ACHIEVE

Dyne THERAPEUTICS

DELIVER

Achieving the Promise of

FORCE

to Deliver for Patients

FORCE

42ND ANNUAL J.P. MORGAN HEALTHCARE CONFERENCE | JANUARY 9, 2024

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OUR MISSION

Life-transforming therapies

for patients with serious muscle diseases

Achieving the Promise of FORCE to Deliver for Patients

ACHIEVE

Potential first-in-class DM1 therapy with differentiated efficacy and safety profile

- ✓ Proof-of-concept achieved for DYNE-101
- ✓ Dose-dependent muscle delivery, DMPK KD, and splicing correction consistent across patients
- ✓ Meaningful functional improvement in myotonia (vHOT) at lowest 1.8 mg/kg dose
- ✓ Favorable safety profile to date; 5.4 mg/kg Q8W cohort fully enrolled [2]

DELIVER

Potential best-in-class DMD exon skipping franchise with differentiated efficacy and safety profile

- ✓ Proof-of-concept achieved for DYNE-251
- ✓ At initial 5.0 mg/kg Q4W dose, DYNE-251 showed compelling profile vs. eteplirsen standard-of-care reported at 6 months:[1]
  - >2.5x higher dystrophin expression with 24x lower PMO dose administered 4x less frequently vs. eteplirsen[1]
  - 2x higher increase in exon skipping vs. eteplirsen[1]
  - ~2x higher change from baseline PDPF vs. eteplirsen[1]
- ✓ Favorable safety profile to date; 20 mg/kg Q4W cohort fully enrolled [2]

Clinical Proof-of-Concept Achieved in ACHIEVE & DELIVER in Early Cohorts
Driving Towards Potentially Transformative Therapies for DM1 & DMD Patients in Later Cohorts

PDPF: percent dystrophin-positive fibers.
1. No head-to-head trials have been conducted comparing DYNE-251 to eteplirsen. Eteplirsen data may not be directly comparable due to differences in trial protocols, dosing regimens and patient populations. Accordingly, these cross-trial comparisons may not be reliable. Eteplirsen data from *J Neuromuscul Dis* 2021; 8(6):989–1001; 2. Data as of December 6, 2023.

Developing Transformative Therapies for People Living with DM1

Overview

- Mutation in the *DMPK* gene
- Onset at any point, depending on DM1 phenotype
- Life expectancy of 45 - 60 years

Clinical Presentation

- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities
- CNS manifestations

Population

- >40,000 (US)
- >74,000 (Europe)

NO approved therapies

OUR APPROACH

Disease-Modifying Nuclear *DMPK* Knockdown

Targeting toxic gain of function *DMPK* RNA to potentially **stop or reverse** disease progression

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

Population

- Adult patients living with DM1
- Ages 18 to 49 years

Primary Endpoints

- Safety and tolerability

Key Secondary

- Pharmacokinetics
- Change from baseline of:
  - Splicing
  - *DMPK* RNA expression
  - Multiple assessments of muscle strength and function

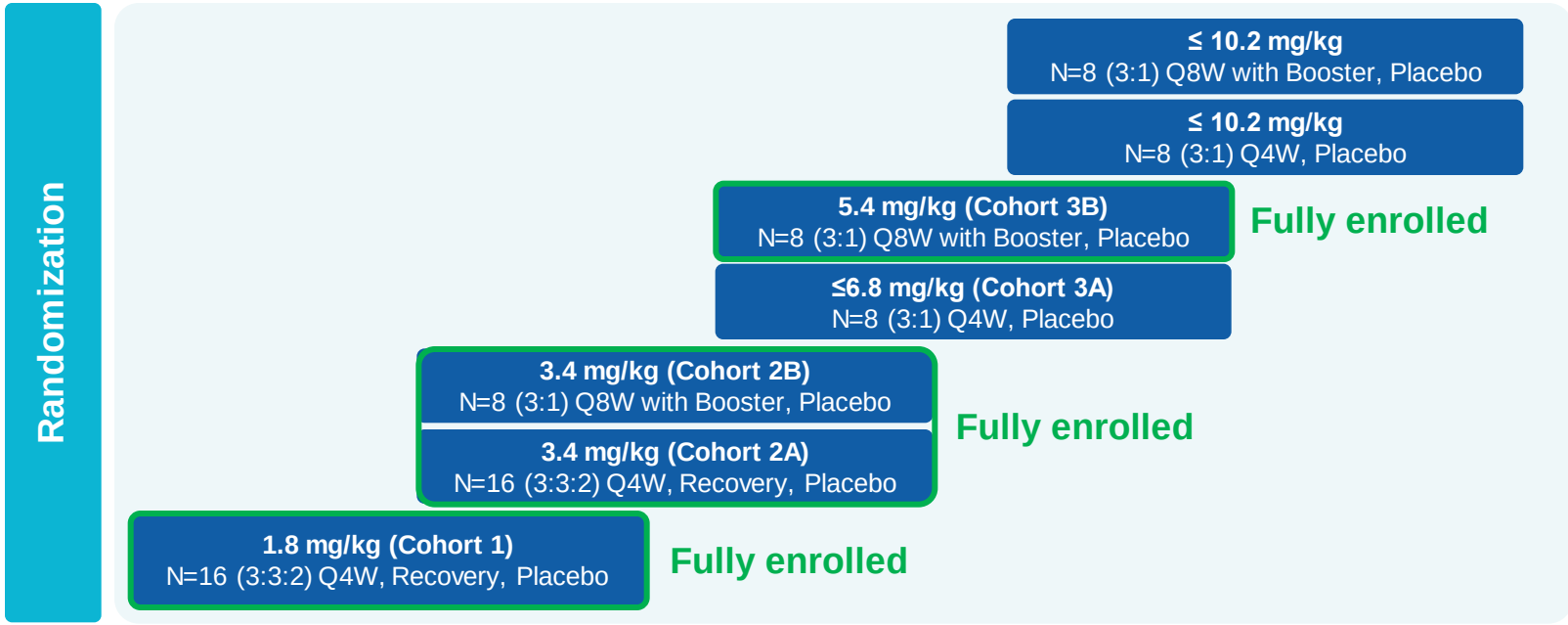
Stages of ACHIEVE

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

ACHIEVE Trial Design

ACHIEVE

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

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 a dose up to 6.8 mg/kg in Cohort 3 and up to 10.2 mg/kg in Cohort 4.

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)

1. Q4W, recovery, and placebo arms are reported together for baseline characteristics.

Safety Profile of DYNE-101 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 in Intensity (Placebo-Controlled Period)

- 2 serious TEAEs unrelated to study drug
  - Atrioventricular block first degree*
  - Pneumonia
- Most common TEAEs (≥5% participant incidence)**
  - Nasopharyngitis (11%)
  - Fatigue (9%)
  - Infusion site rash (9%)
  - Headache (9%)
  - Procedural pain (7%)
  - Diarrhea (7%)
- 1 severe, non-serious, TEAE, unrelated to study drug
  - Recurrence of worsening AV block in participant with the 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

Additional Safety Data

- No participants have demonstrated anemia or thrombocytopenia[3]
- No participants have demonstrated kidney injury[4]

* 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

Favorable Safety Profile, with ~300 Doses Administered To Date, Has Supported Dosing Up to 6.8 mg/kg [2]

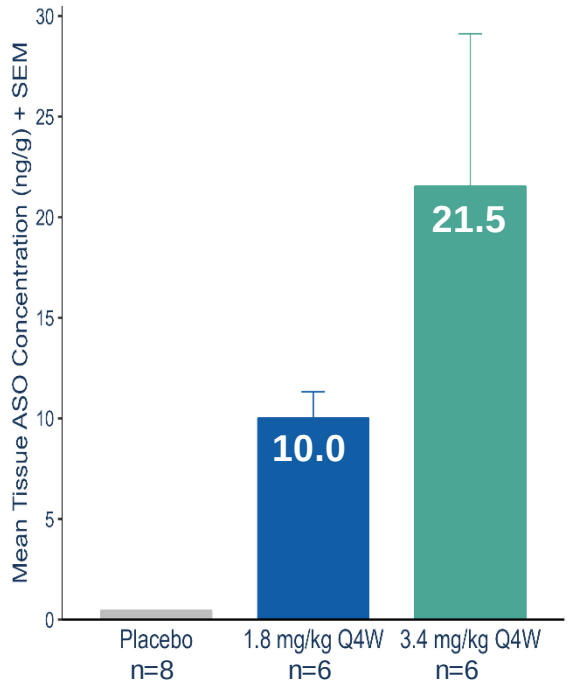
1. Data as of December 6, 2023; 2. Number of doses administered in ACHIEVE to date reflects doses administered across all study periods (MAD, OLE, LTE); 3. Treatment emergent HGB or PLT persistently below LLN or reported AE. 4.Treatment emergent and persistently abnormal renal parameters or reported AE.

