ACHIEVE

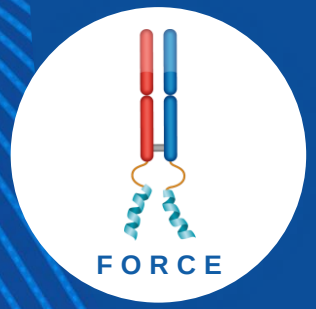
Dyne® THERAPEUTICS

DELIVER

Achieving the Promise of

FORCE

to Deliver for Patients



ACHIEVE & DELIVER CLINICAL DATA UPDATE | JANUARY 3, 2024

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Program

Opening remarks
Joshua Brumm, President & CEO

DYNE-101 ACHIEVE Trial Data
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on Myotonic Dystrophy Type 1 (DM1)
Valeria A. Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Professor of Neurology, University of Milan and a Principal Investigator for the ACHIEVE Trial

Q&A

Program

DYNE-251 DELIVER Trial Data
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on Duchenne Muscular Dystrophy (DMD)
Perry Shieh, M.D., Ph.D., Professor of Neurology and Pediatrics at the David Geffen School of Medicine at UCLA and a Neurologist at the Ronald Reagan UCLA Medical Center in Los Angeles and a Principal Investigator for the DELIVER Trial

Q&A

Closing remarks
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Q&A

OUR MISSION

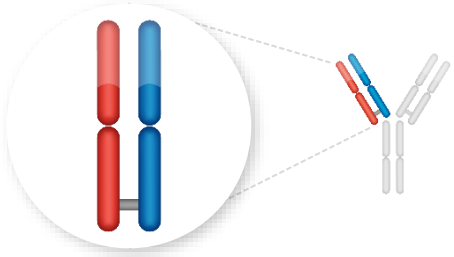
Life-transforming therapies

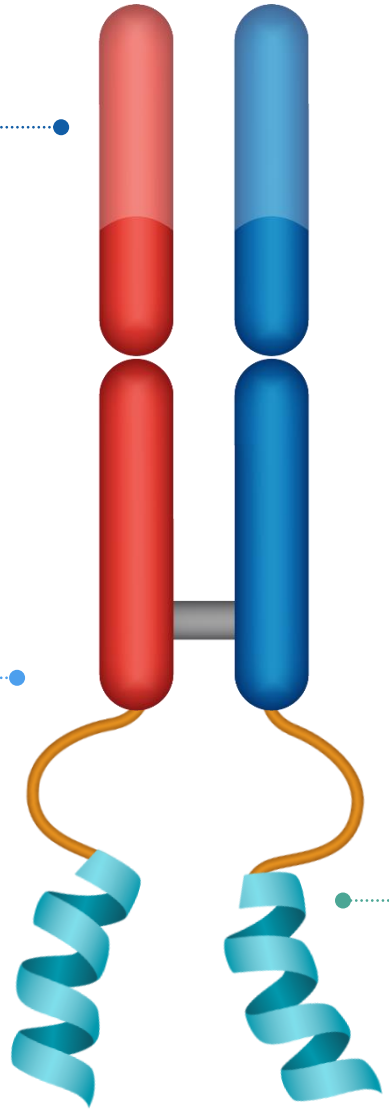
for patients with serious muscle diseases

Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



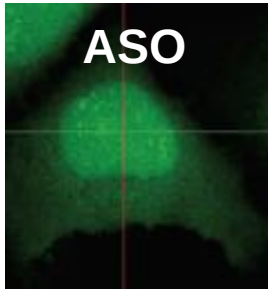


LINKER

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

Adapted from Ohrt T., et al. *Nucleic Acids Res* 2006;34:1369.

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.

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Q&A

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

DM1 Community Urgently Needs Treatment Options

“There was a period where I allowed myself to grieve. I think we all need that. The grief of not having other children, the grief of having a body that changes, the grief of seeing the disease in others.

I see my brother deteriorating, and he's 15 years younger than me and he looks older than me. It's scary.

In a nutshell, it's a huge, complex disease. It not only affects every muscle in your body, but also your brain, cognition, your stamina, your endurance. And also, I think myotonic dystrophy is not just a physical disability, it also involves mental health.”

Sarah

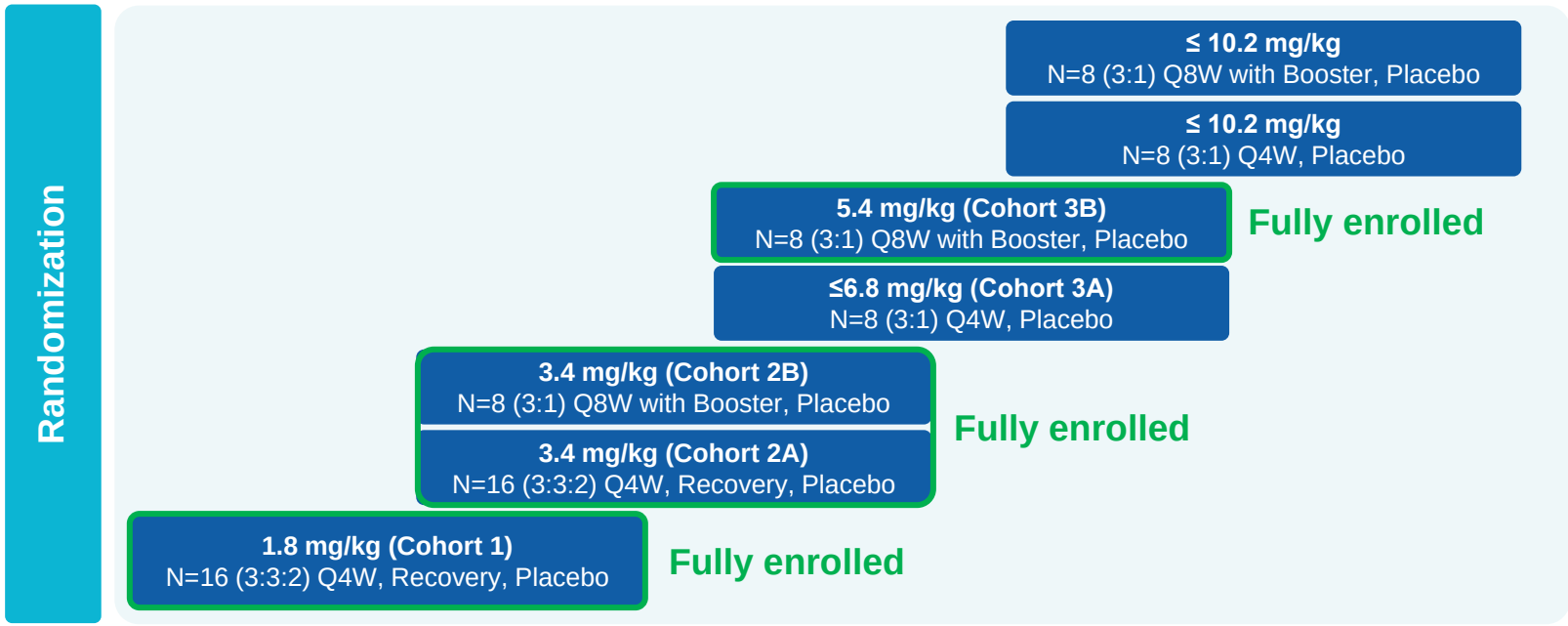
Phase 1/2 Clinical Trial to Evaluate DYNE-101 in Patients with DM1

Population	Primary Endpoints	Key Secondary	Stages of ACHIEVE
• Adult patients living with DM1 • Ages 18 to 49 years	• Safety and tolerability	• Pharmacokinetics • Change from baseline of: – Splicing – *DMPK* RNA expression – Multiple assessments of muscle strength and function	• 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

