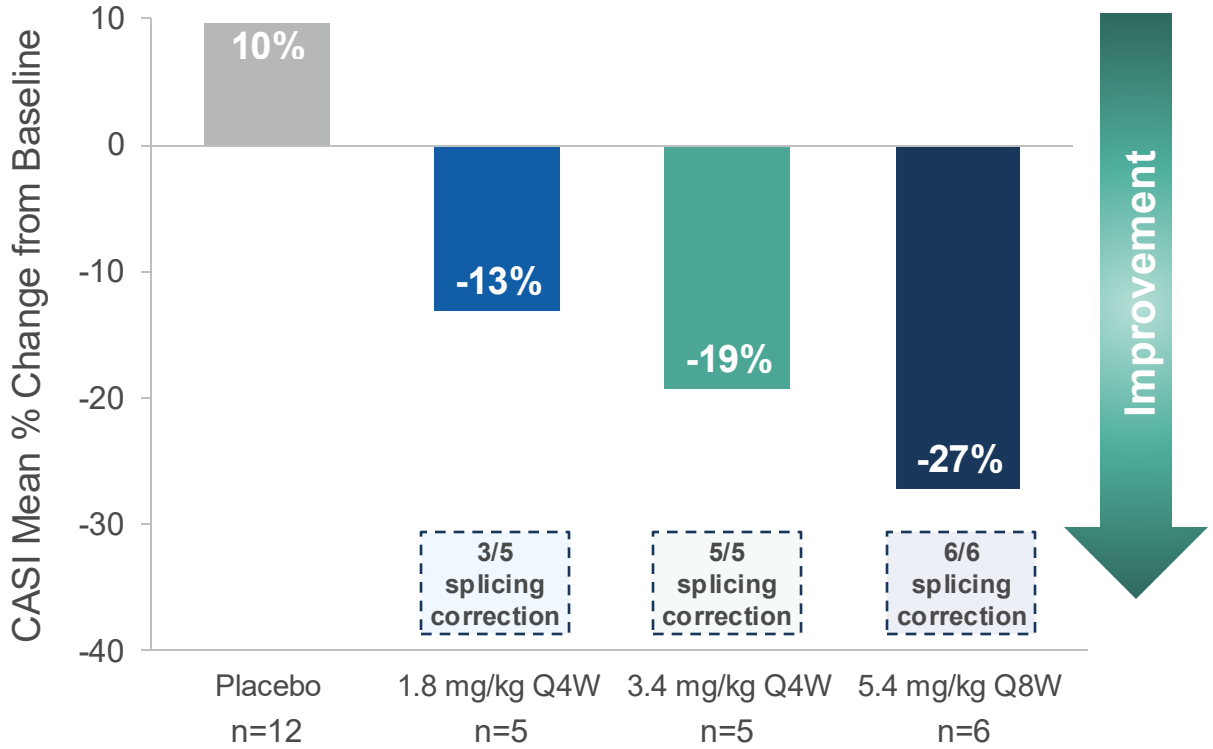
# Monthly Dosing of DYNE-101 Demonstrated Dose-dependent Delivery and Consistent Splicing Correction at 3 Months




## ASO Muscle Concentration




## CASI-22




One post-baseline sample in 3.4 mg/kg Q4W treatment group not included within splicing assay as the sample did not meet QC criteria.
SEM, standard error of mean.
Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P.