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

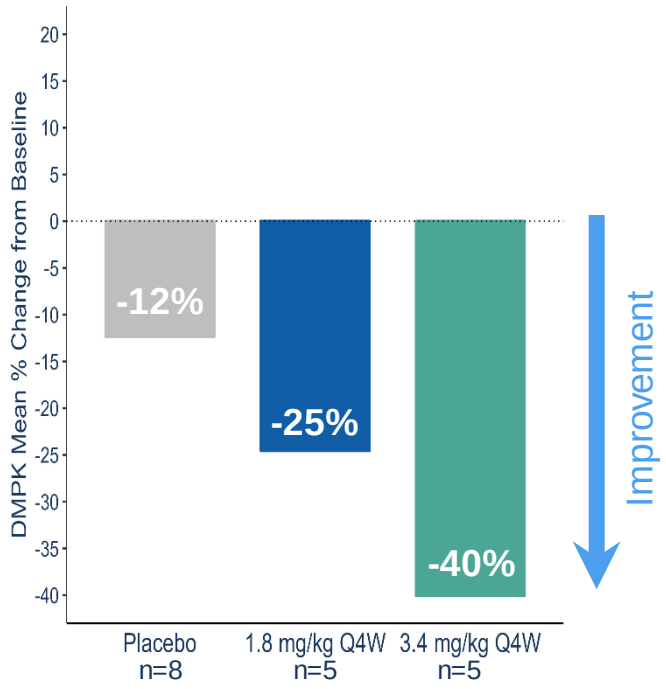
PK → Muscle Delivery

PD → Total *DMPK* Knockdown → Splicing

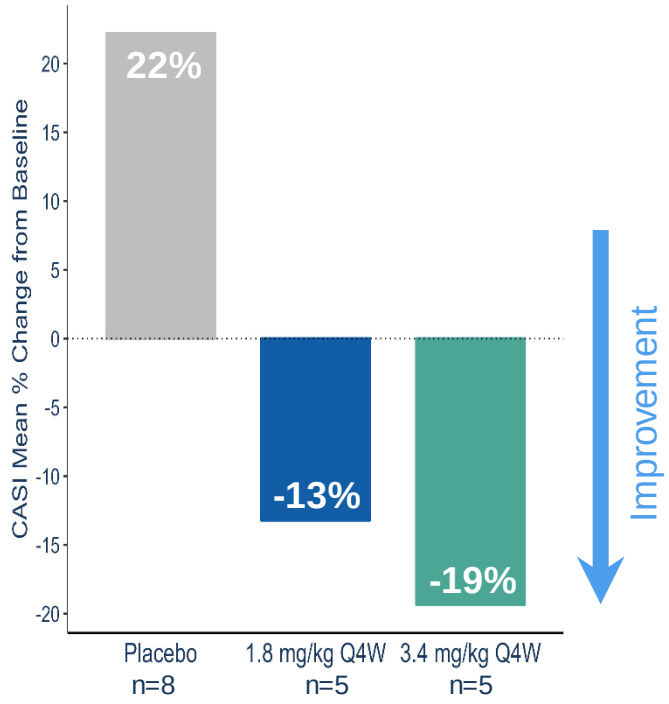
ASO Muscle Concentration



DMPK KD



CASI-22

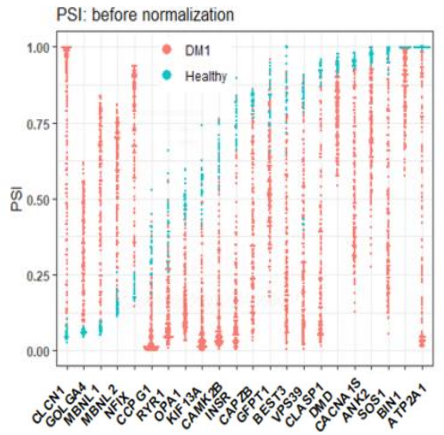


Favorable Safety Profile, with ~300 Doses Administered To Date, Has Supported Dosing Up to 6.8 mg/kg [1]

1. Number of doses administered in ACHIEVE to date reflects doses administered across all study periods (MAD, OLE, LTE).

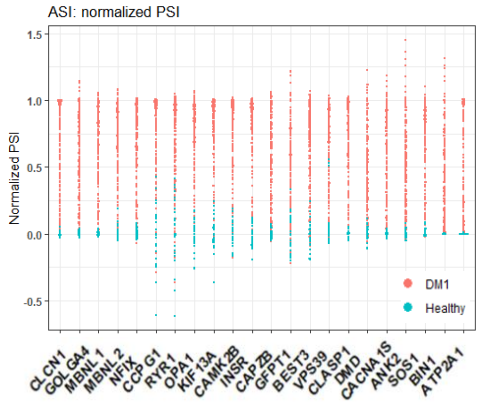
DMCRN NHS Enabled Establishment of Composite Alternative Splicing Index (CASI) as Biomarker Correlating with Clinical Function in DM1

PSI = Percent Spliced In



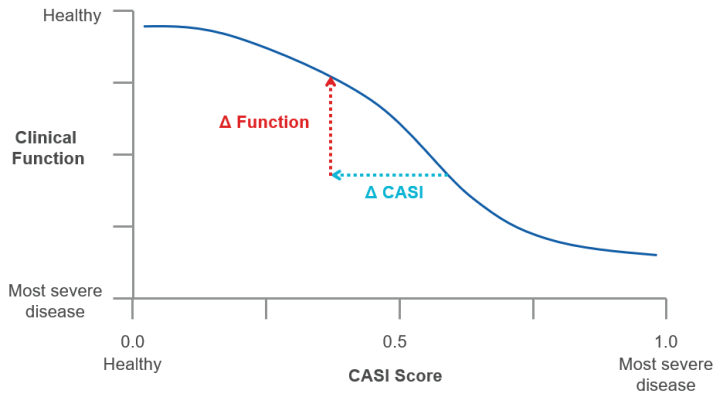
Targeted sequencing reads to calculate Percent Spliced In (PSI) of specific exons

ASI: Alternative Splicing Index



Normalize to reference PSI from healthy controls and patients from DM1 natural history studies [1]

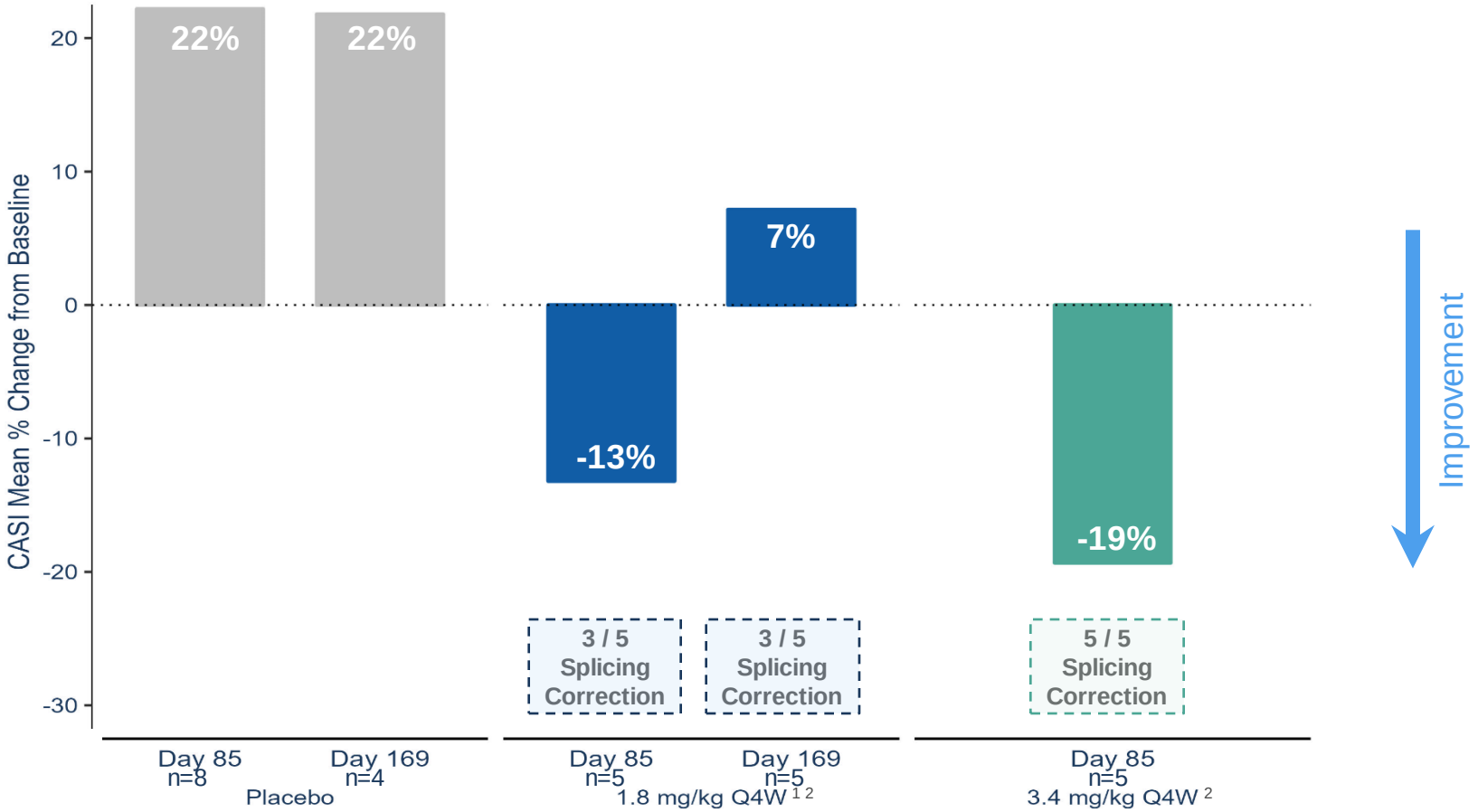
CASI: Composite Alternative Splicing Index