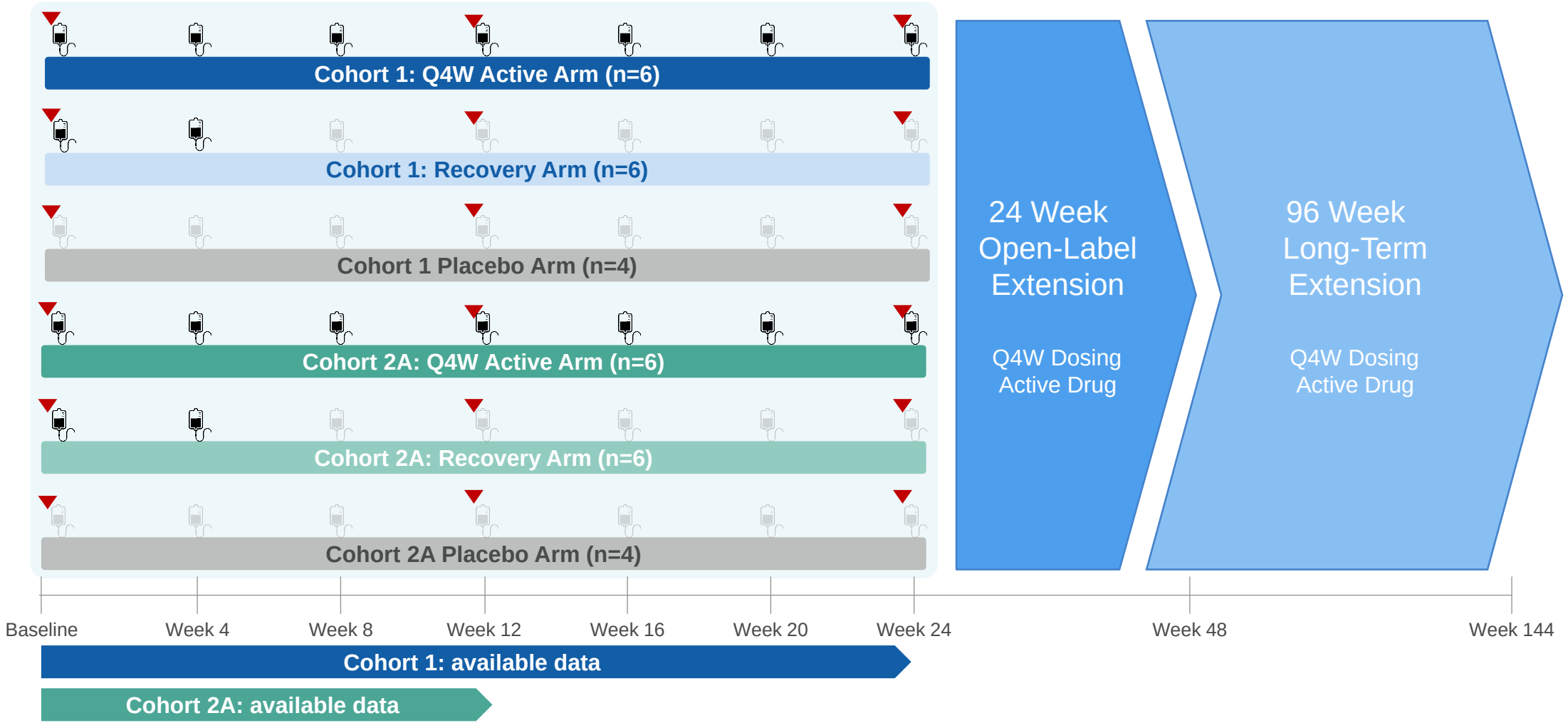
Global Strategy & Adaptive Trial Design To Enable Rapid Achievement of Potentially Registrational Clinical Data

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.

Dosing Arms & Schedule

ACHIEVE

Biopsy [1] DYNE-101 Placebo



1. Needle biopsies taken from alternating TA muscles prior to dosing at baseline, Day 85, and Day 169.

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]

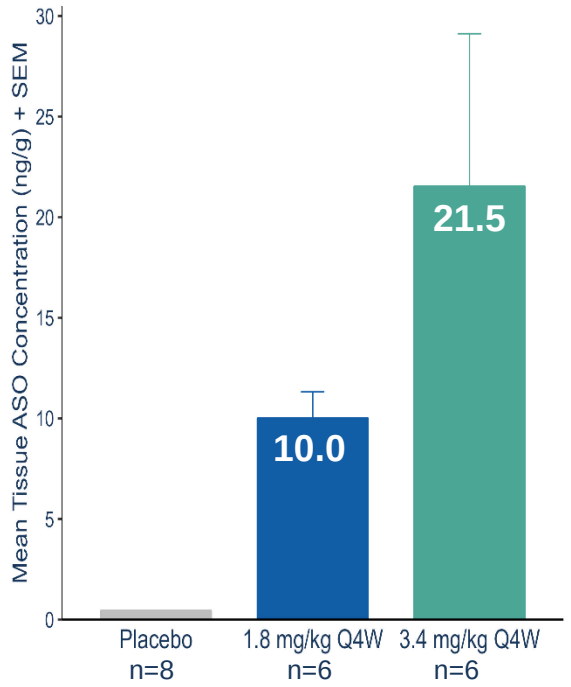
1. Data as of December 6, 2023; 2. Number of doses administered in ACHIEVE to date reflects doses administered across all study periods (MAD, OLE, LTE); 3. Treatment emergent HGB or PLT persistently below LLN or reported AE. 4.Treatment emergent and persistently abnormal renal parameters or reported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