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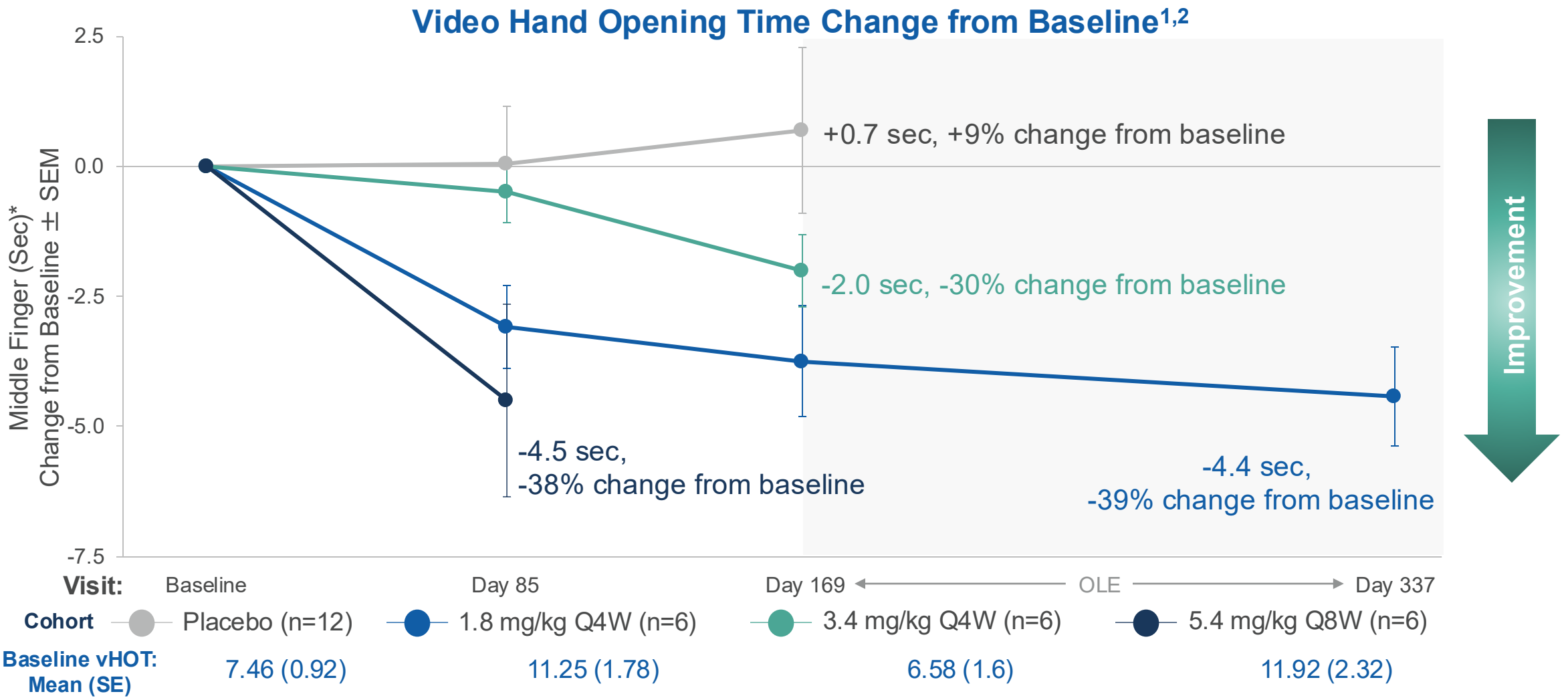
# Treatment with DYNE-101 Resulted in Continued Improvement in Functional Myotonia at 6 and 12 Months




*Middle finger (sec) is the average of all myotonia trials for an individual participant in ACHIEVE.
Note: Placebo group includes 12 participants at Day 85 and 8 participants at Day 169. Mean percent change from baseline for placebo group are based on baseline values from 12 patients.
sec, seconds; SE, standard error.
1. Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P; 2. Dyne Corporate presentation. September 2024.