Compute the mean of normalized PSI from a panel of 22 genes.
0 representing median score of healthy subjects; 1 representing 95th percentile severity of DM1 patients

1. Reference PSI described within Thornton CA et al., *Lancet Neurol*, 2023; 22: 218–228; DMCRN NHS: Myotonic Dystrophy Clinical Research Network natural history study.

Dose-Dependent Splicing Correction with Consistency of Response Achieved At Higher Doses Across 22-Gene Panel



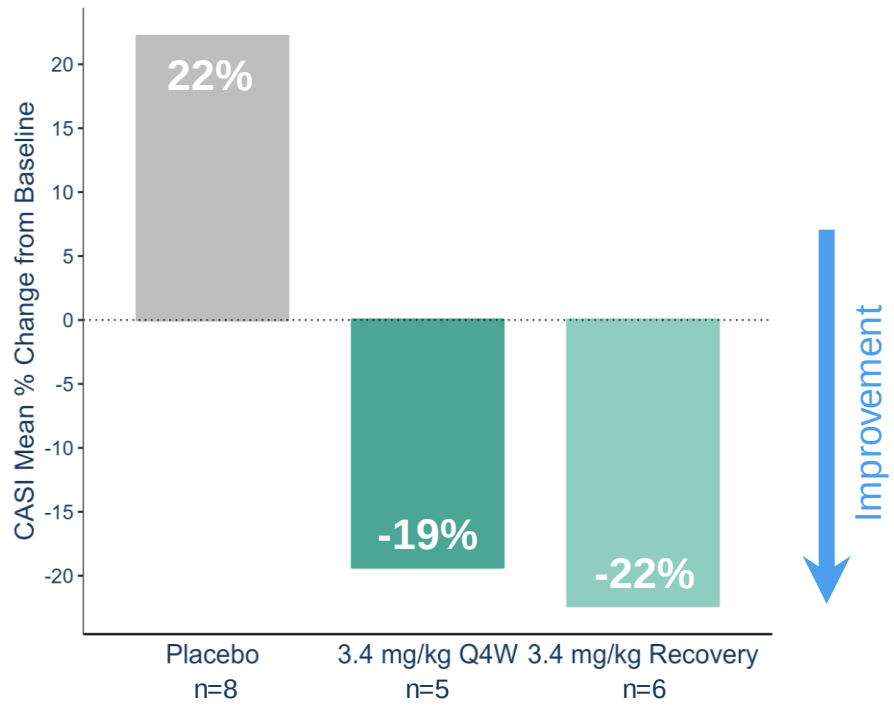
- **Dose response**
  - DYNE-101 3.4 mg/kg Q4W demonstrated mean 19% correction of splicing from baseline at Day 85 vs. 13% correction for 1.8 mg/kg Q4W
- **Consistency of response**
  - All evaluable participants in 3.4 mg/kg Q4W demonstrated splicing correction across 22-gene panel

Mean % Change = mean of change from baseline / mean of baseline

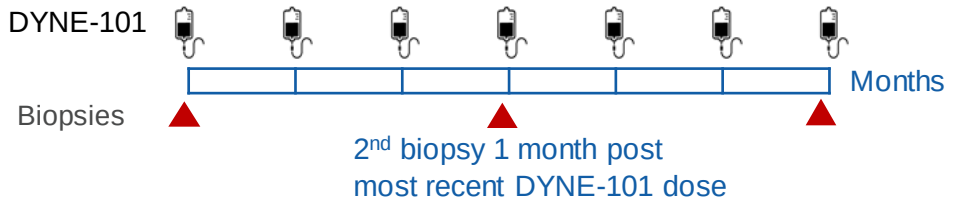
1. Within the 1.8 mg/kg Q4W cohort, the same patients that demonstrated splicing correction at Day 85 continued to show splicing correction at Day 169; patients who did not show correction at Day 85, exhibited further increase in CASI between Day 85 and Day 169. 2. One baseline sample in 1.8 mg/kg Q4W treatment group and one Day 85 sample in 3.4 mg/kg Q4W treatment group not included within DMPK KD and splicing assay due to the sample did not meet QC criteria.