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

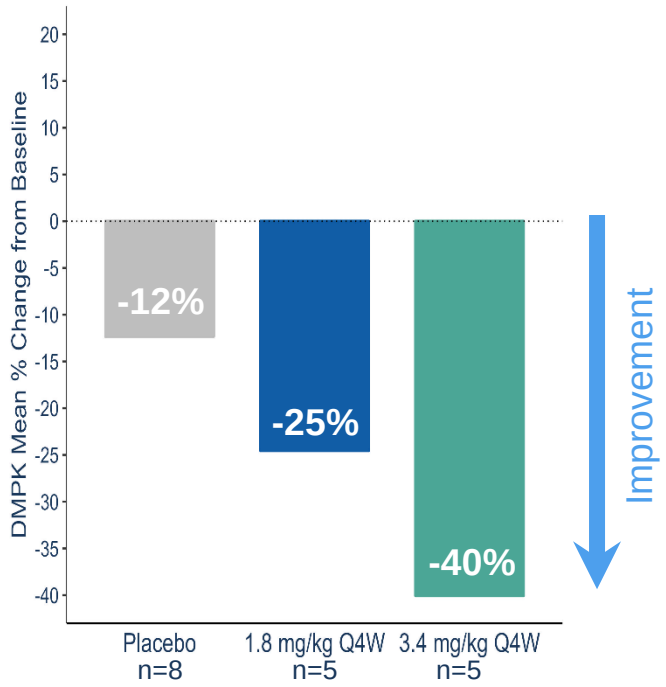
PK → Muscle Delivery

PD → Total *DMPK* Knockdown → Splicing

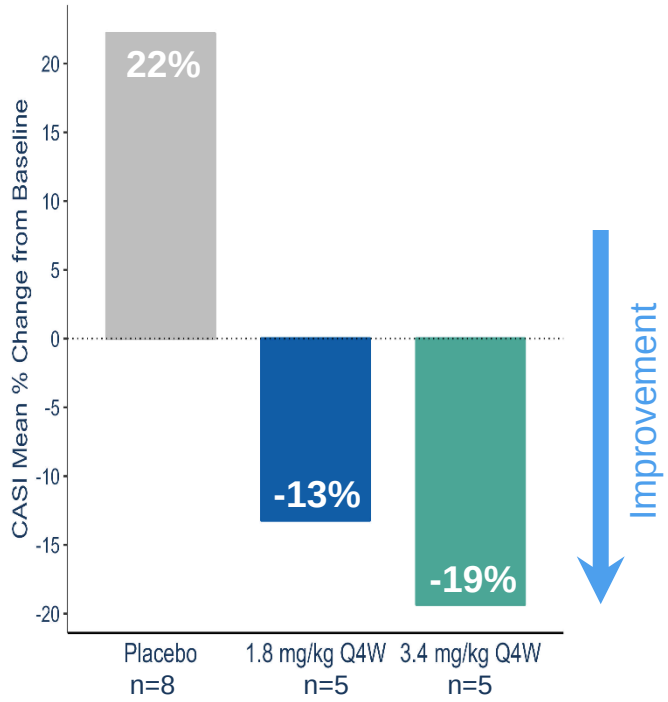
ASO Muscle Concentration



DMPK KD



CASI-22



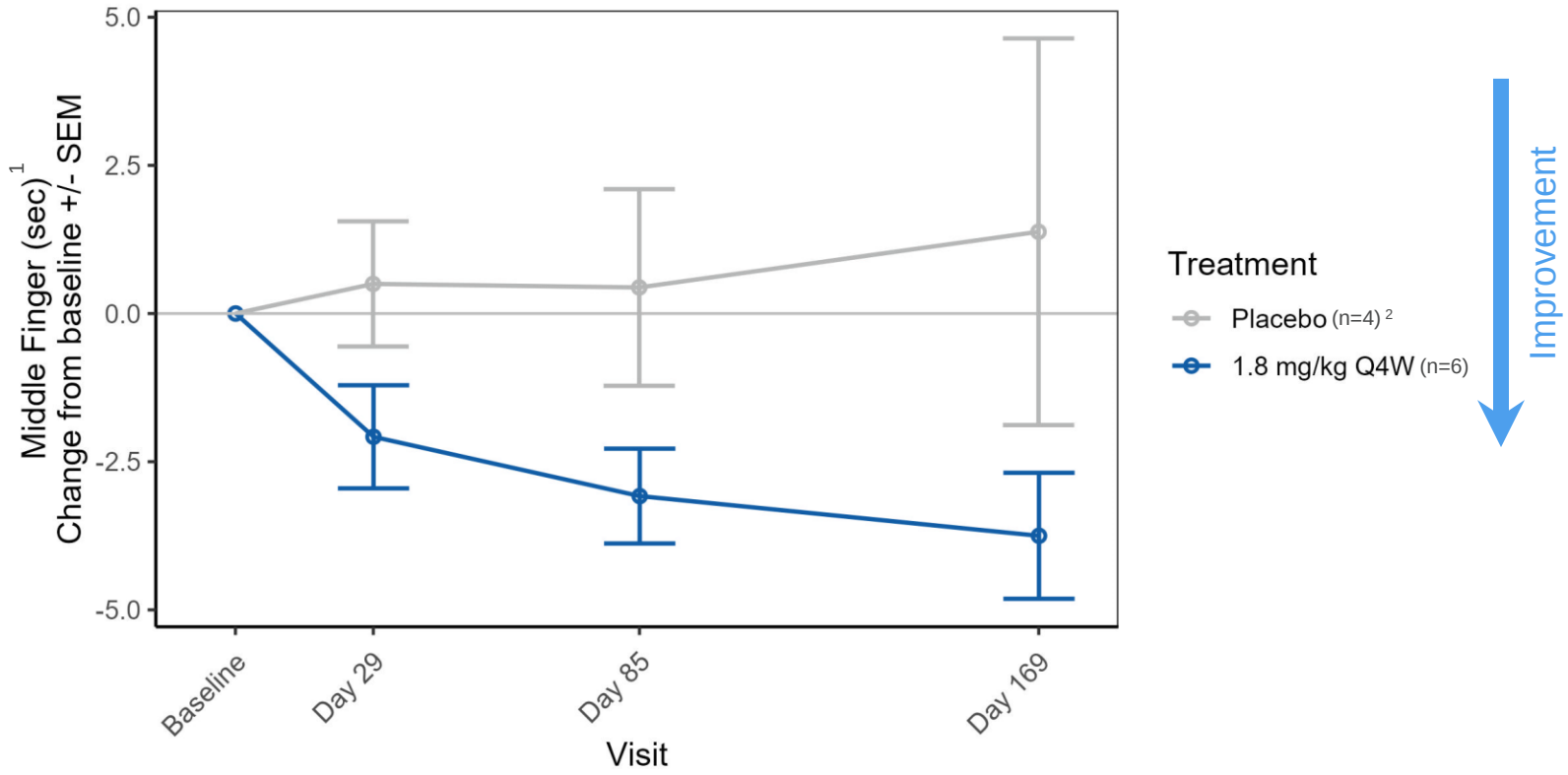
Favorable Safety Profile, with ~300 Doses Administered To Date, Has Supported Dosing Up to 6.8 mg/kg [1]

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

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

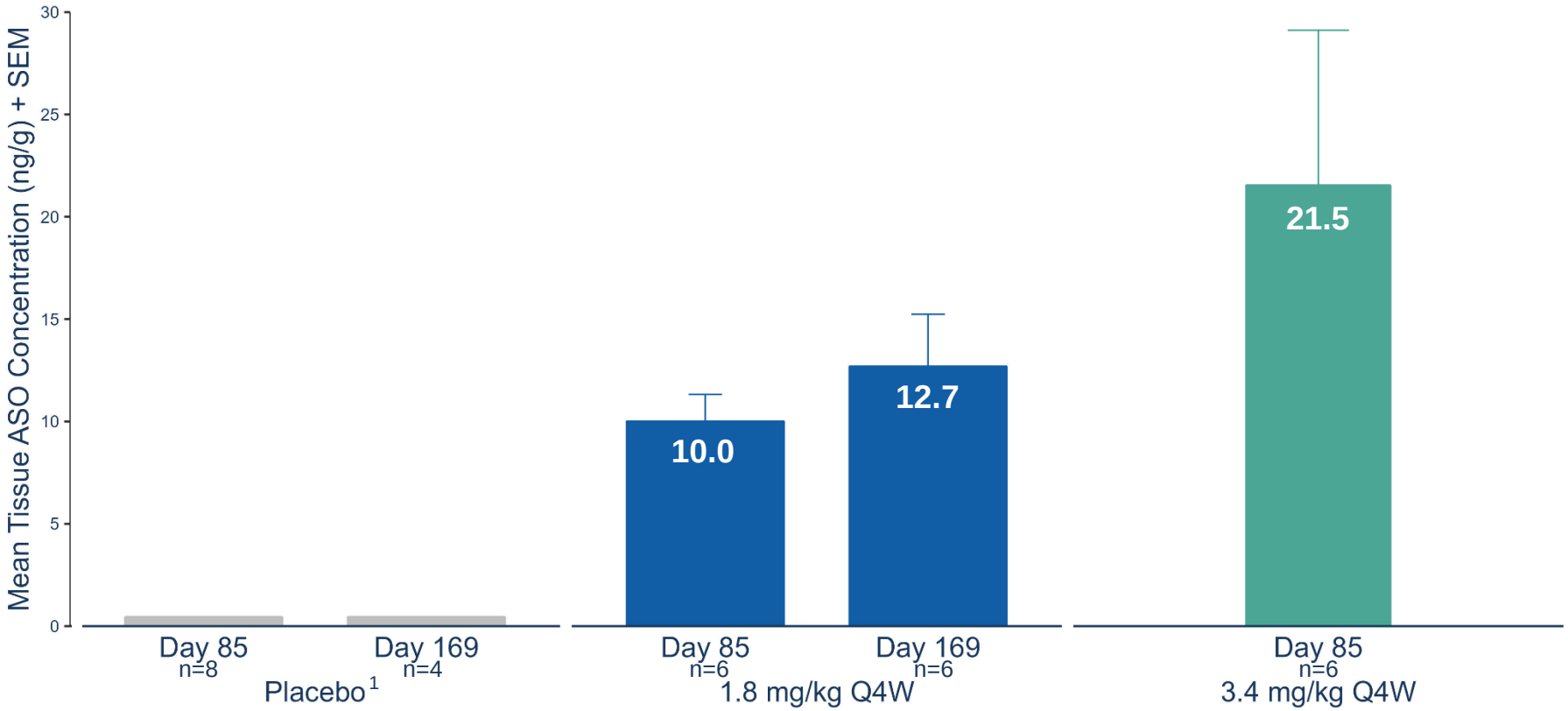
vHOT middle finger change from baseline



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.