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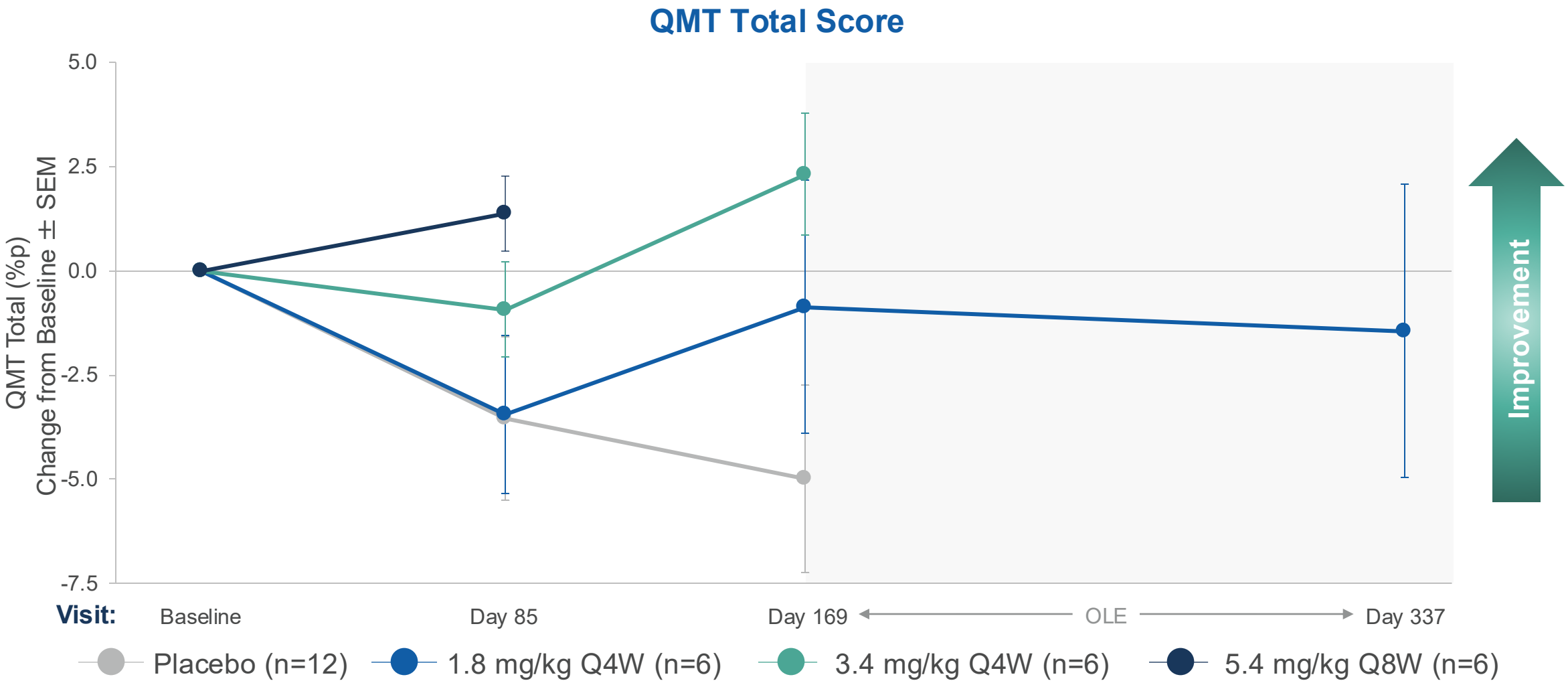
# DYNE-101 Demonstrated Improvement in Muscle Strength
## Measured by Quantitative Muscle testing (QMT)




Note: Mean percent change from baseline for placebo group is based on baseline values from 12 patients. Placebo group includes 12 participants at Day 85 and 8 participants at Day 169.
Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P.