Recovery Data Supports Less Frequent Dosing Regimen

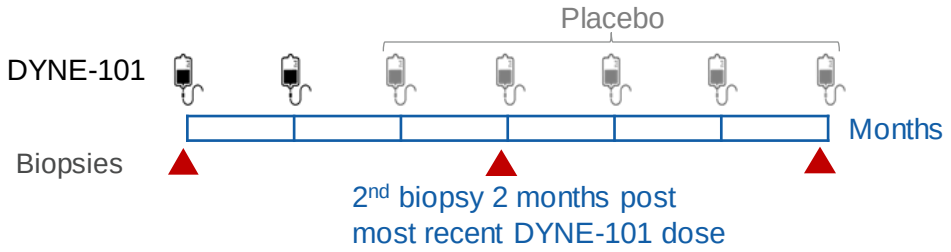
CASI-22



Q4W Active Arm



Q4W Recovery Arm

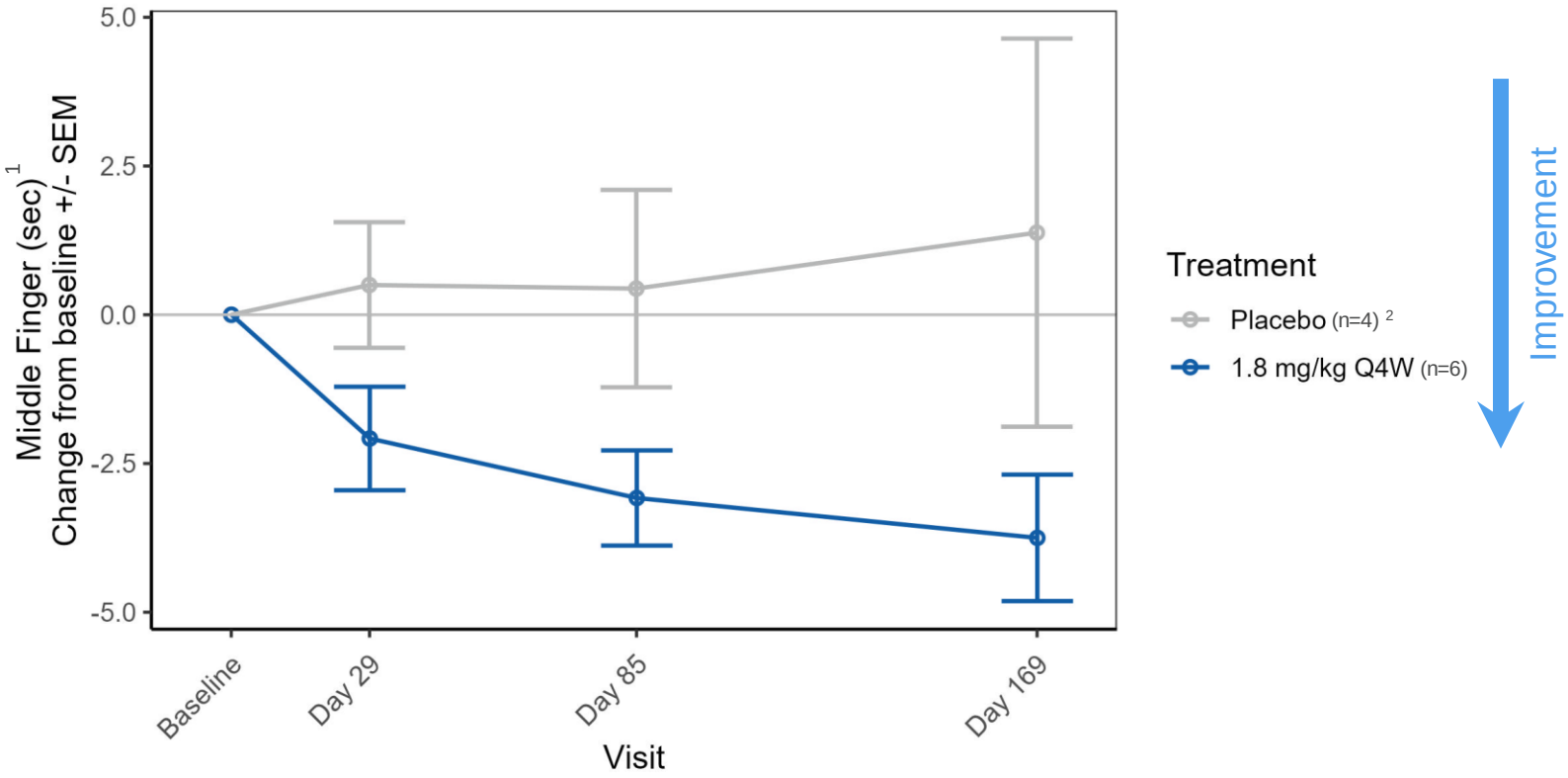


Robust Splicing Correction in Both Active and Recovery Arm with 3.4 mg/kg Dose

Continued Improvement in Functional Myotonia at 6 Months

1.8 mg/kg Q4W myotonia benefit increased from 3.1 seconds at 3 Months to 3.8 seconds at 6 Months

vHOT middle finger change from baseline

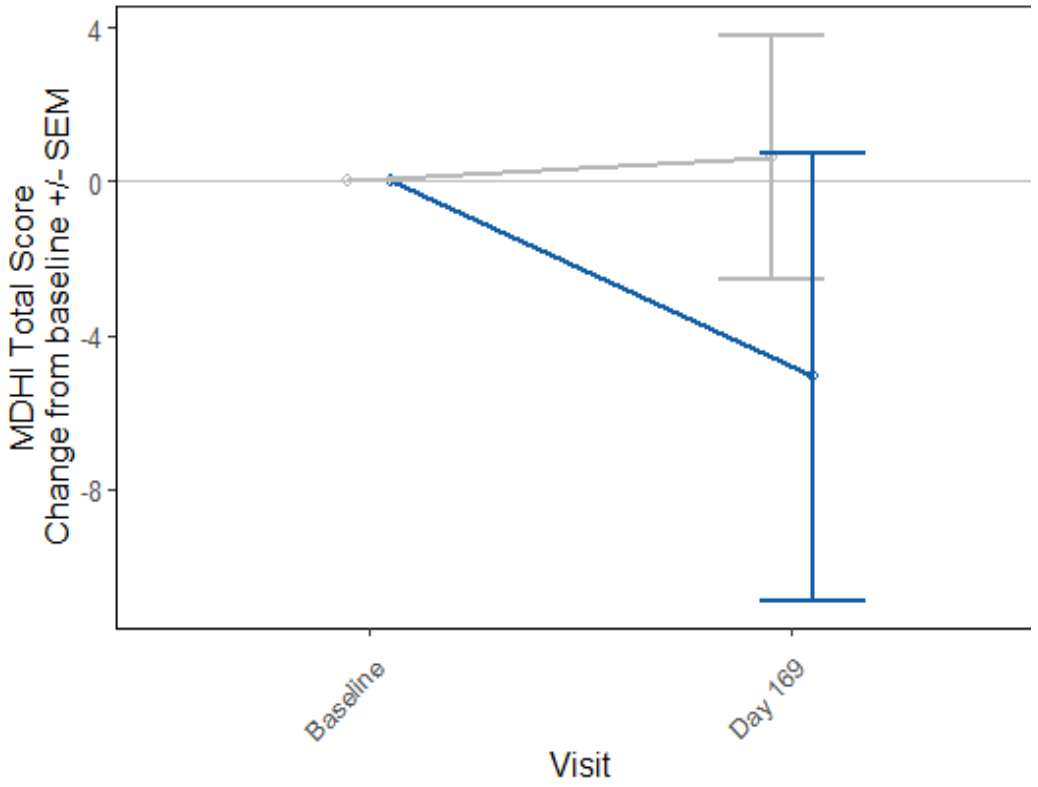


1. Middle Finger (sec) is the average of all myotonia trials for an individual participant in ACHIEVE; 2. Four participants randomized to placebo arm in 1.8 mg/kg cohort; n=4 at Day 169.

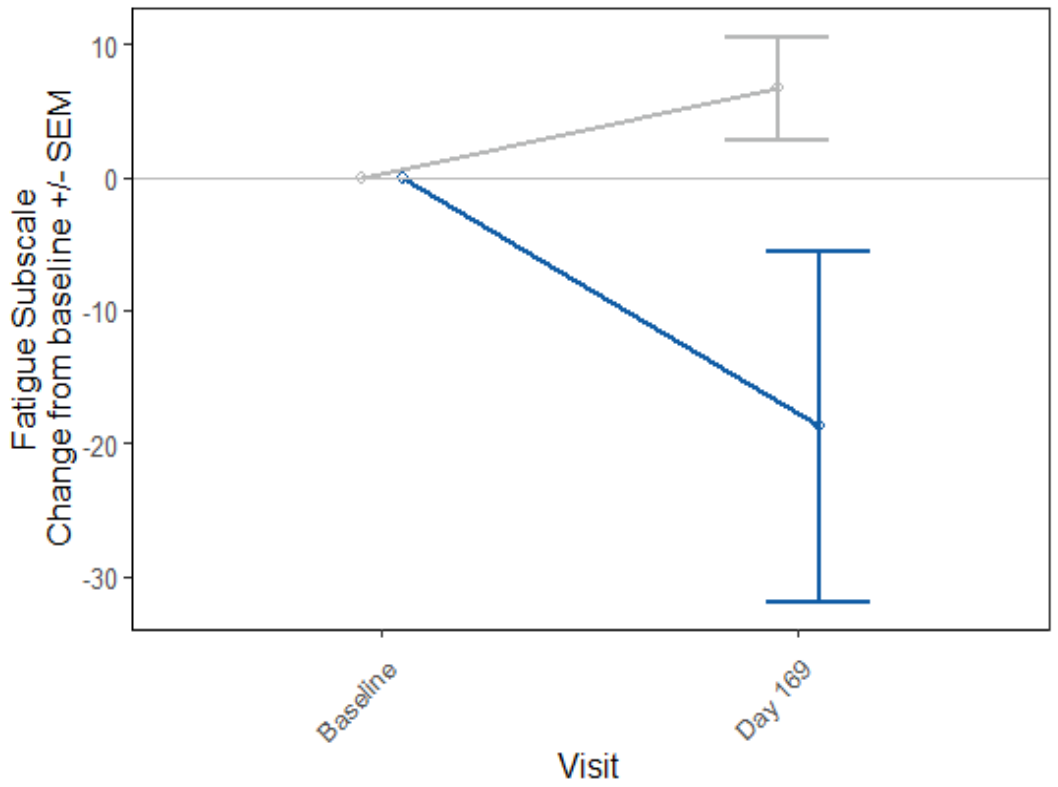
Patient Reported Outcomes Beginning to Show Effect at Lowest Dose in ACHIEVE

Improvement in MDHI total and fatigue subscale, suggesting potential benefit in CNS

Total MDHI change from baseline



Fatigue change from baseline



Improvement

Placebo (n=4) 1.8 mg/kg Q4W (n=6)

Notes: Patient-reported outcomes (PRO), including Myotonic Dystrophy Health Index (MDHI) collected at Day 169.