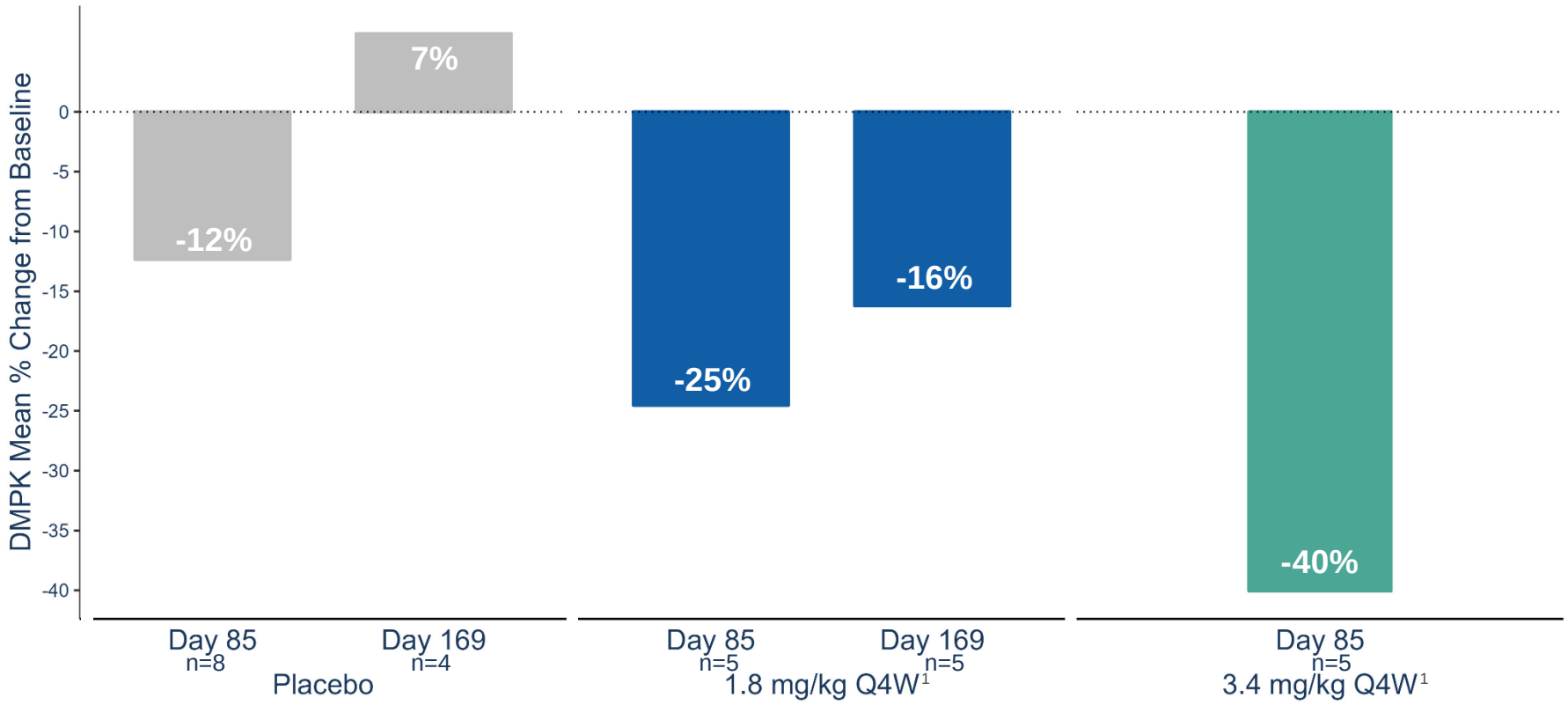
DYNE-101 Drove Robust, Dose-Dependent Delivery of ASO to Muscle

ASO Muscle Concentration



1. Placebo values were below the LLQ at Day 85 and Day 169. LLOQ is 0.85 ng/g.

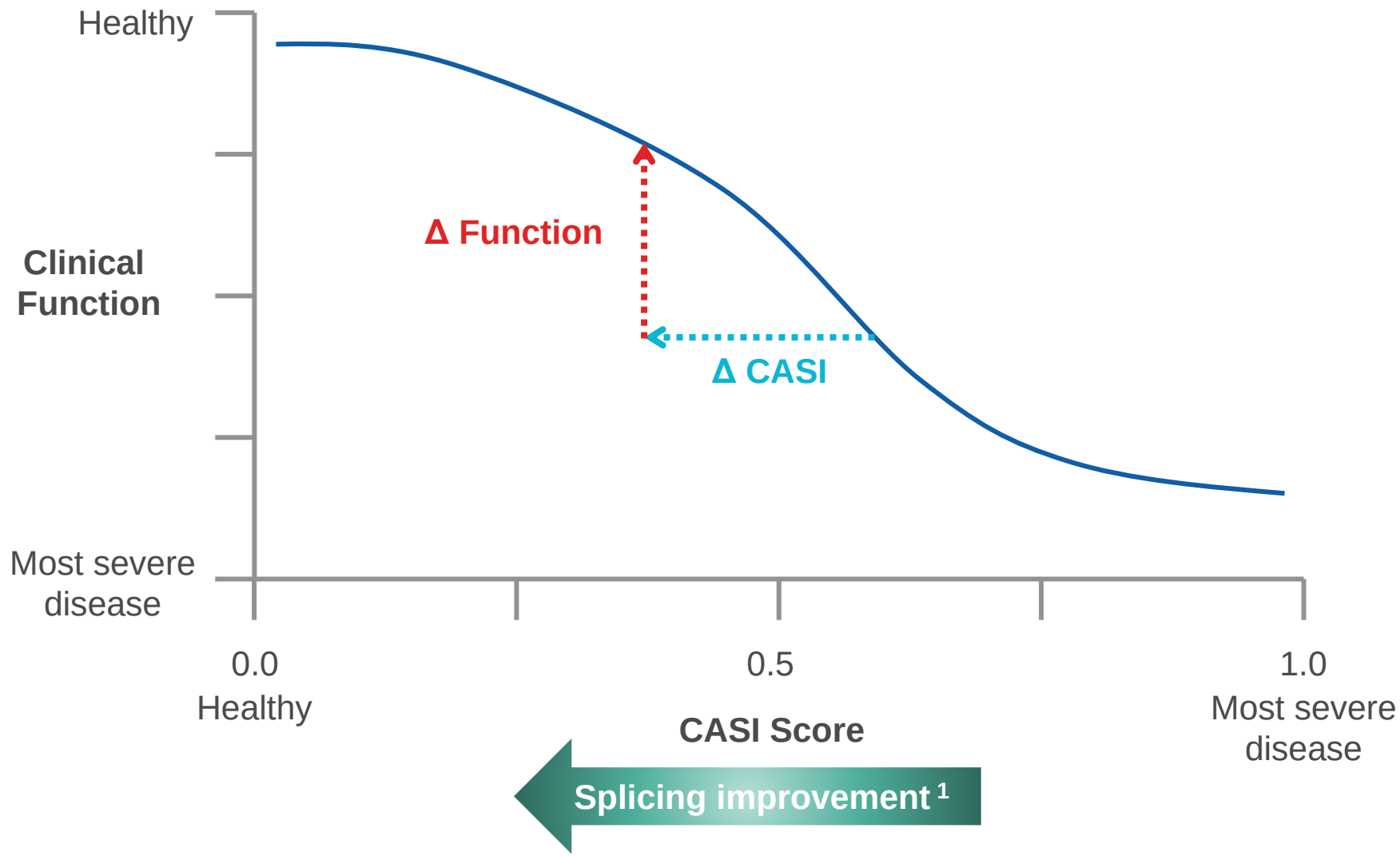
Achieved Dose-Dependent Target Engagement to Modify DM1 Biology



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

1. 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.

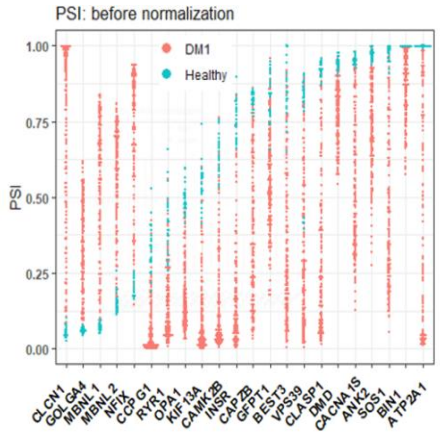
Correction of Splicing Index by DYNE-101 is Expected to Generate Functional Improvement



1. Chart for illustrative purposes only; illustrates how splicing improvement is expected to improve function; does not reflect any particular preclinical or clinical results.

