Initial Data from the ACHIEVE Trial of DYNE-101 in Adults with Myotonic Dystrophy Type 1 (DM1)

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Disclosures

- I have received consulting fees and participated on a Data Monitoring Safety Board or Advisory Board for Arrowhead Pharmaceuticals, Avidity Biosciences, BioMarin Pharmaceutical, Dyne Therapeutics, Facio Biotherapies, Fulcrum Therapeutics, PepGen, Teva Pharmaceuticals, and Vertex Pharmaceuticals.

- 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.

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Acknowledgements

ACHIEVE participants and their families

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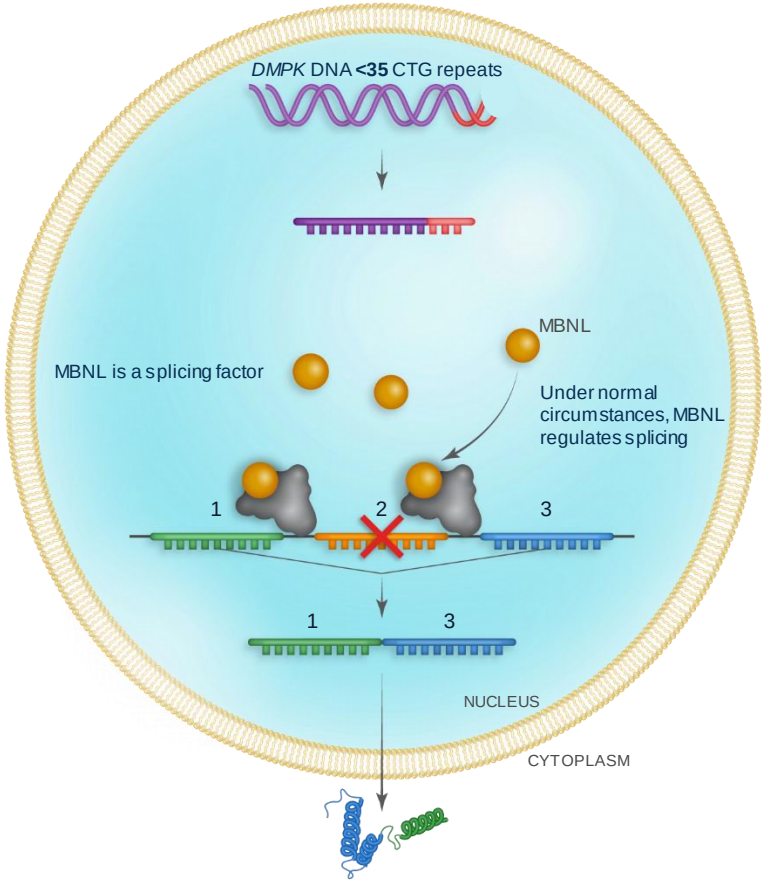
For more information visit the ACHIEVE clinical trial posting ClinicalTrials.gov ClinicalTrials.gov Identifier:NCT05481879 or clinicaltrialsregister.eu EudraCT Number:2022-000889-18.

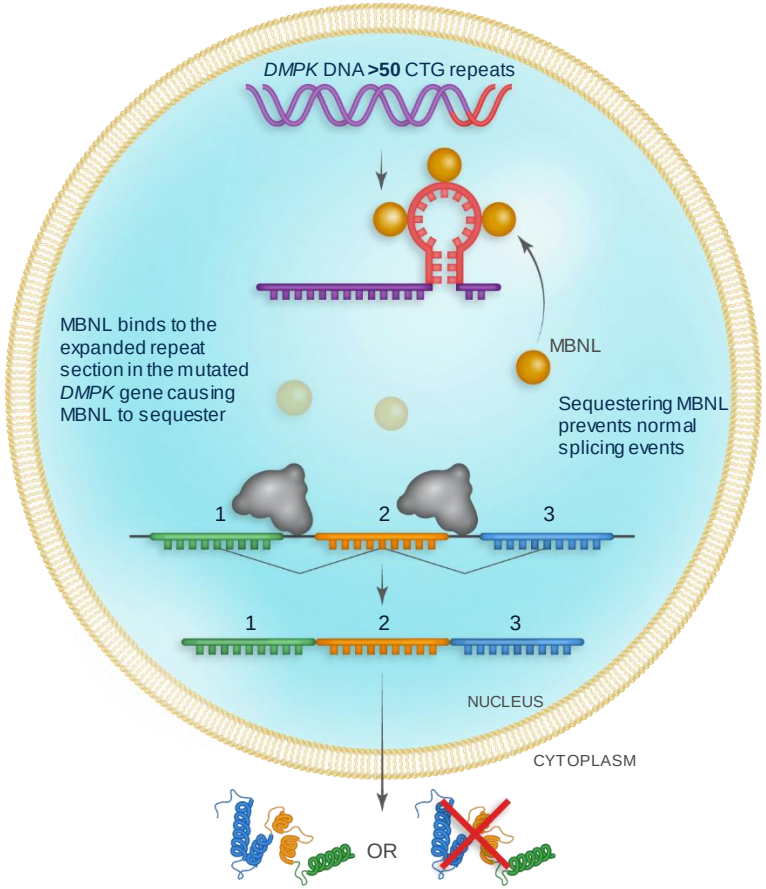
Spliceopathy in DM1 Drives the Multisystem Disease Manifestations

NORMAL SPLICING



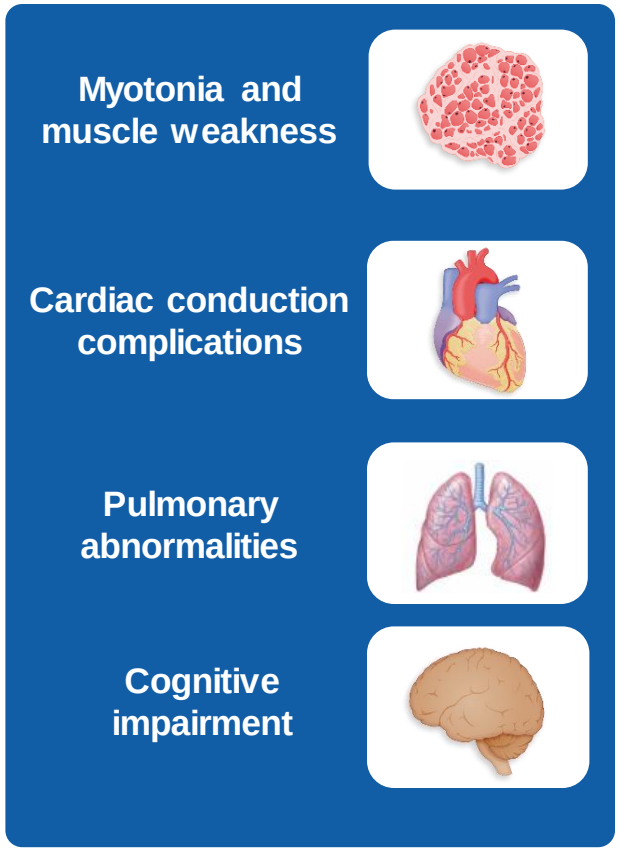
Normal splicing leads to **appropriate protein synthesis**