ACHIEVE Data Demonstrated Robust Effect in DM1 Patients

Initial ACHIEVE Clinical Data

- Dose-dependent muscle delivery, DMPK KD, and splicing correction consistent across patients
- Meaningful functional improvement in myotonia (vHOT) at lowest 1.8 mg/kg dose
- Early indication of durable effect beyond monthly dosing supports exploration of Q8W
- Favorable safety profile to date; 5.4 mg/kg Q8W cohort fully enrolled [1]

DYNE-101 Proof-of-Concept Achieved

DYNE-101: Next Steps

Optimizing dose and dose regimen in 2024

Next clinical update from ACHIEVE expected in H2'24

1. Safety data as of December 6, 2023.

Building a Global DMD Franchise of Transformative Therapies

Overview

- Mutation in the *DMD* gene that encodes for dystrophin
- Onset in first few years of life
- Life expectancy ~30 years

Clinical Presentation

- Muscle weakness
- Progressive loss of function
- Loss of ambulation
- Respiratory/cardiac failure

Population

- ~12,000 - 15,000 (US)
- ~ 25,000 (Europe)

Current Approved Exon 51 Therapies Only Increased Dystrophin Production <1%

OUR APPROACH

Potential Best-in-class Targeted Exon Skipping

Increase dystrophin expression and enable less frequent dosing to potentially **stop or reverse disease progression**

Phase 1/2 Clinical Trial to Evaluate DYNE-251 in Patients with DMD

Population

- Male patients with DMD with mutations amenable to exon 51 skipping therapy
- Ages 4 to 16 years
- Ambulant and non-ambulant

Primary Endpoints

- Safety and tolerability
- Change from baseline in dystrophin protein levels by Western Blot

Key Secondary Endpoints

- Pharmacokinetics
- Change from baseline of:
  - Exon 51 skipping levels
  - Muscle tissue PDPF
  - Multiple assessments of muscle function, including NSAA score and certain timed functional tests

Stages of DELIVER

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

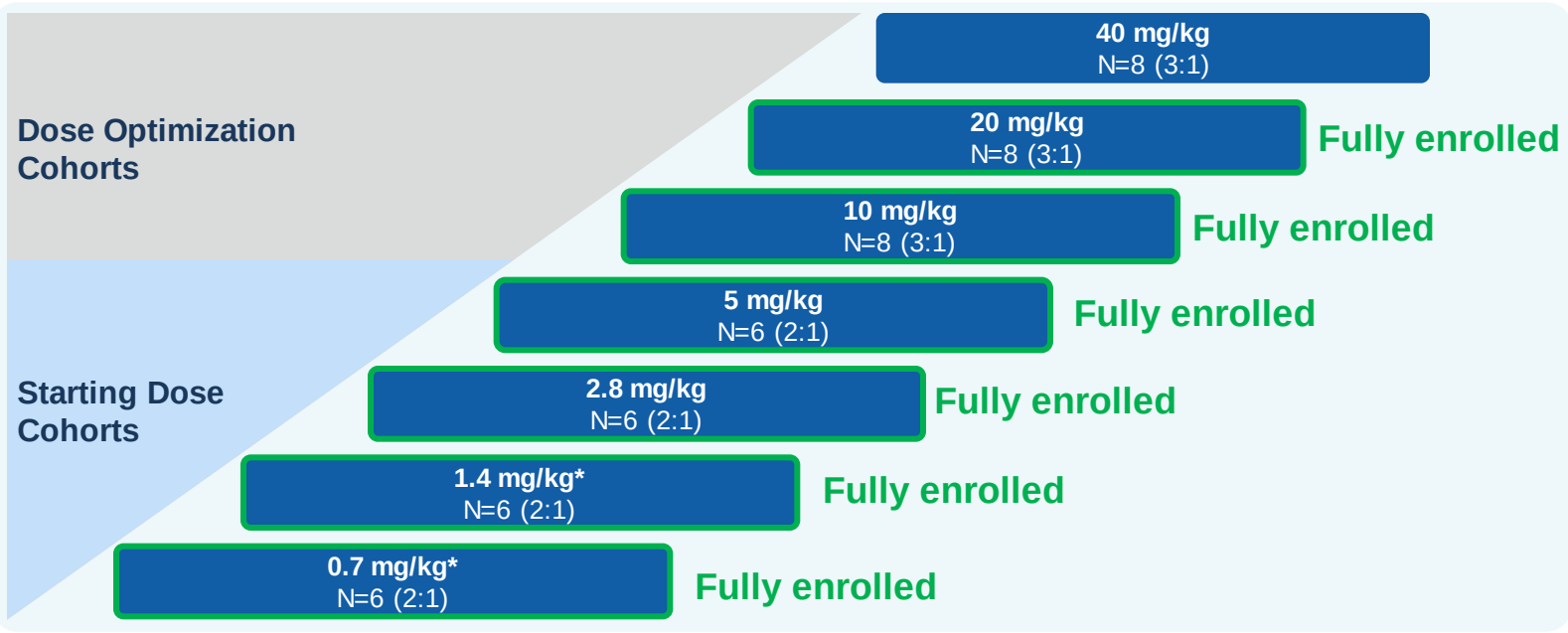
PDPF: percent dystrophin-positive fibers; NSAA: North Star Ambulatory Assessment

DELIVER Trial Design

DELIVER

Global, Randomized, Placebo-Controlled Stage Evaluating Once Monthly Administration of DYNE-251 in Ambulant and Non-Ambulant Male DMD Patients with Mutations Amenable to Exon 51 Skipping Therapy

Randomization



MAD Study Details

- IV administration of DYNE-251 or placebo every 4 weeks
- Muscle biopsies: Baseline and 24 weeks in 2.8 mg/kg and higher cohorts
- Patients in MAD study escalated to highest tolerable dose in OLE and LTE

Global Trial Designed to be Registrational and to Enable Rapid Achievement of Predicted Pharmacologically Active Dose Levels

Dyne THERAPEUTICS

Patient cohorts will be dosed from 0.7 mg/kg to 40 mg/kg in the U.S. Outside the U.S., patient cohorts will be dosed from 5 mg/kg to 40 mg/kg. Doses provided refer to PMO component of DYNE-251.
* Muscle biopsies taken at baseline and 24 weeks in 2.8 mg/kg and higher cohorts; biopsies not taken in 0.7 mg/kg and 1.4 mg/kg cohorts.

DELIVER Baseline Participant Characteristics: By Cohort

	Cohort 1 0.7 mg/kg (N=6)	Cohort 2 1.4 mg/kg (N=6)	Cohort 3 2.8 mg/kg (N=6)	Cohort 4 5 mg/kg (N=6)
Age (years) (mean (SD))	10.8 (2.2)	7.8 (3.3)	10.7 (2.9)	8.3 (2.8)
BMI (kg/m^2) (mean (SD))	19.5 (3.4)	18.6 (2.3)	22.2 (6.3)	20.9 (1.6)
Age of Symptom Onset (years) (mean SD))	3.7 (1.8)	4.5 (2.1)	2.8 (1.8)	3.7 (3.1)
Corticosteroid dosing regimen (n (%))[1] Daily Other	 4 (66.7%) 2 (33.3%)	 4 (66.7%) 3 (50.0%)	 5 (83.3%) 1 (16.7%)	 6 (100.0%) 0
Prior DMD Therapy (n (%)) Eteplirsen Other	 4 (66.7%) 2 (33.3%)	 2 (33.3%) 1 (16.7%)	 5 (83.3%) 0	 1(16.7%) 0

Note: Q4W and placebo arms are reported together for baseline characteristics.
1. Historical corticosteroid regimen based on medical history; a participant can be counted in multiple categories.