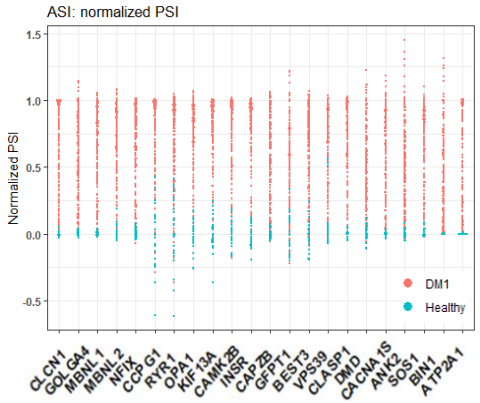
DMCRN NHS Enabled Establishment of Composite Alternative Splicing Index (CASI) as Biomarker Correlating with Clinical Function in DM1

PSI = Percent Spliced In



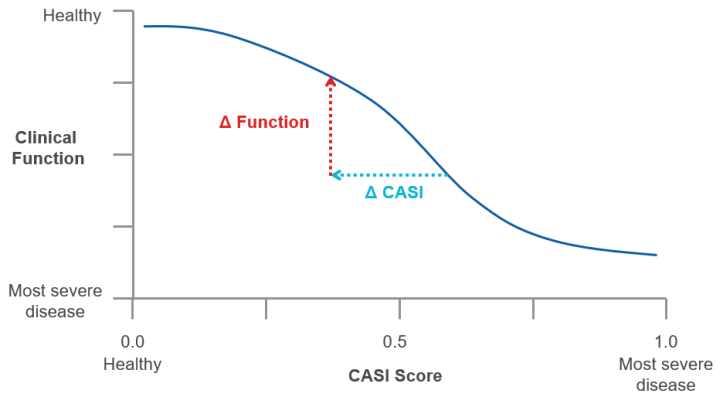
Targeted sequencing reads to calculate Percent Spliced In (PSI) of specific exons

ASI: Alternative Splicing Index



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

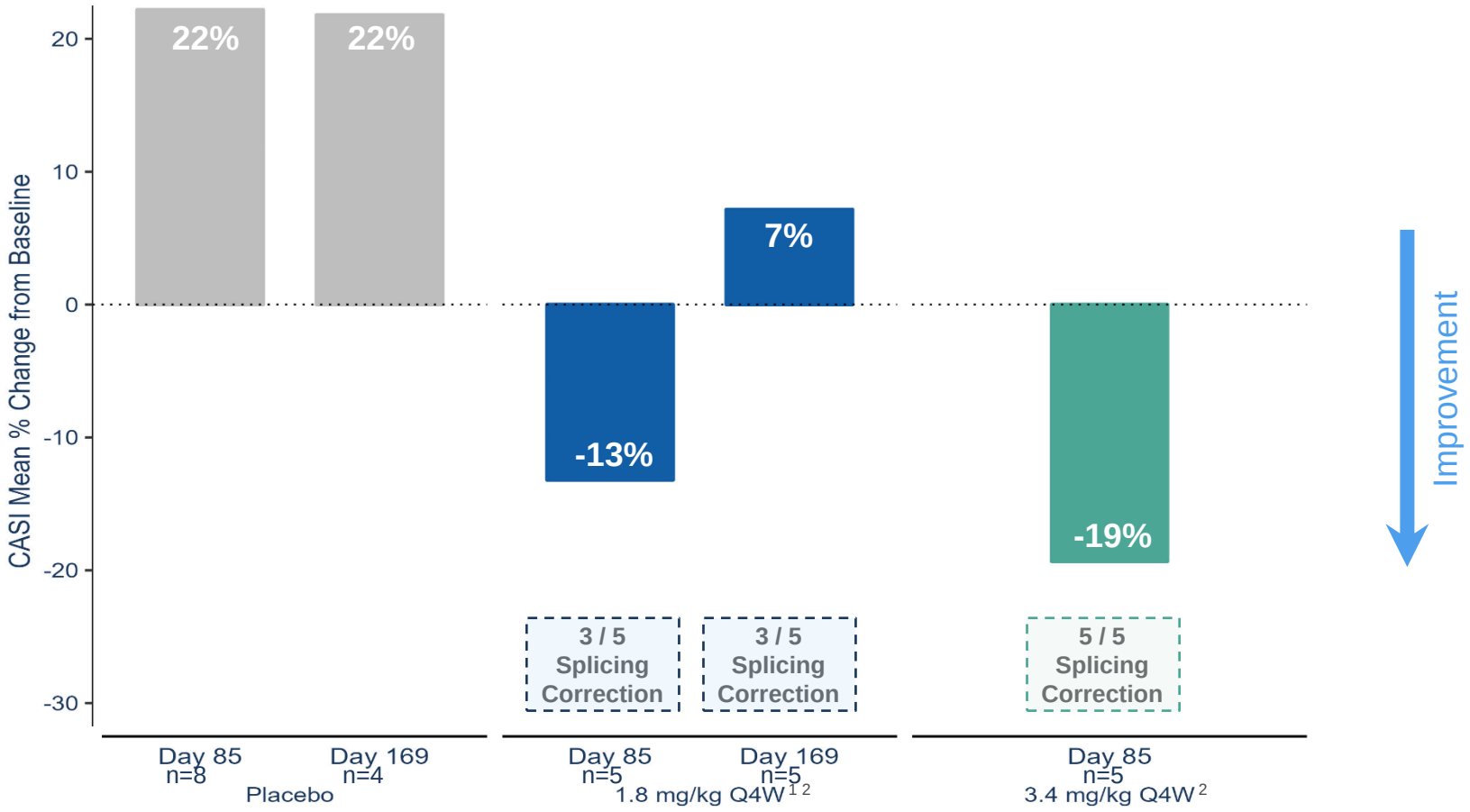
CASI: Composite Alternative Splicing Index



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

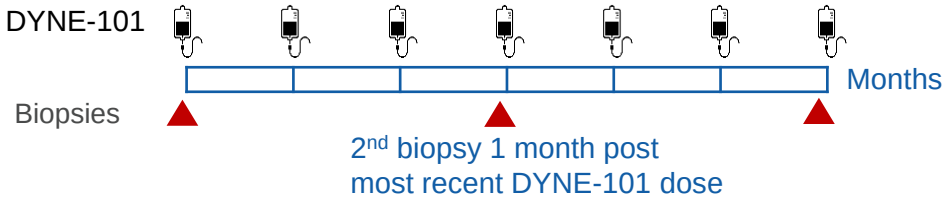


- **Dose response**
  - DYNE-101 3.4 mg/kg Q4W demonstrated mean 19% correction of splicing from baseline at Day 85 vs. 13% correction for 1.8 mg/kg Q4W
- **Consistency of response**
  - All evaluable participants in 3.4 mg/kg Q4W demonstrated splicing correction across 22-gene panel

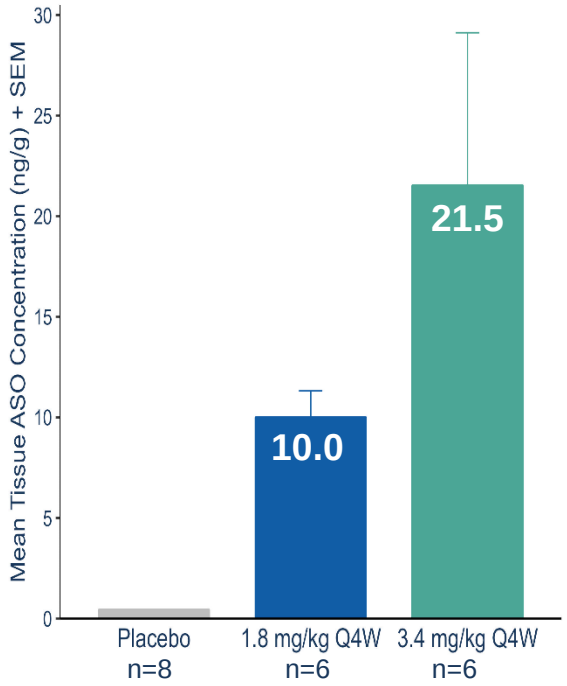
Mean % Change = mean of change from baseline / mean of baseline

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.