DM1 SPLICEOPATHY



Abnormal splicing may either **reduce protein synthesis,** or **production dysfunctional proteins**

CONSEQUENCES OF SPLICEOPATHY



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

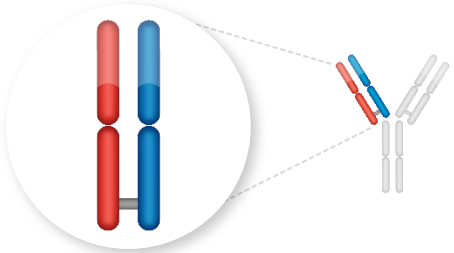
Goal of Treatment: Address the Genetic Cause of DM1 to Correct Splicing and Improve Function

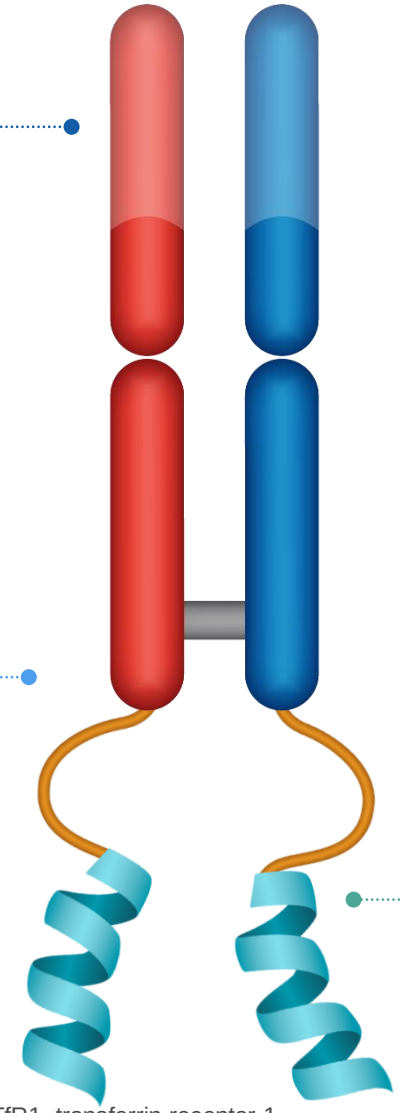
CTG, cytosine-thymine-guanine; DM1, myotonic dystrophy type 1; DMPK dystrophia myotonica protein kinase; MBNL, muscleblind-like.

FORCE™ Platform-Based Oligonucleotide Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



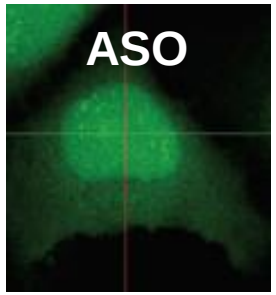


LINKER

Clinically validated, 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 Ohrt T., et al. *Nucleic Acids Res* 2006;34:1369.

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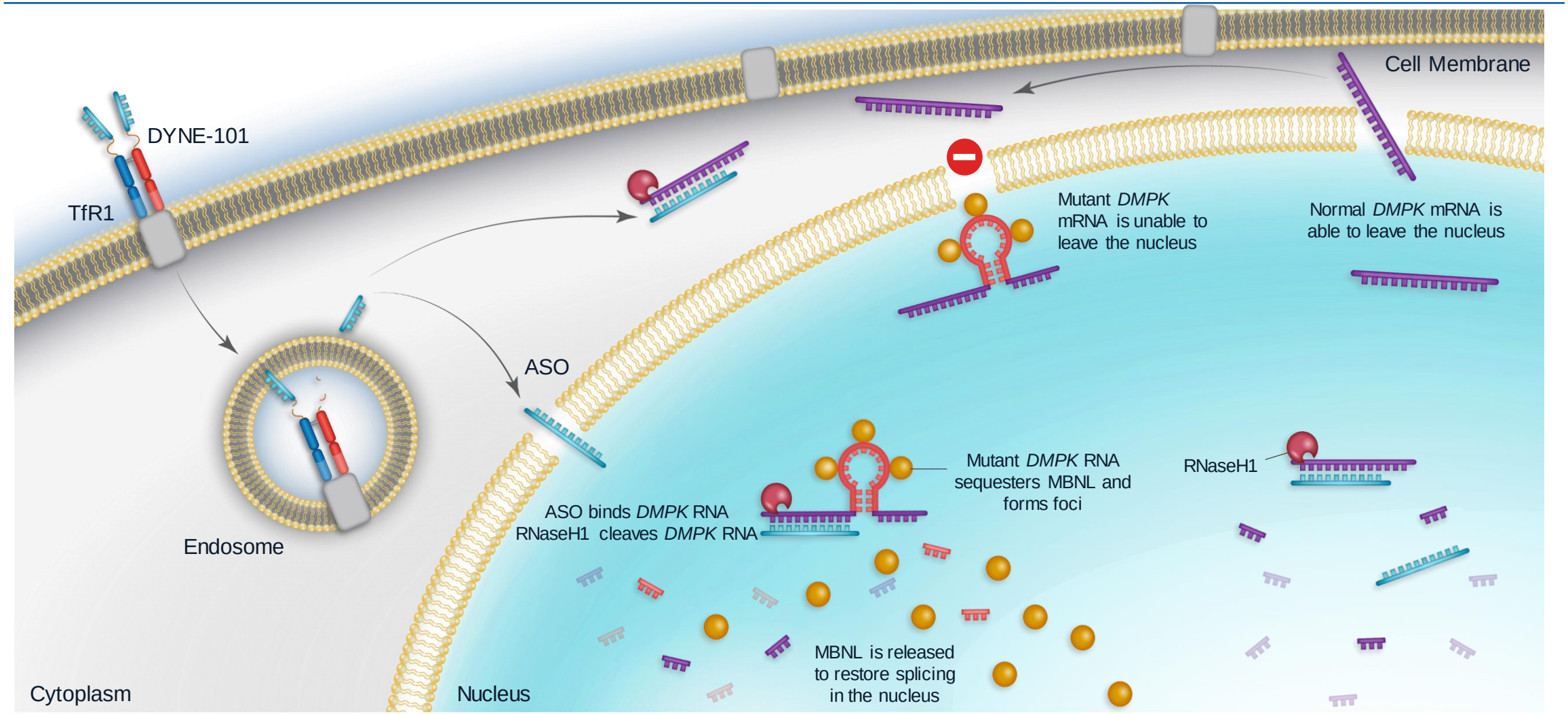
DYNE-101 Is Designed to Target Mutant Nuclear *DMPK* RNA to Correct Splicing



ASO, antisense oligonucleotide; DMPK, dystrophia myotonica protein kinase; MBNL, muscleblind-like; TfR1, transferring receptor 1.
Image depicts intended mechanism of action of DYNE-101.