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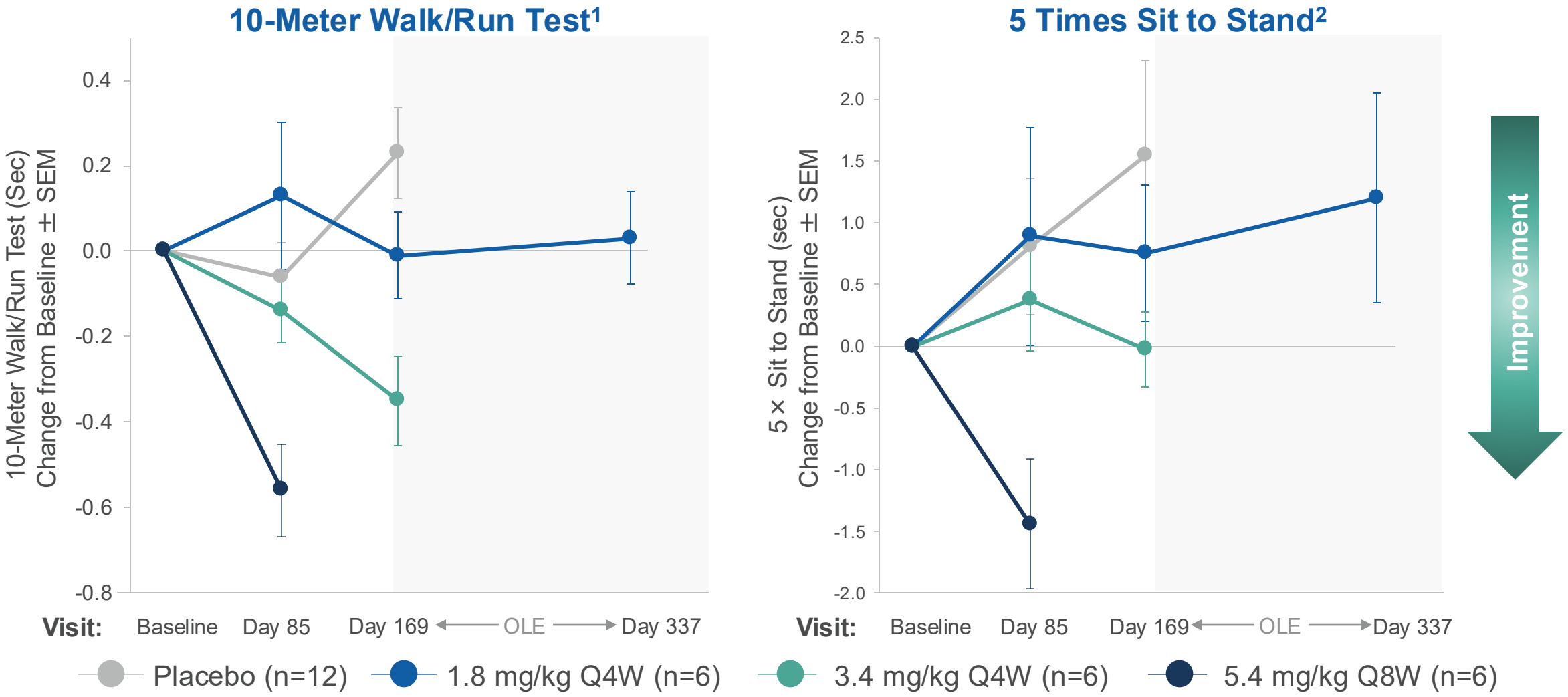
# DYNE-101 Demonstrated Early and Sustained Potential Benefit Across Multiple Timed Function Tests




Note: Mean percent change from baseline for placebo group is based on baseline values from 12 patients. Placebo group includes 12 participants at Day 85 and 8 participants at Day 169.