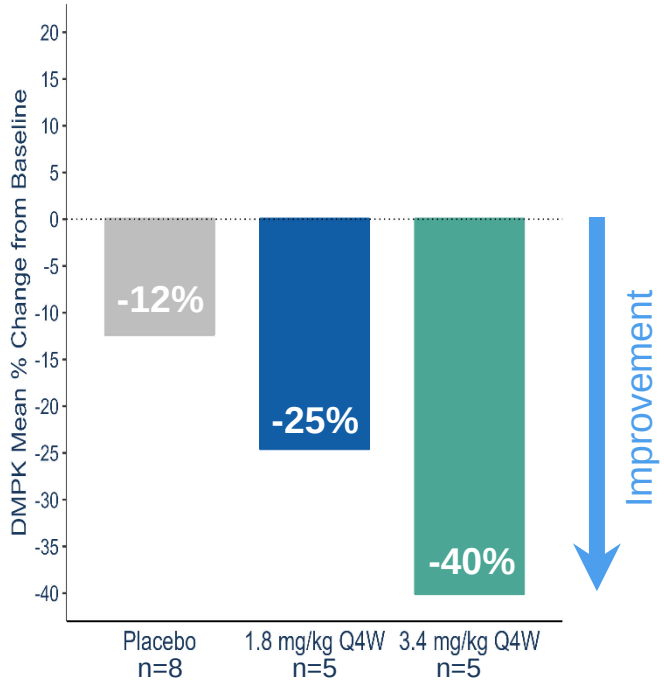
Monthly Dosing of DYNE-101 Demonstrated Robust Delivery, DMPK Knockdown and Splicing Correction at 3 Months



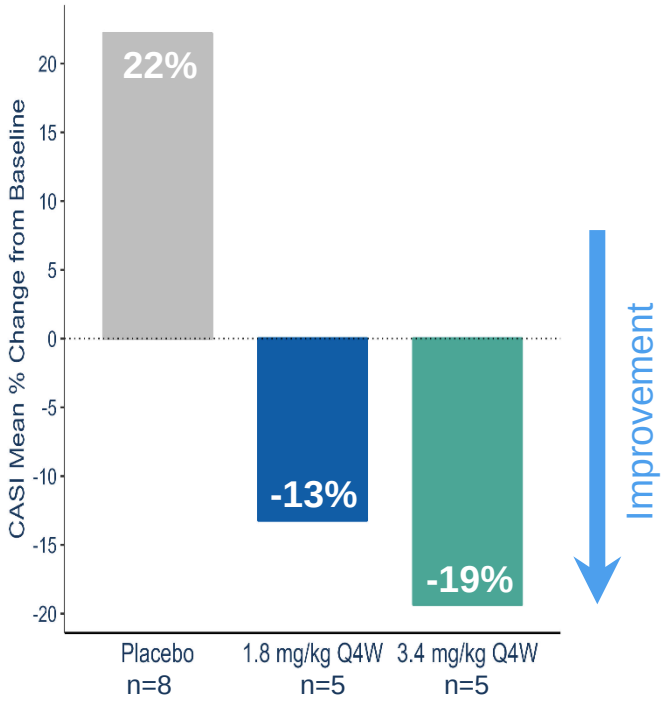
ASO muscle concentration



DMPK KD

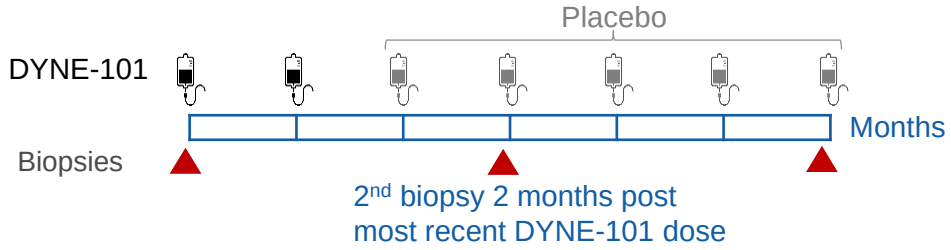


CASI-22

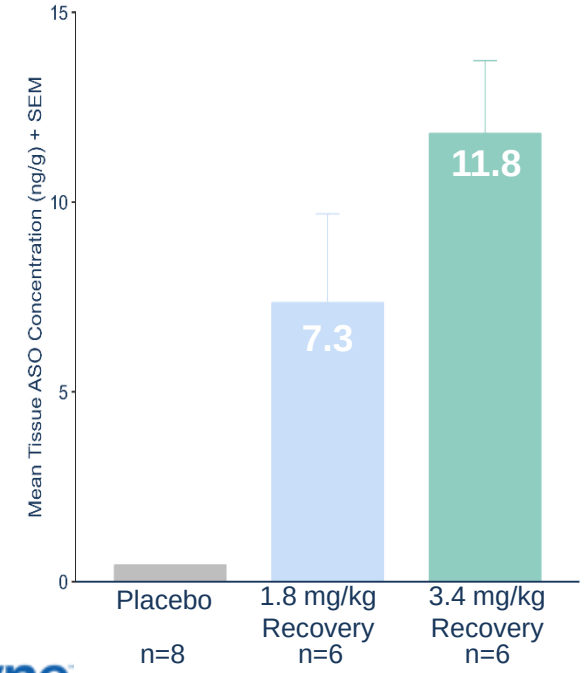


Recovery Data Supports Less Frequent Dosing Regimen

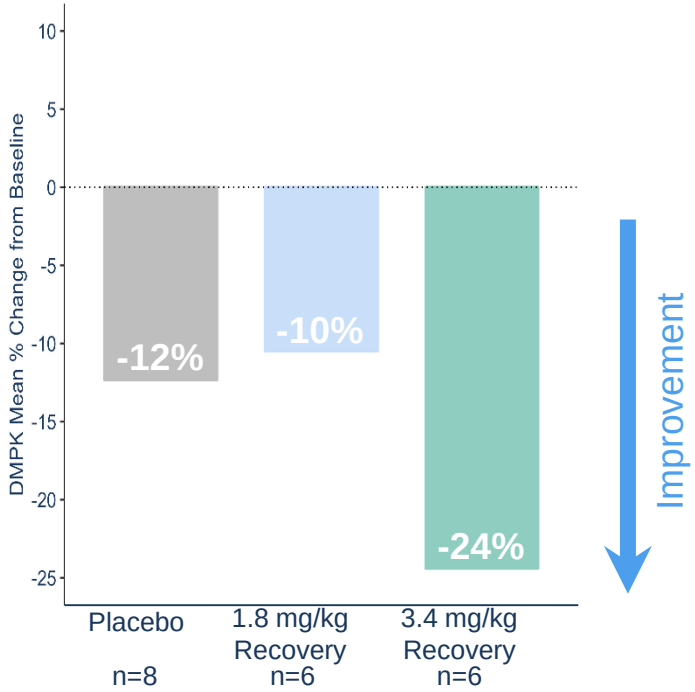
Recovery Arm at Day 85 Reflect 2 Doses of DYNE-101 with Biopsy 2 Months Post Last Dose