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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

Key Secondary

- Pharmacokinetics
- Change from baseline of:
  - Splicing index (CASI-22)
  - *DMPK* RNA expression
  - Multiple assessments of muscle strength and function

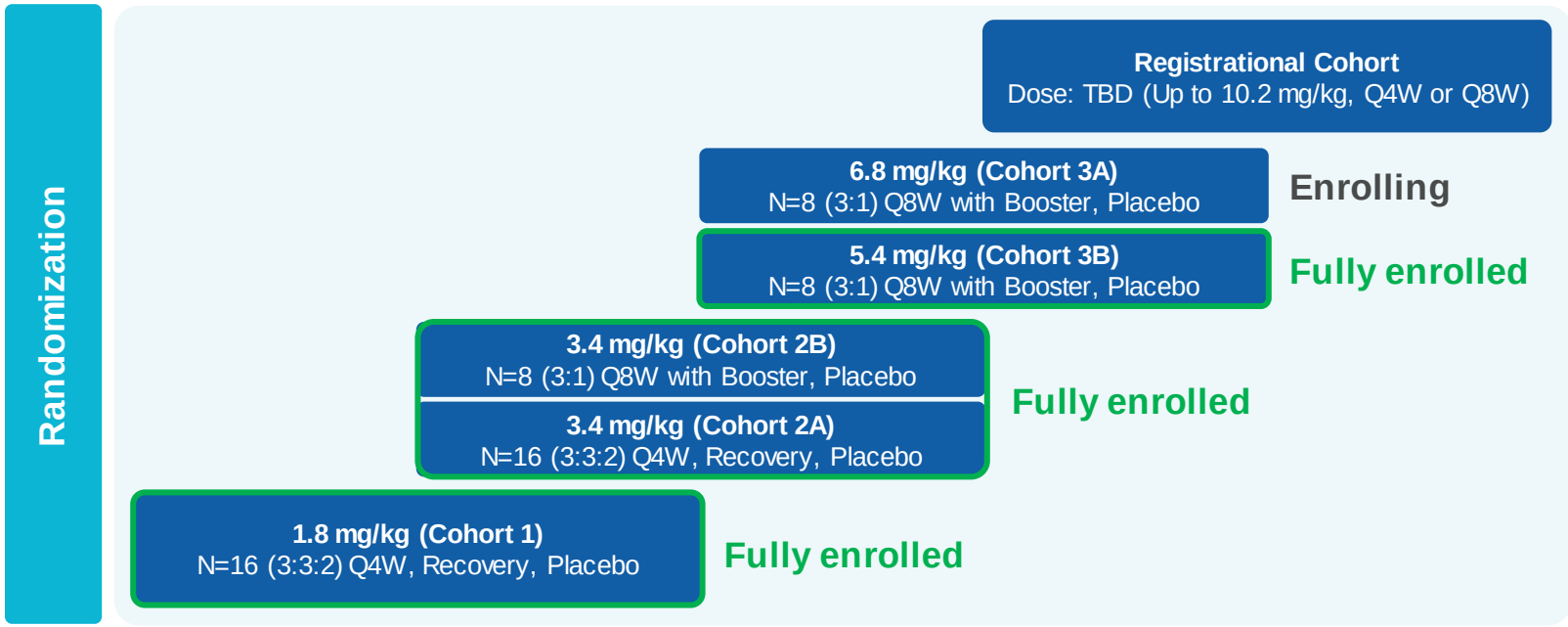
Stages of ACHIEVE

- Multiple Ascending Dose (MAD): 24 weeks
- Open-Label Extension (OLE): 24 weeks
- Long-Term Extension (LTE): 96 weeks

DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase.
For more information visit the ACHIEVE clinical trial posting on ClinicalTrials.gov Identifier:NCT05481879 or clinicaltrialsregister.eu EudraCT Number:2022-000889-18.

ACHIEVE Trial Design

Global, Randomized, Placebo-Controlled Stage 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

Global Strategy & Adaptive Trial Design To Enable Rapid Achievement of Potentially Registrational Clinical Data

DM1, myotonic dystrophy type 1; LTE, long-term extension; MAD, multiple ascending dose; OLE, open-label extension; Q4W, every 4 weeks dosing.
Doses provided refer to ASO 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. Study protocol allows for dosing up to 10.2 mg/kg.
For more information visit the ACHIEVE clinical trial posting on ClinicalTrials.gov ClinicalTrials.gov Identifier:NCT05481879 or clinicaltrialsregister.eu EudraCT Number:2022-000889-18.

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Baseline Participant Characteristics

	Cohort 1 1.8 mg/kg (N=16)[1]	Cohort 2A 3.4 mg/kg (N=16)[1]
Age (years) (mean (SD))	34.6 (10.4)	34.3 (7.6)
Female (n (%))	7 (43.8%)	3 (18.8%)
BMI (kg/m^2) (mean (SD))	22.4 (5.3)	23.8 (3.8)
CASI (mean (SD))	0.62 (0.26)	0.67 (0.20)
CTG Repeats (mean (SD))	375 (217)	527 (241)
vHOT (sec) (middle finger average) (mean (SD))	11.2 (4.3)	8.0 (5.7)
MDHI Total (mean (SD))	25 (20)	25 (20)

BMI, body mass index; CASI, composite alternative splicing index; CTG, cytosine-thymine-guanine; MDHI, myotonic dystrophy health index; SD, standard deviation; vHOT, video hand opening time.
1. Q4W, recovery, and placebo arms are reported together for baseline characteristics.