1. Dyne Corporate presentation. September 2024; 2. Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P.

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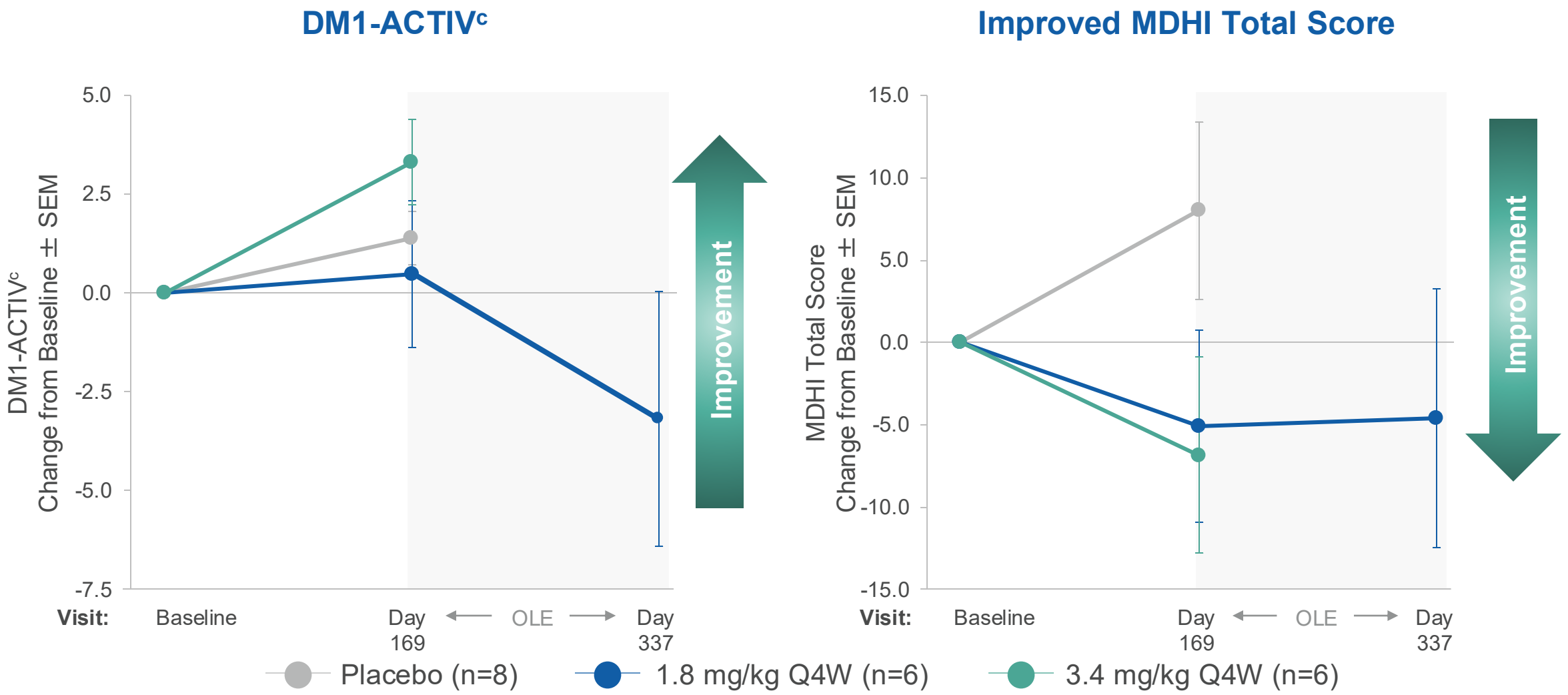
# DYNE-101 Demonstrated Clinical Benefit Based on Well-validated PROs




PROs, including DM1-ACTIVc and MDHI collected at baseline, Day 169 and Day 337.
Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P.

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# Summary

- **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**[1,2]
- The Phase 1/2 **ACHIEVE** trial is an ongoing, randomized, placebo-controlled global trial of DYNE-101 in adults with DM1 aged 18–49 years. In the MAD portion of ACHIEVE:[3]
  - DYNE-101 was **well tolerated**
  - DYNE-101 was **delivered** effectively to **skeletal muscle**
  - DYNE-101 showed **dose-dependent** and **consistent splicing correction**
  - DYNE-101 led to **early improvements** in **multiple functional endpoints**
  - DYNE-101 led to **improvements** in well validated **patient-reported outcomes**

1. López-Martínez A, et al. *Genes (Basel)*. 2020;11:1109; 2. Zanotti S. Presentation at the 26th American Society of Gene and Cell Therapy Annual Meeting. May 17, 2023. Los Angeles, USA. Abstract 82; 3. Wolf D, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P.

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# Acknowledgements

## ACHIEVE participants and their families


Dyne THERAPEUTICS

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For more information visit the ACHIEVE clinical trial posting ClinicalTrials.gov ClinicalTrials.gov Identifier:NCT05481879 or clinicaltrialsregister.eu EudraCT Number:2022-000889-18.