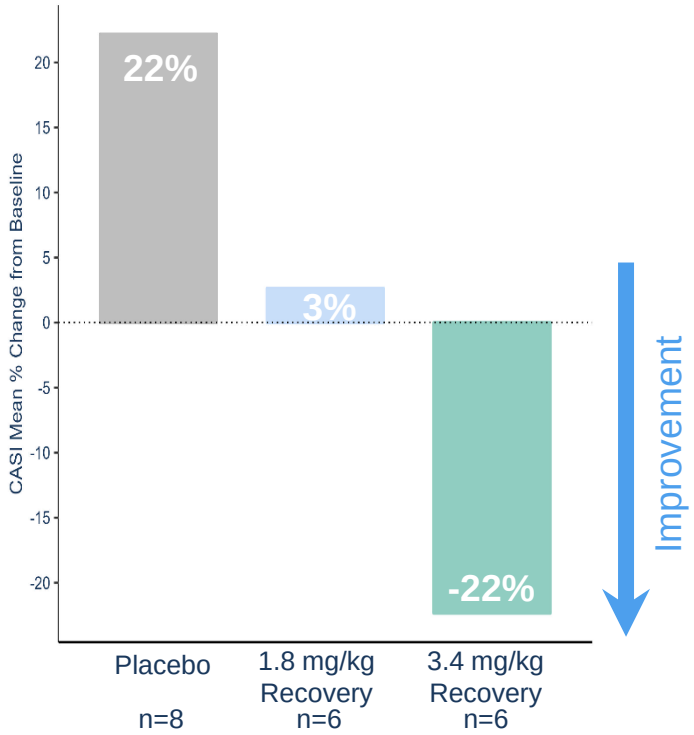
ASO muscle concentration



DMPK KD



CASI-22



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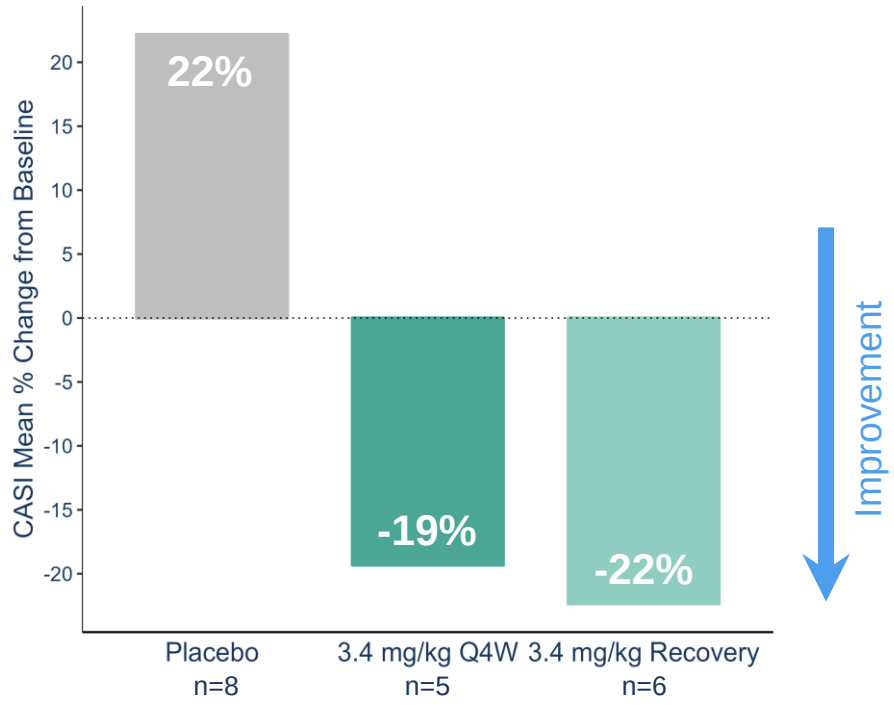
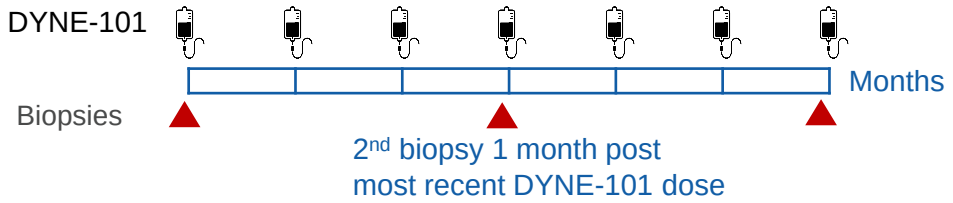
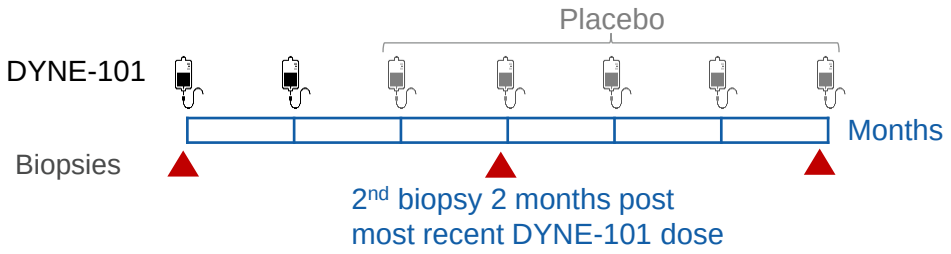
CASI-22