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DYNE-101 Safety Profile Is Favorable to Date

Summary of Treatment Emergent Adverse Events (TEAEs) – Placebo-Controlled Period[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=5	Overall (N=45)
Any TEAE	16 (100%)	13 (81%)	5 (63%)	1 (20%)	35 (78%)
Any related TEAE	6 (38%)	6 (38%)	0	1 (20%)	13 (29%)
Any serious TEAE	2 (13%)	0	0	0	2 (4%)
Any serious related TEAE	0	0	0	0	0
Any TEAE leading to withdrawal from study drug	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0

Most TEAEs Were Mild or Moderate

- 2 serious TEAEs unrelated to study drug
  - Atrioventricular block first degree*
  - Pneumonia
- Most common TEAEs (≥5% participant incidence)**
  - Nasopharyngitis (11%)
  - Fatigue, infusion site rash, headache (9% each)
  - Procedural pain, diarrhea (7% each)
- 1 severe, non-serious, TEAE, unrelated to study drug
  - Recurrence of worsening AV block in participant with SAE of AV block
- Liver enzyme elevations have been observed in ~18% 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 dose-dependent increase in TEAEs

Additional Safety Data

- No participants have demonstrated anemia or thrombocytopenia[2]
- No participants have demonstrated kidney injury[3]

AV, atrioventricular; TEAE, treatment-emergent adverse event; Q4W, every 4 week dosing.
* Transient worsening of atrioventricular (AV) block in a participant with ongoing medical history of first-degree AV block. ** All cohorts combined; preferred terms are reported
1. Data as of December 6, 2023; 2. Treatment emergent HGB or PLT persistently below LLN or reported AE. 3.Treatment emergent and persistently abnormal renal parameters or reported AE.
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.

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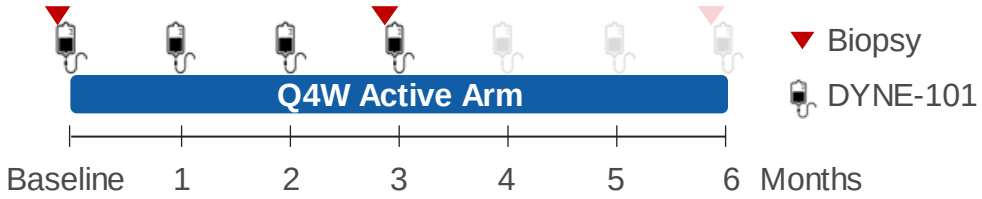
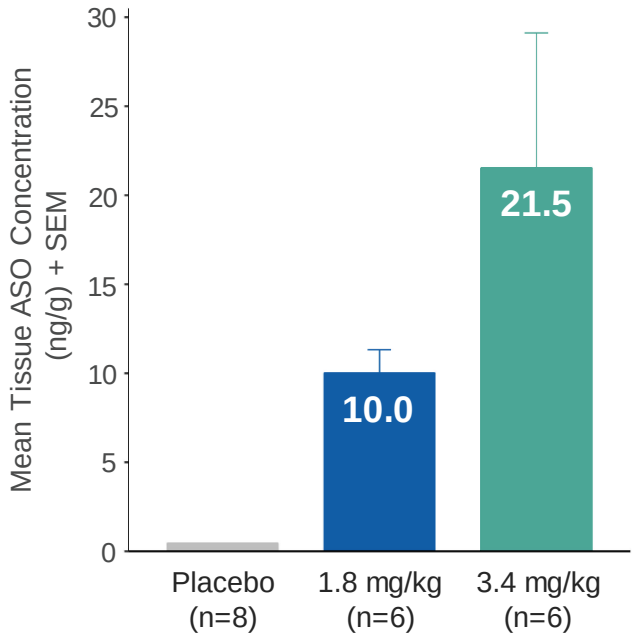
DYNE-101 Demonstrated Dose-Dependent Muscle Drug Concentration, *DMPK* Knockdown, and Splicing at 3 Months