Safety Profile of DYNE-251 Is Favorable to Date

Summary of Treatment Emergent Adverse Events (TEAEs) – Placebo-Controlled Period [1]

TEAE Category	Participants with ≥1 TEAE – n (%)						
	0.7mg/kg Q4W N=6	1.4 mg/kg Q4W N=6	2.8 mg/kg Q4W N=6	5 mg/kg Q4W N=6	10mg/kg Q4W N=8	20mg/kg Q4W N=5	Overall* N=37
Any TEAE	4 (67%)	6 (100%)	3 (50%)	4 (67%)	6 (75%)	1 (20%)	24 (65%)
Any related TEAE	1 (17%)	2 (33%)	0	3 (50%)	1 (13%)	0	7 (19%)
Any serious TEAE	0	0	0	0	0	1 (20%)	1 (3%)
Any serious related TEAE	0	0	0	0	0	0	0
Any TEAE leading to withdrawal from study drug	0	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0	0

Most TEAEs Were Mild or Moderate in Intensity – Placebo-Controlled Period

- 1 serious TEAE unrelated to study drug
  - Dehydration due to gastroenteritis
- Most common TEAEs (≥10% participant incidence)*
  - Headache (16%)
  - Nasopharyngitis (16%)
  - Vomiting (14%)
  - Infusion related reaction (11%)**
  - Fall (11%)
  - Cough (11%)

Additional Safety Data

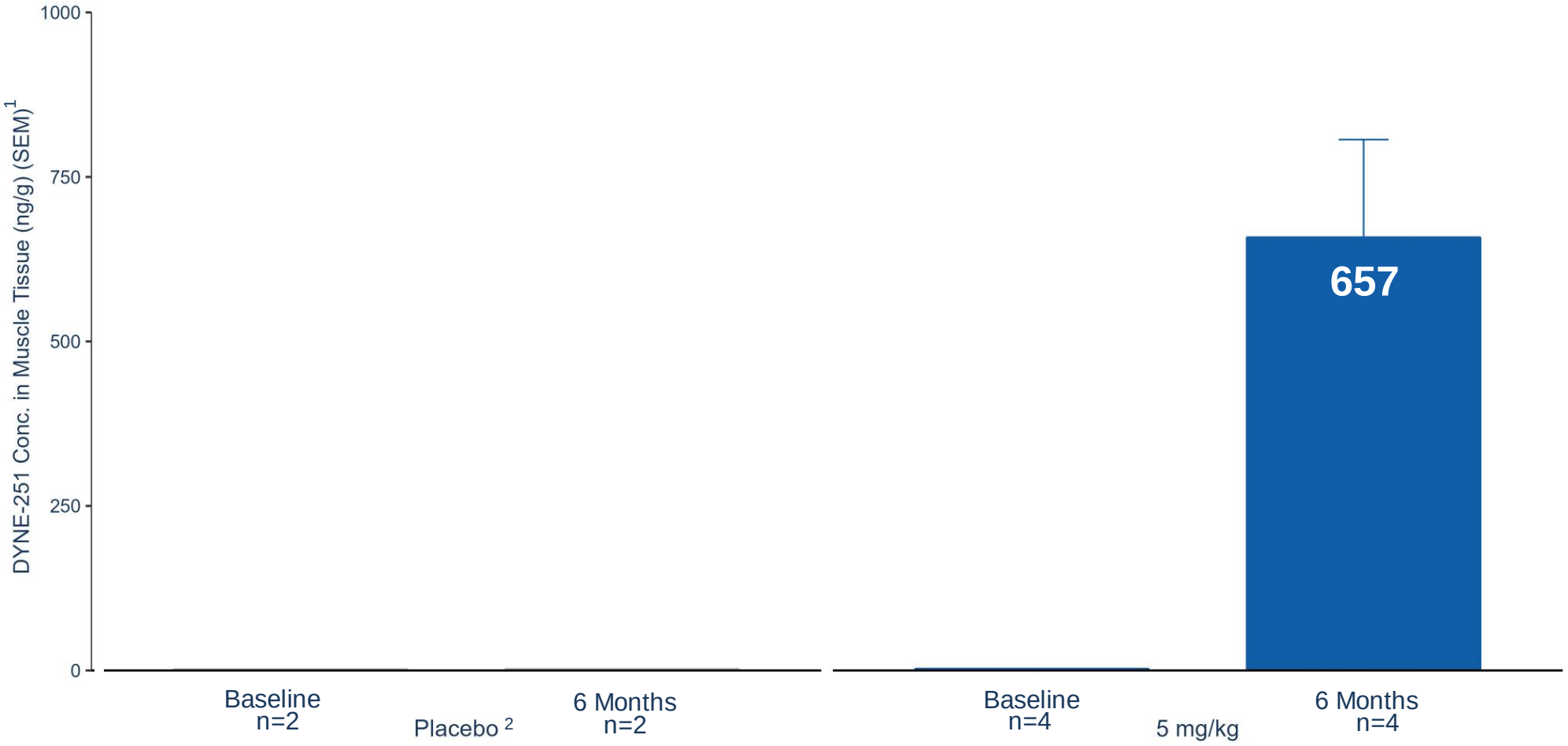
- No participants have demonstrated anemia or thrombocytopenia [3]
- No participants have demonstrated kidney injury [4]
- No participants have demonstrated clinically meaningful changes in electrolytes, including magnesium

* All cohorts combined
** All infusion related reactions have been mild and moderate in intensity; dosing has continued in all participants

Favorable Safety Profile, with ~275 Doses Administered To Date, Has Supported Dosing Up to 20 mg/kg [2]

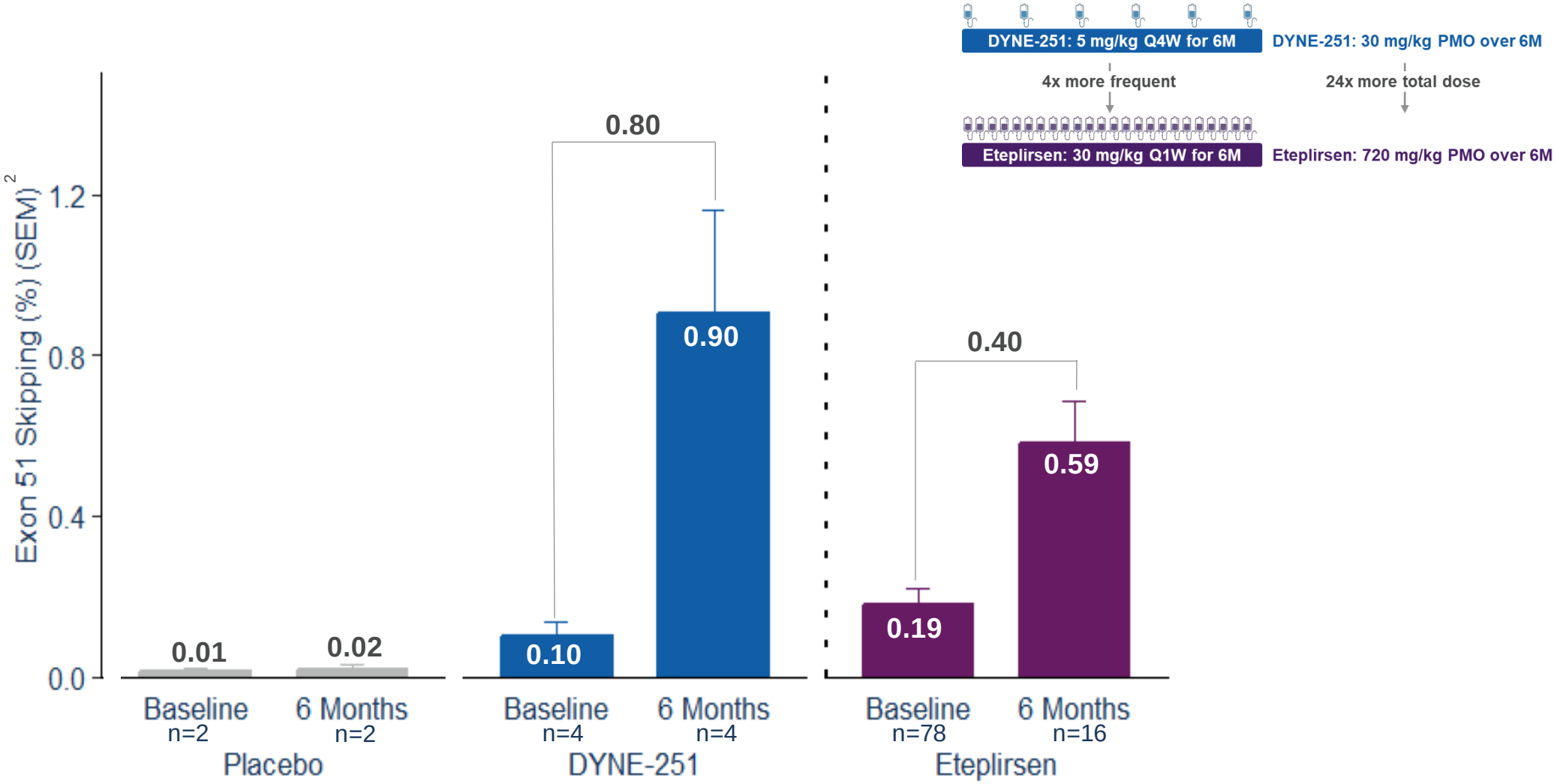
1. Data as of December 6, 2023; 2. Number of doses administered in DELIVER to date reflects doses administered across all study periods (MAD, OLE, LTE) in DELIVER; 3. Treatment emergent HGB or PLT persistently below LLN or reported AE. 4. Treatment emergent and persistently abnormal renal parameters or reported AE.