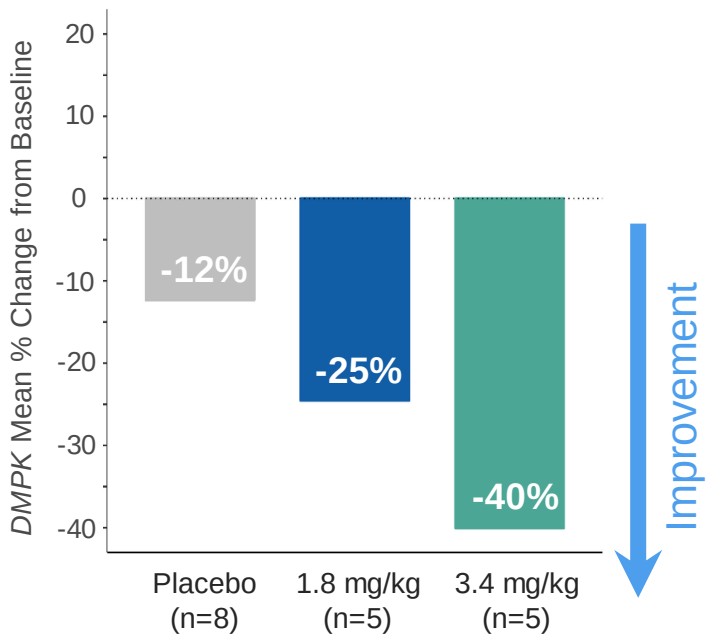


Muscle Delivery | Total *DMPK* Knockdown | Splicing

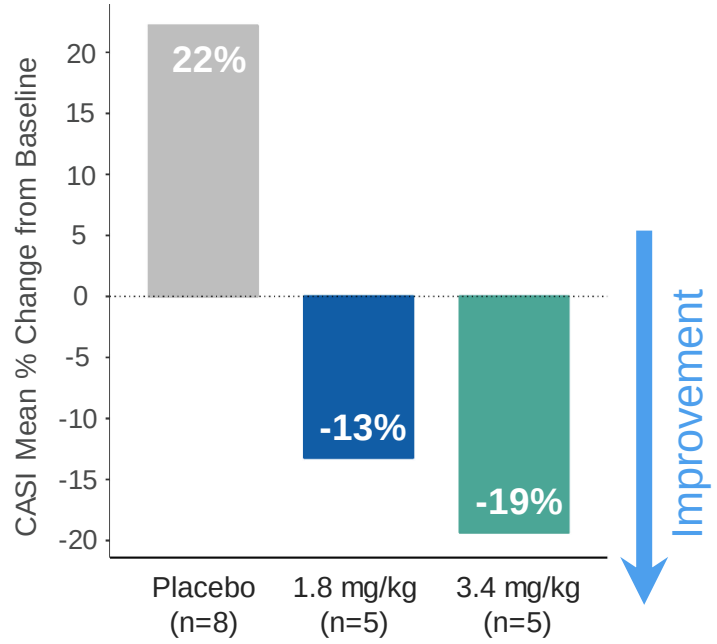
ASO Muscle Concentration



DMPK KD



CASI-22



ASO, antisense oligonucleotide; CASI, composite alternative splicing index; DMPK, dystrophia myotonica protein kinase; KD, knockdown; Q4W, every 4 week dosing; SEM, standard error of the mean.
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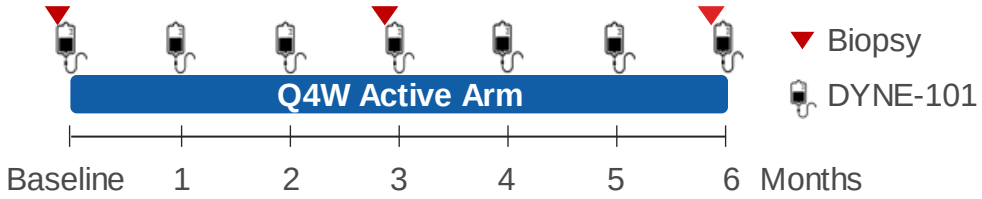
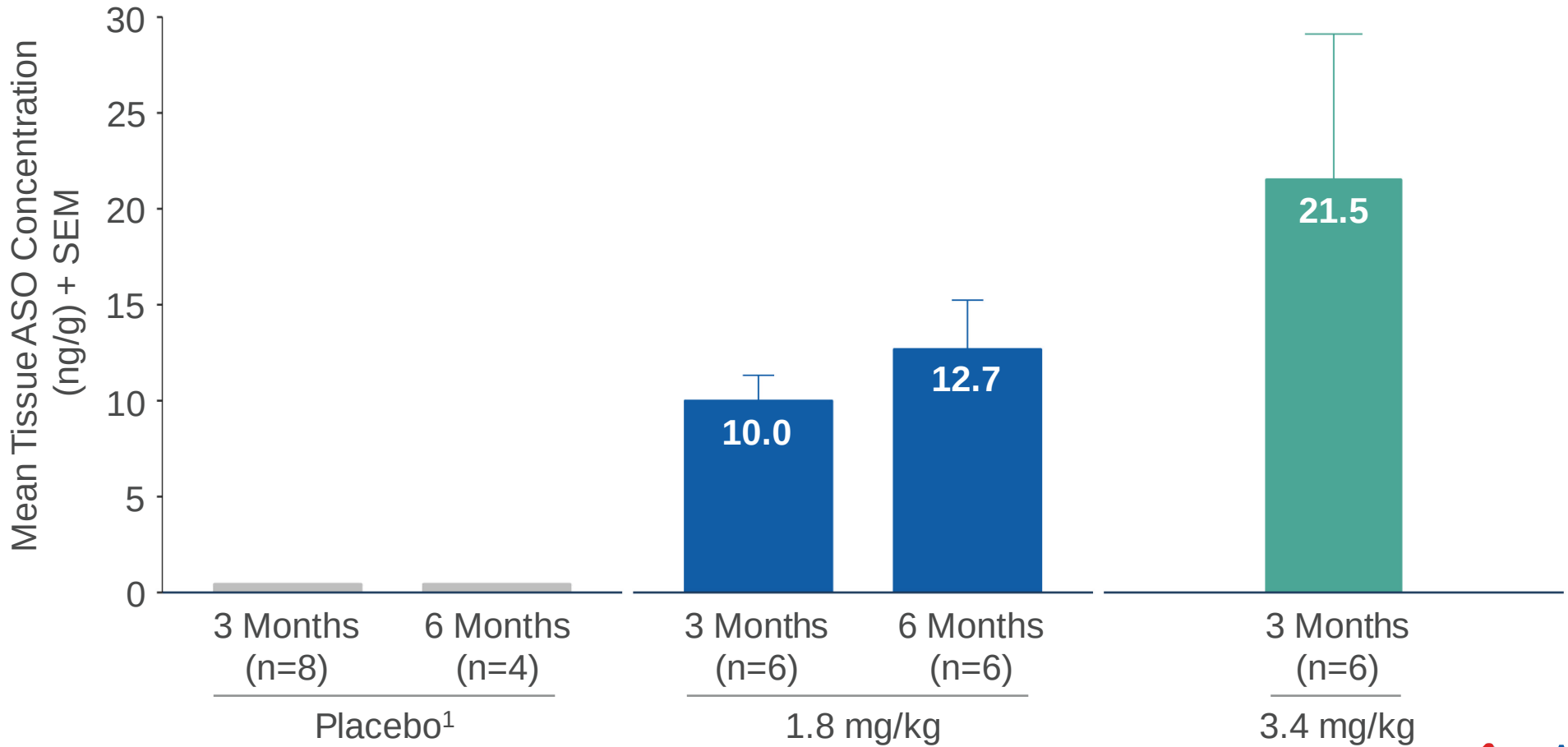
DYNE-101 Drove Robust, Dose-Dependent Delivery of ASO to Muscle





ASO, antisense oligonucleotide; Q4W, every 4 week dosing; SEM, standard error of the mean.
1. Placebo values were below the LLQ at 3 Months and 6 Months. LLOQ is 0.85 ng/g.
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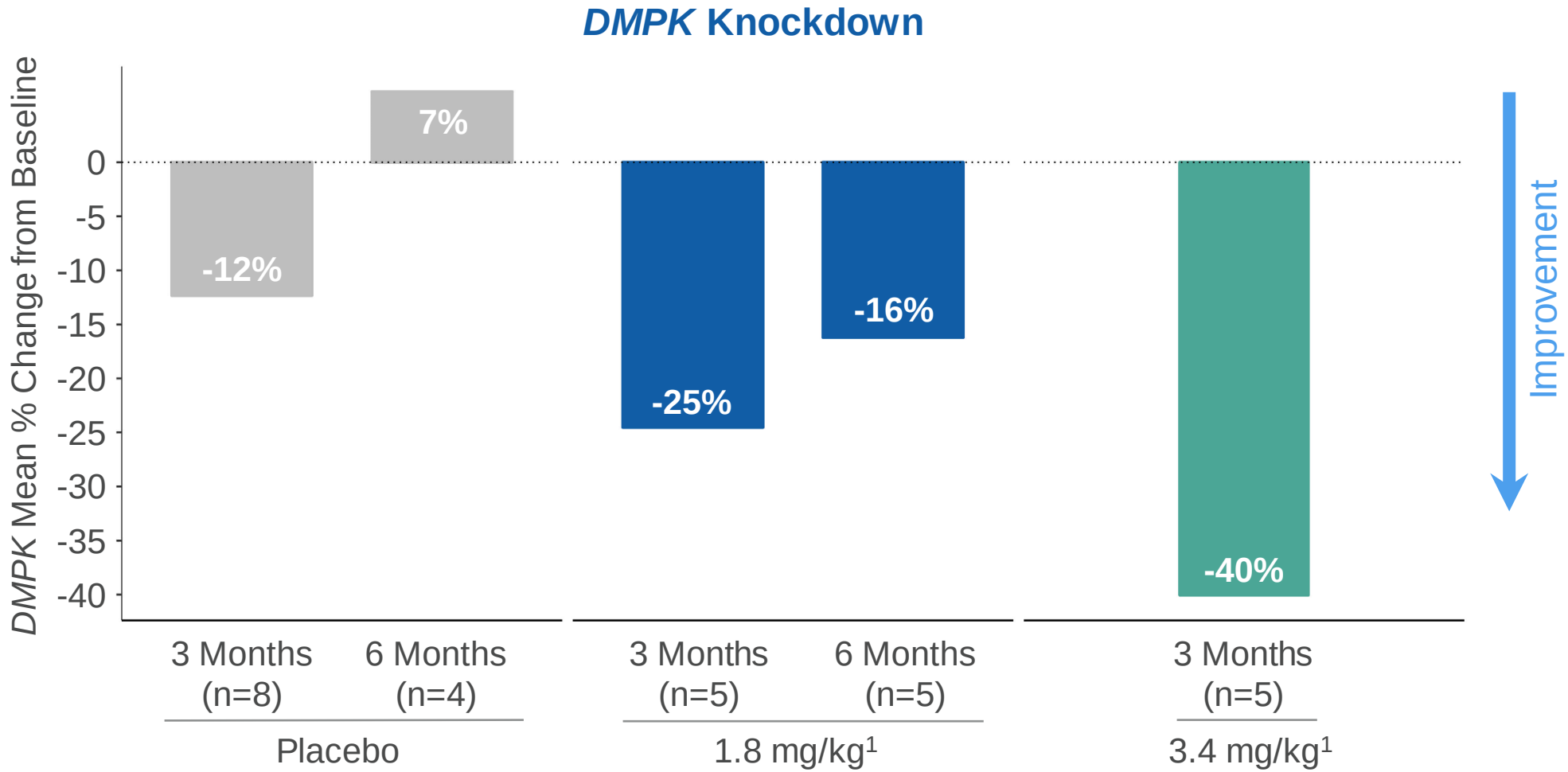
Achieved Dose-Dependent Target Engagement to Modify DM1 Biology

Dose response: Greater *DMPK* knockdown at 3.4 mg/kg compared to 1.8 mg/kg dose level



DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase.
1. One baseline sample in 1.8 mg/kg Q4W group and one 3 Month sample in 3.4 mg/kg Q4W group not included in *DMPK* KD and splicing assay due to the sample not meeting QC criteria.
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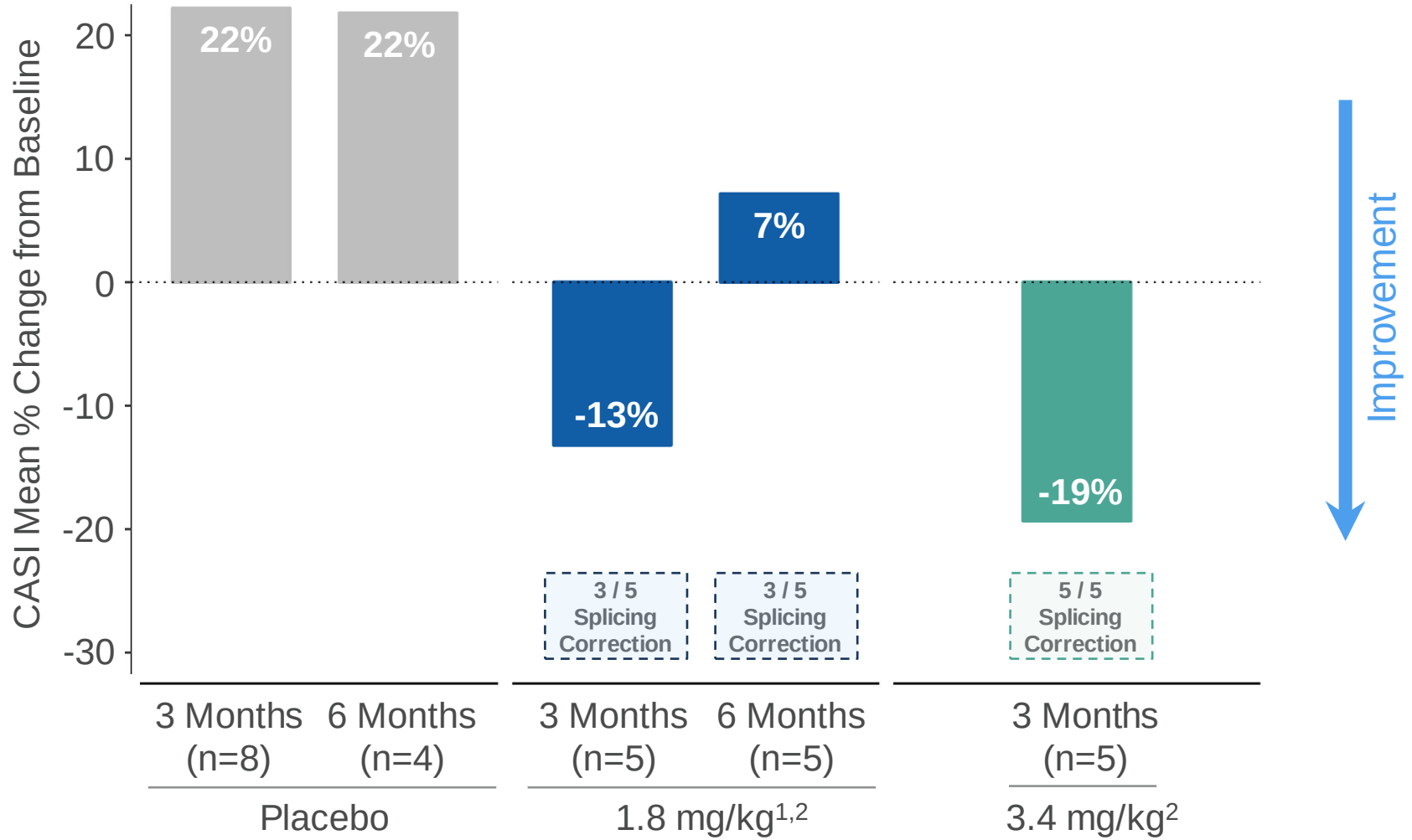
Dose-Dependent Splicing Correction with Consistency of Response Achieved At Higher Doses Across 22-Gene Panel