DYNE-251 Drove Robust Delivery of PMO to Muscle



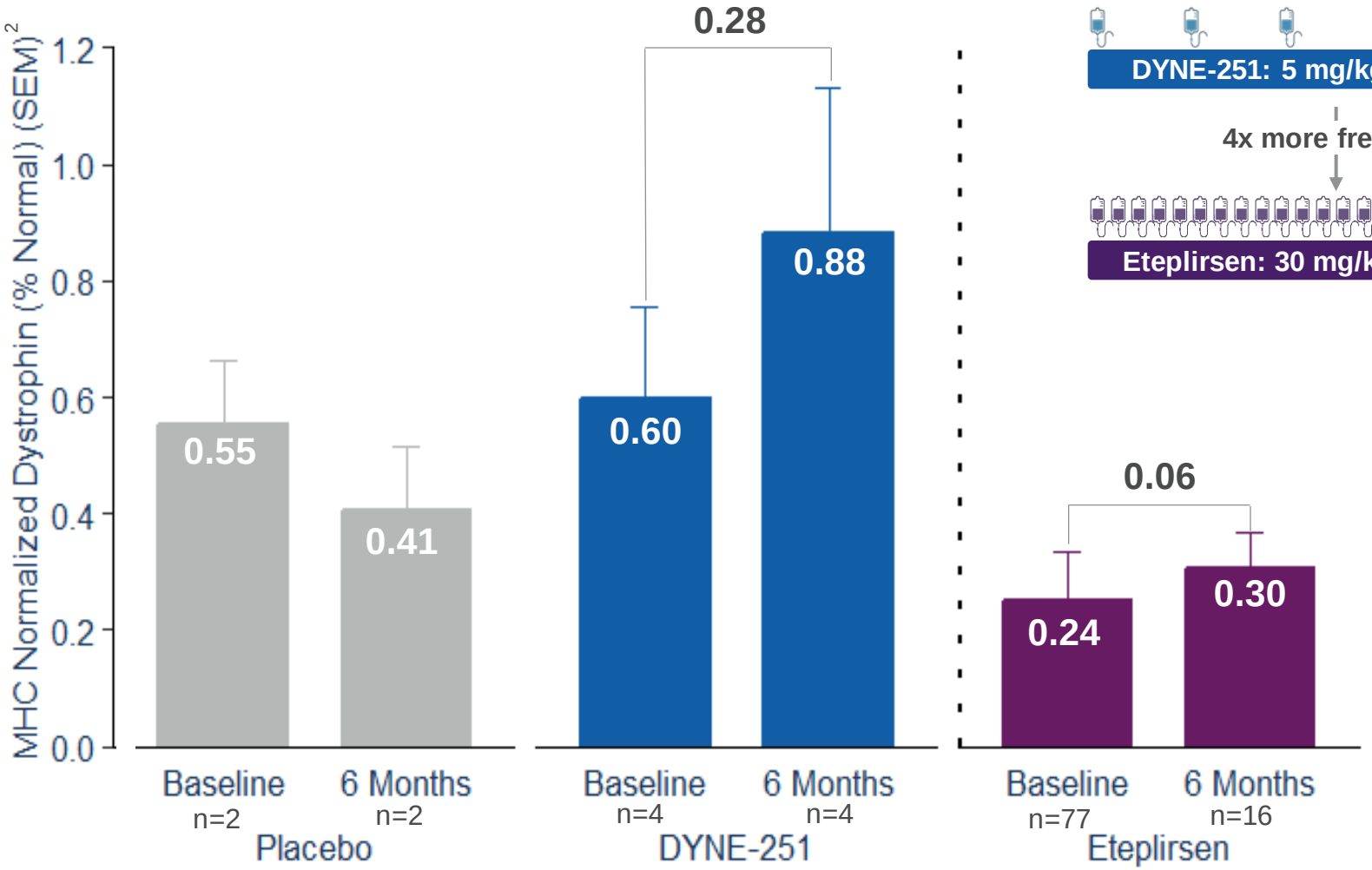
1. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER; 2. Placebo values at baseline and 6 Months were below LLOQ.; LLOQ = 1.57 ng/g.

DYNE-251 Showed 2 Fold Higher Increase in Exon Skipping at 6 Months than Reported in Eteplirsen Study [1]



1. No head-to-head trials have been conducted comparing DYNE-251 to eteplirsen. Eteplirsen data may not be directly comparable due to differences in trial protocols, dosing regimens and patient populations. Accordingly, these cross-trial comparisons may not be reliable. Eteplirsen data from *J Neuromuscul Dis* 2021; 8(6):989–1001; 2. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER and Week 24 for eteplirsen data.

DYNE-251 Showed >2.5 Fold Higher Dystrophin at 6 Months than Eteplirsen Study with 24 Fold Lower PMO Dose Administered 4 Times Less Frequently [1]



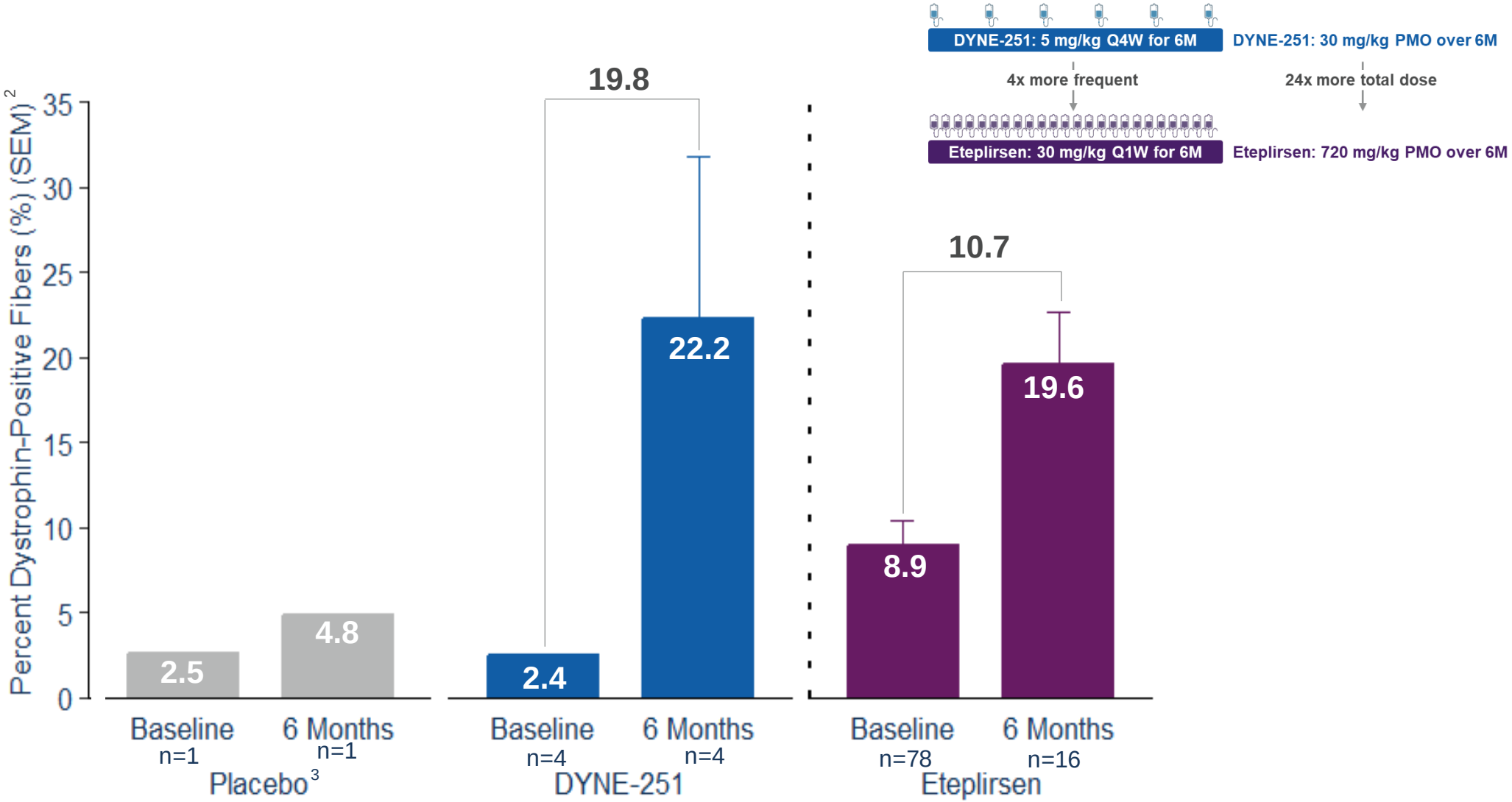
DYNE-251: 30 mg/kg PMO over 6M

24x more total dose

Eteplirsen: 720 mg/kg PMO over 6M

1. No head-to-head trials have been conducted comparing DYNE-251 to eteplirsen. Eteplirsen data may not be directly comparable due to differences in trial protocols, dosing regimens and patient populations. Accordingly, these cross-trial comparisons may not be reliable. Eteplirsen data from *J Neuromuscul Dis* 2021; 8(6):989–1001; 2. MHC normalized; DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER and Week 24 for eteplirsen data.