- **Dose response**
  - DYNE-101 3.4 mg/kg Q4W demonstrated mean 19% correction of splicing from baseline at Day 85 vs. 13% correction for 1.8 mg/kg Q4W
- **Consistency of response**
  - All evaluable participants in 3.4 mg/kg Q4W demonstrated splicing correction across 22-gene panel

CASI, composite alternative splicing index; Q4W, every 4 week dosing. Mean % Change = mean of change from baseline / mean of baseline
1. Within the 1.8 mg/kg Q4W cohort, the same patients that demonstrated splicing correction at 3 Months continued to show splicing correction at 6 Months; patients who did not show correction at 3 Months, exhibited further increase in CASI between 3 Months and 6 Months. 2. One baseline sample in 1.8 mg/kg Q4W treatment group and one 3 Month sample in 3.4 mg/kg Q4W treatment group not included in *DMPK* KD and splicing assay due to the sample not meeting QC criteria.
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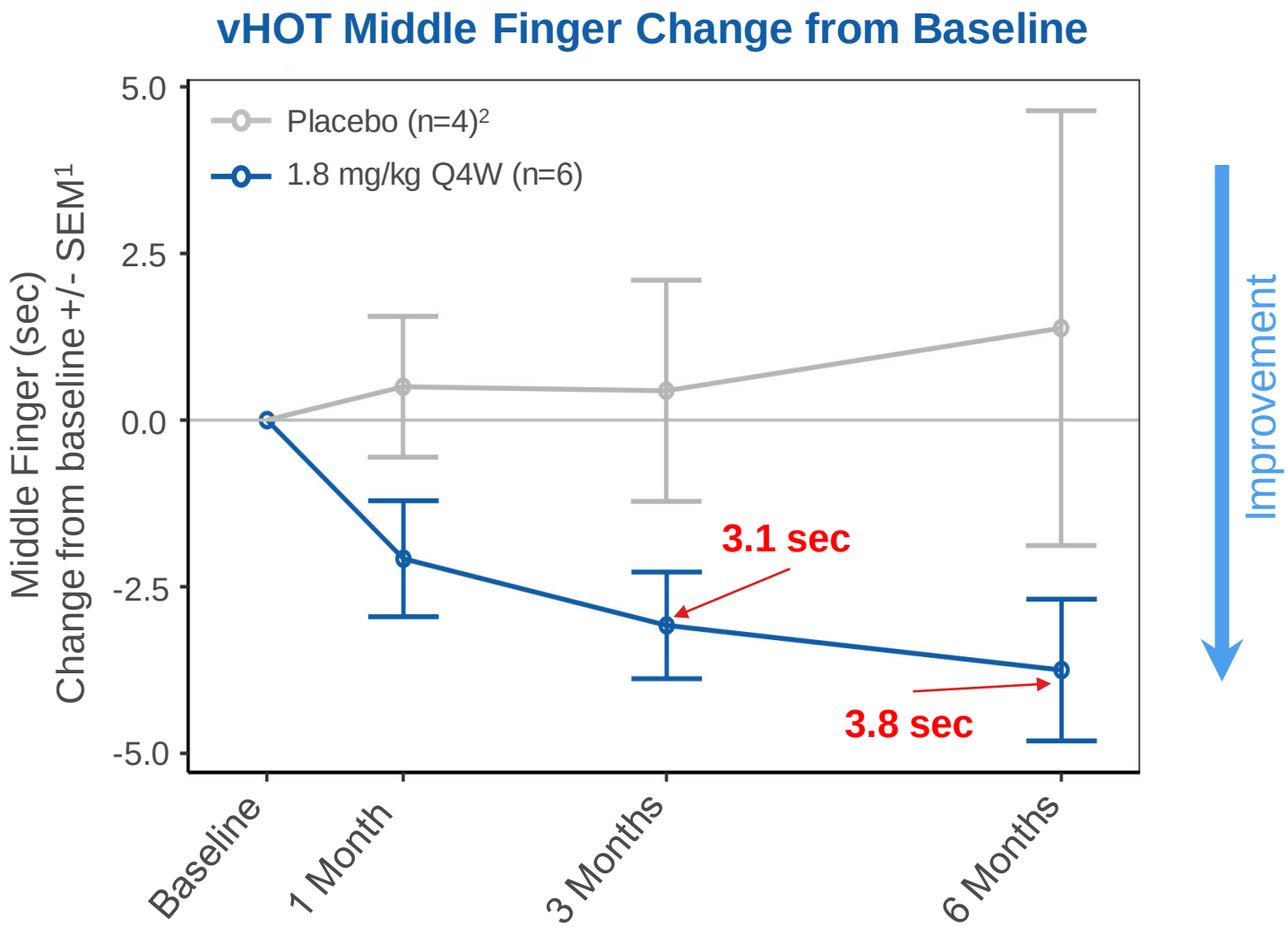
DYNE-101 Showed Continued Improvement in Functional Myotonia at 6 Months



Q4W, every 4 weeks dosing; SEM, standard error of the mean; vHOT, video hand opening time. 1. Middle Finger (sec) is the average of all myotonia trials for an individual participant in ACHIEVE; 2. Four participants randomized to placebo arm in 1.8 mg/kg cohort; n=4 at 6 Months.
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Demonstration of DYNE-101 Impact on Myotonia at Lowest Dose

Baseline

On Treatment

Cohort 1 Participant

1.8 mg/kg Q4W

Q4W, every 4 weeks dosing.
Patient myotonia videos have been altered to preserve blinding protocol of ACHIEVE trial and patient privacy.
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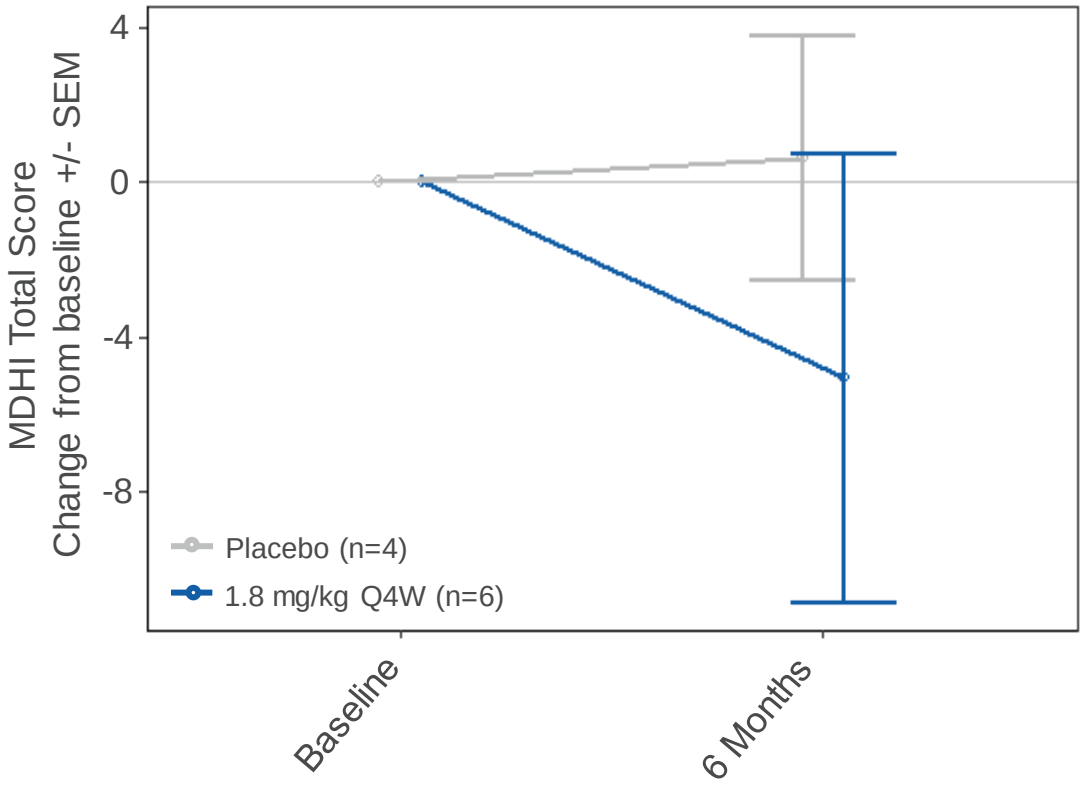
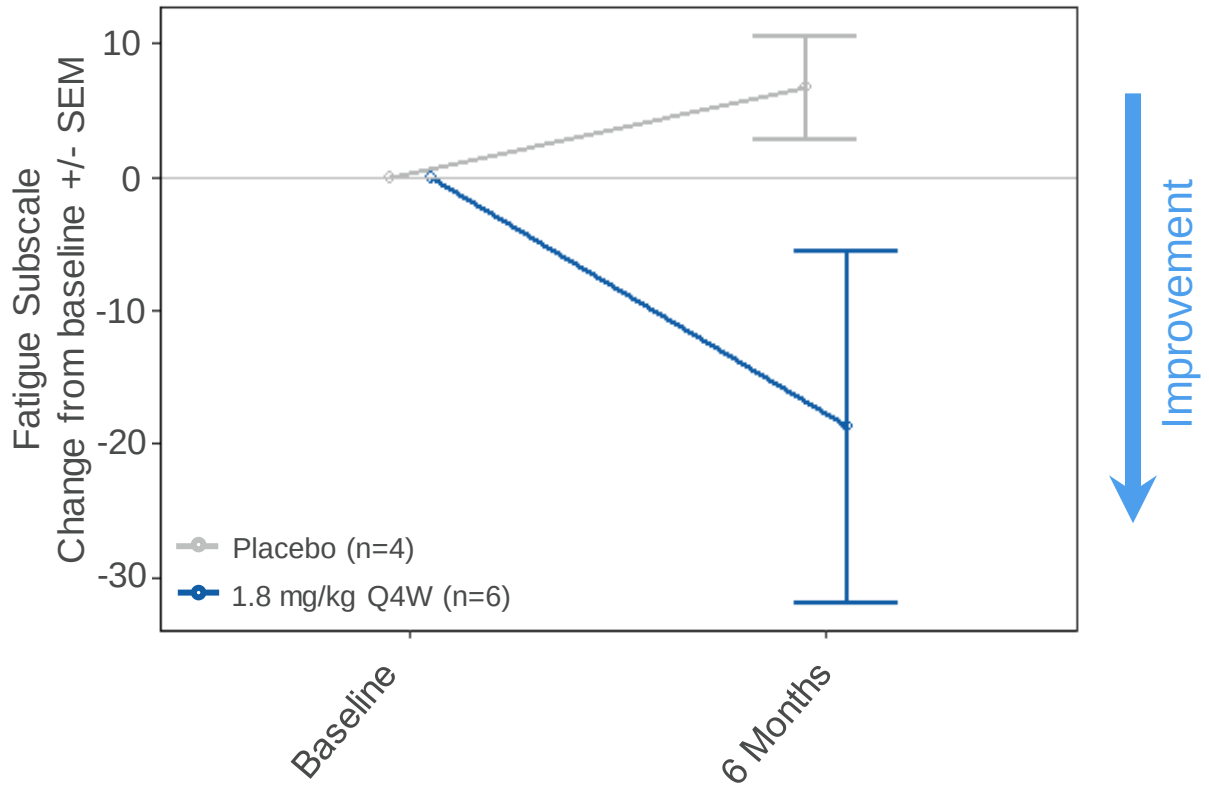
Patient Reported Outcomes Beginning to Show Effect at Lowest Dose in ACHIEVE

Improvement in MDHI total and fatigue subscale suggest a potential benefit in the CNS

Total MDHI Change from Baseline



Fatigue Change from Baseline



CNS, central nervous system; MDHI, myotonic dystrophy health index; PRO, patient reported outcomes; Q4W, every 4 weeks dosing; SEM, standard error of the mean.
Patient-reported outcomes, including MDHI collected at 6 Months.
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Summary

- DYNE-101 consists of a TfR1-binding Fab conjugated to an ASO designed against mutant nuclear *DMPK* RNA to correct splicing.
- ACHIEVE is an ongoing, randomized, placebo-controlled global Phase 1/2 trial of DYNE-101 in adults with DM1.
- **The safety profile of DYNE-101 is favorable to date**[1], with the majority of TEAEs reported as mild or moderate.
  - The trial is fully enrolled through the 5.4 mg/kg cohort and favorable safety profile has supported dosing up to 10.2 mg/kg.
- Initial data from the MAD portion of ACHIEVE demonstrated **dose-dependent muscle delivery, *DMPK* KD, and splicing correction** following treatment with DYNE-101.
- There was **functional improvement in myotonia (vHOT) at the lowest 1.8 mg/kg (ASO equivalent) dose** and early signs of potential improvement in MDHI.
- These initial data support the continued clinical development of DYNE-101 for the treatment of DM1.

ASO, antisense oligonucleotide; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; Fab, fragment antibody; KD, knockdown; MAD, multiple ascending dose; MDHI, myotonic dystrophy health index; TfR1, transferrin receptor 1; vHOT, video hand opening time.

1. Data as of December 6, 2023.

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