DYNE-251 Showed ~2 Fold Higher Change from Baseline in PDPF than Reported in Eteplirsen Study [1]



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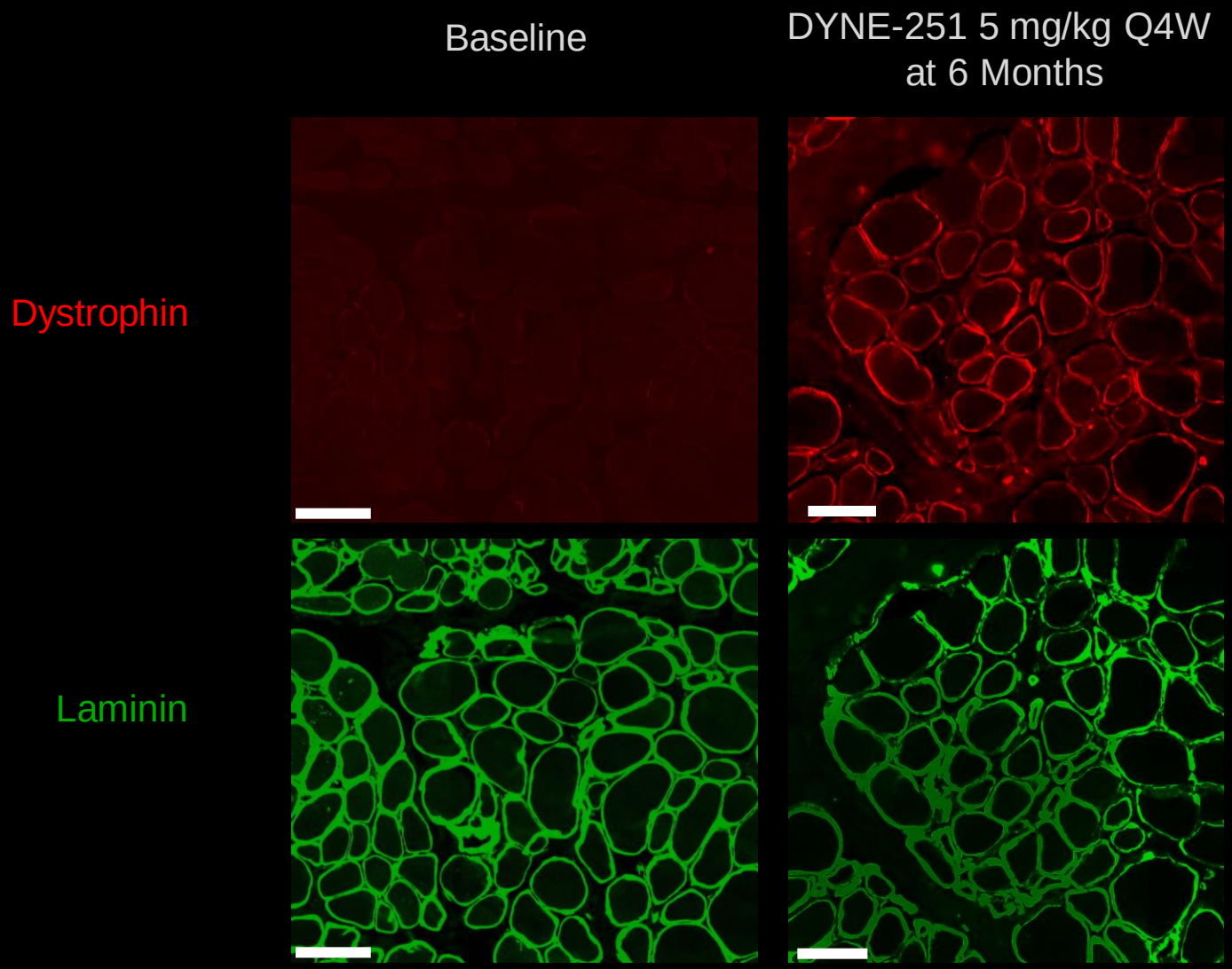
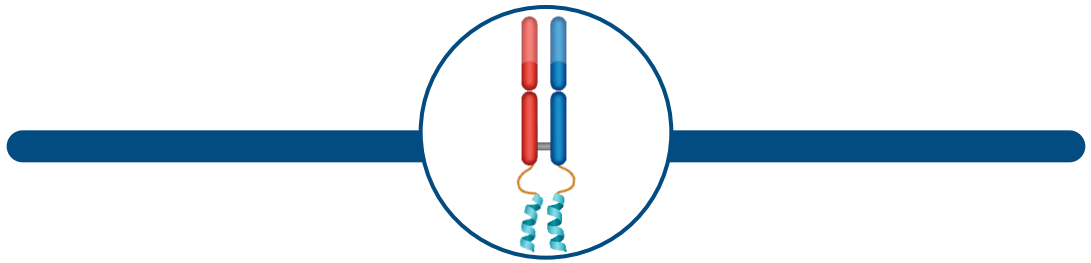
PDPF: Clear Improvement in Dystrophin Localization to Sarcolemma



Notes: DELIVER biopsy taken approximately 28 days after most recent dose. Notes: scale bar is 100 µm.

FORCE Positions Dyne With Leading Role in Evolving DMD Therapeutic Landscape

FORCE



Potency	✓ Targeted muscle delivery, near full-length dystrophin
Durability	✓ Durable target engagement
Dosing	✓ Re-dosable, titratable
Tolerability	✓ Favorable safety profile
Manufacturing	✓ Well-established, scalable

- Muscle delivery is the challenge
- Dyne founded to achieve targeted, receptor-mediated delivery to skeletal, cardiac and smooth muscle
  - Initial clinical data validates FORCE's targeted delivery to muscle
- Non-targeted delivery modalities face significant challenges, including an acceptable therapeutic index
  - Specifically, PPMO doses required to achieve potentially clinically meaningful exon skipping levels in NHPs may not be attainable in humans
- SMA landscape strong analogue to DMD with ZOLGENSMA (gene therapy) and SPINRAZA (oligo) playing an important role in evolving standard of care

DELIVER Data Demonstrated Potential for DMD Exon Skipping Franchise with Differentiated Efficacy and Safety Profile

Initial DELIVER Clinical Data

- At initial 5.0 mg/kg Q4W dose, DYNE-251 showed compelling profile vs. eteplirsen standard-of-care reported at 6 months: [1]
  - >2.5x higher dystrophin expression with 24x lower PMO dose administered 4x less frequently vs. eteplirsen [1]
  - 2x higher increase in exon skipping vs. eteplirsen [1]
  - ~2x higher change from baseline PDPF vs. eteplirsen [1]
- Favorable safety profile to date; 20 mg/kg Q4W cohort fully enrolled [2]
- Supports further development of DMD global franchise

DYNE-251 Proof-of-Concept Achieved

DYNE-251: Next Steps

Optimizing dose and dose regimen in 2024

Next clinical update from DELIVER expected in H2'24

PDPF: percent dystrophin-positive fibers.

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Achieved Clinical Proof-of-Concept Across Both DM1 & DMD

ACHIEVE | DELIVER

Delivered on the Promise of FORCE: Enhanced Delivery of Therapeutics to Muscle

Compelling Biomarker & Functional Data from Early Dose Cohorts vs. Published Competitor Data in Both DM1 & DMD

Favorable Safety & Tolerability Supporting Dose Escalation

ACHIEVE	DELIVER
Fully Enrolled Through 5.4 mg/kg	**Fully Enrolled Through 20 mg/kg**
Next Update Expected in H2 2024	**Next Update Expected in H2 2024**

In 2024, Focus Turns to Optimization of Dose & Dose Regimen in Potentially Registrational Programs