Q4W Active Arm



Q4W Recovery Arm

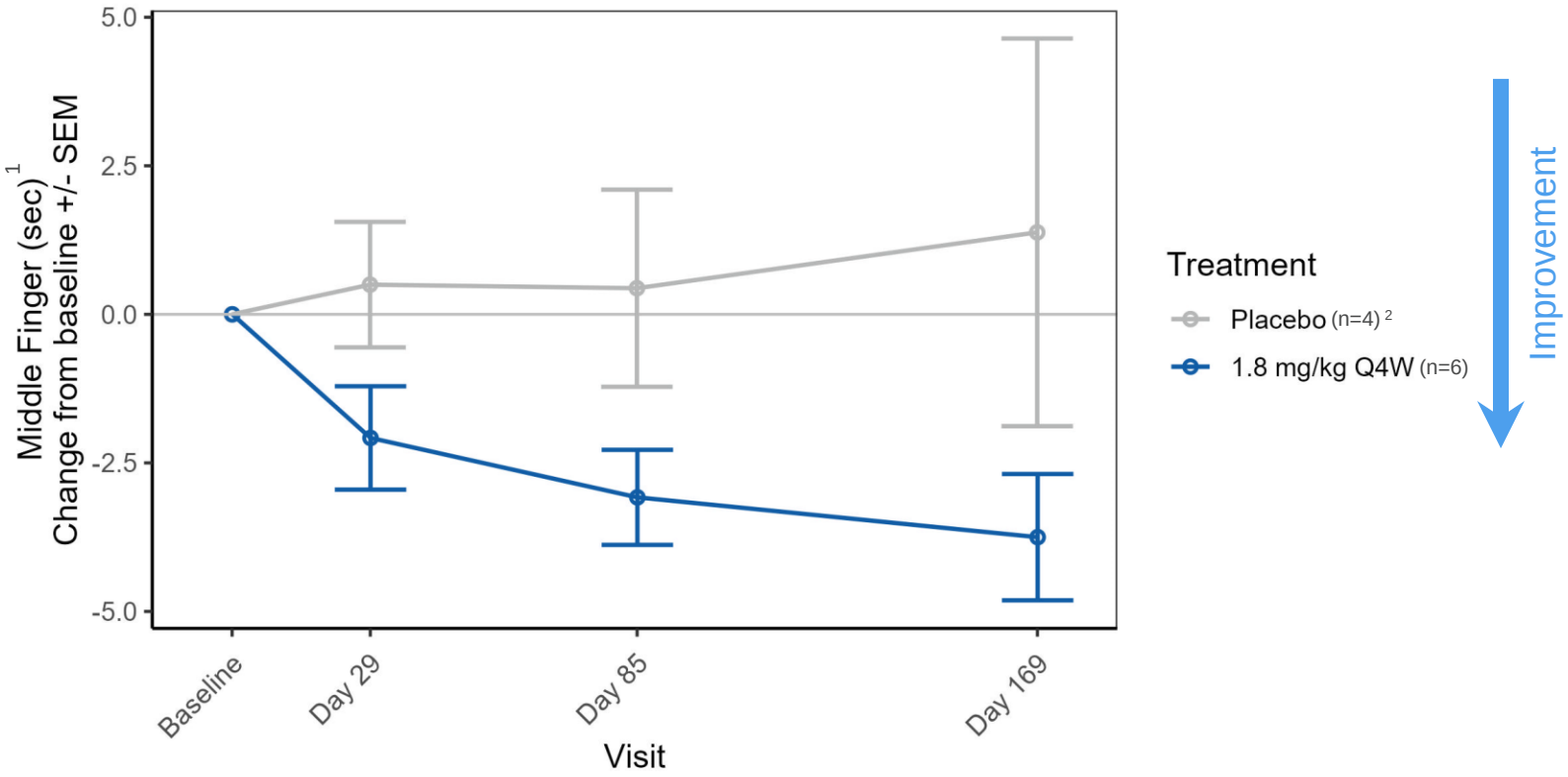


Robust Splicing Correction in Both Active and Recovery Arm with 3.4 mg/kg Dose

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

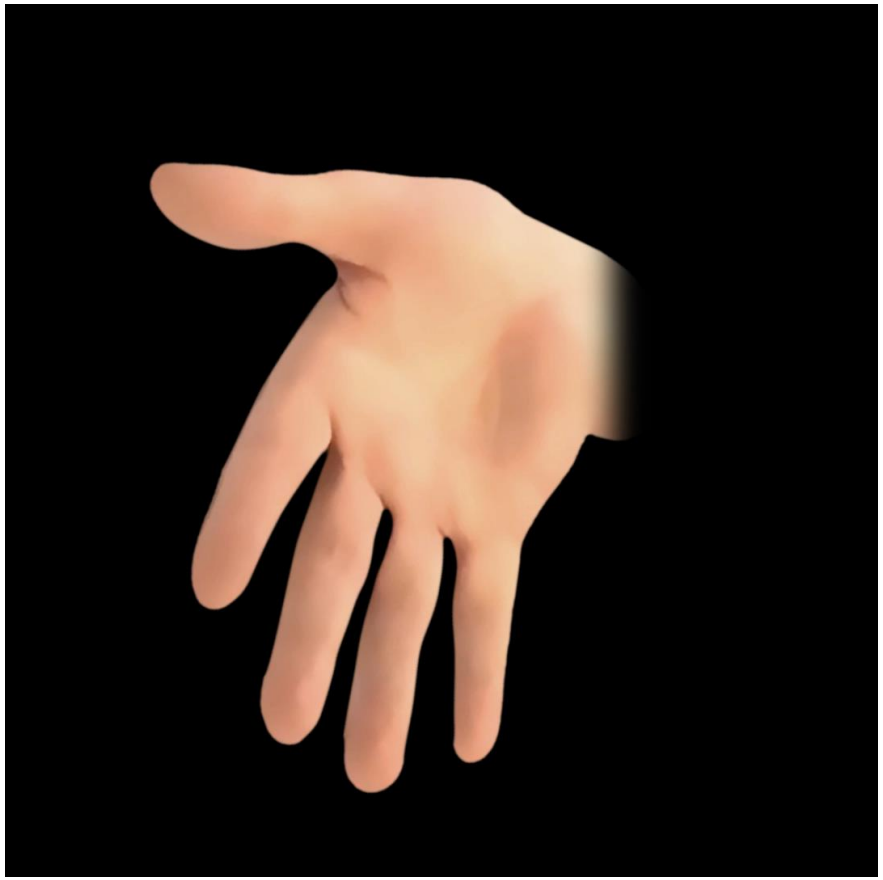
vHOT middle finger change from baseline



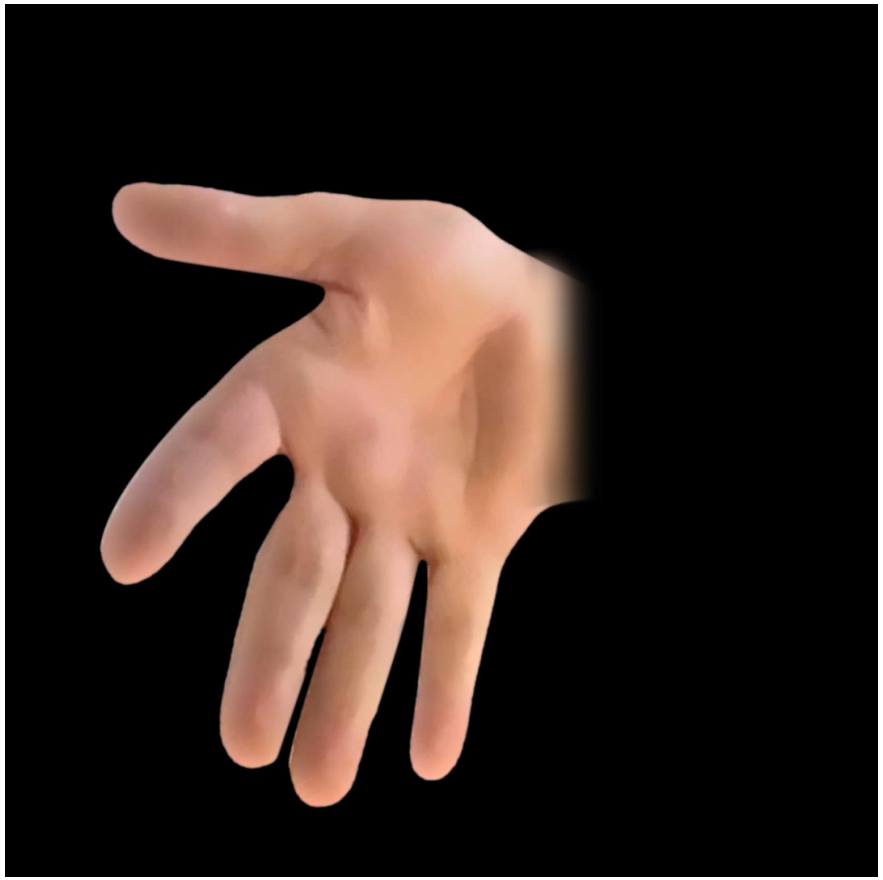
1. Middle Finger (sec) is the average of all myotonia trials for an individual participant in ACHIEVE; 2. Four participants randomized to placebo arm in 1.8 mg/kg cohort; n=4 at Day 169.

Demonstration of DYNE-101 Impact on Myotonia at Lowest Dose

Baseline



On Treatment



Cohort 1 Participant

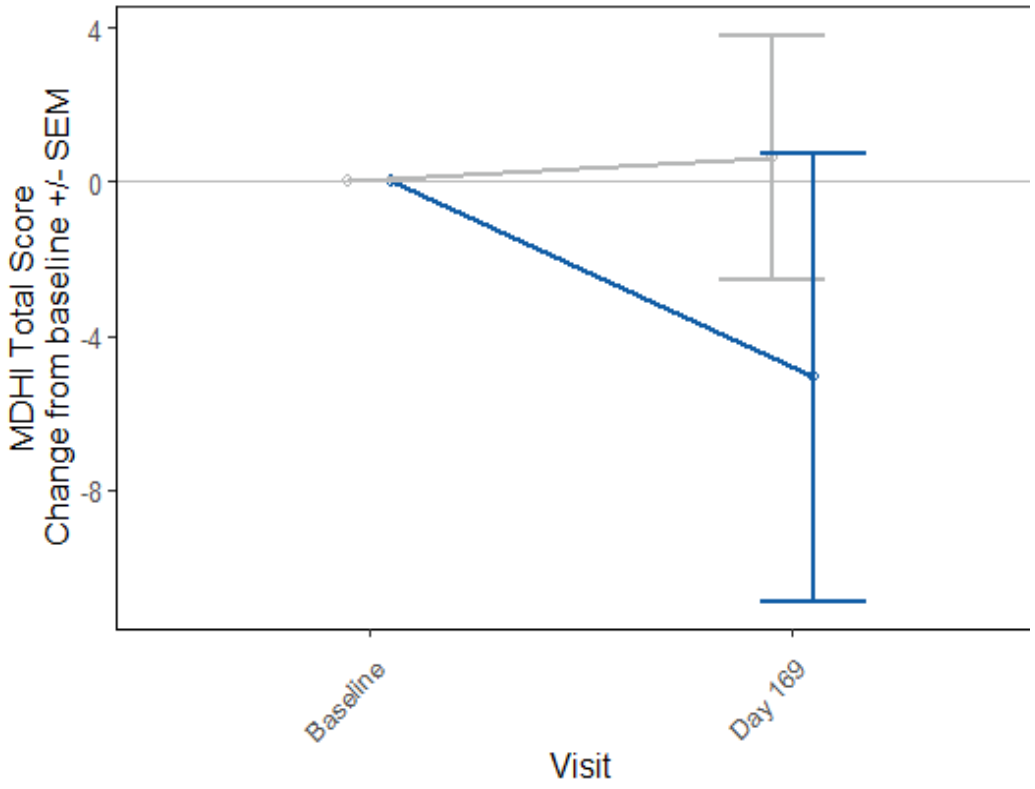
1.8 mg/kg Q4W

Note: Patient myotonia videos have been altered to preserve blinding protocol of ACHIEVE trial and patient privacy.

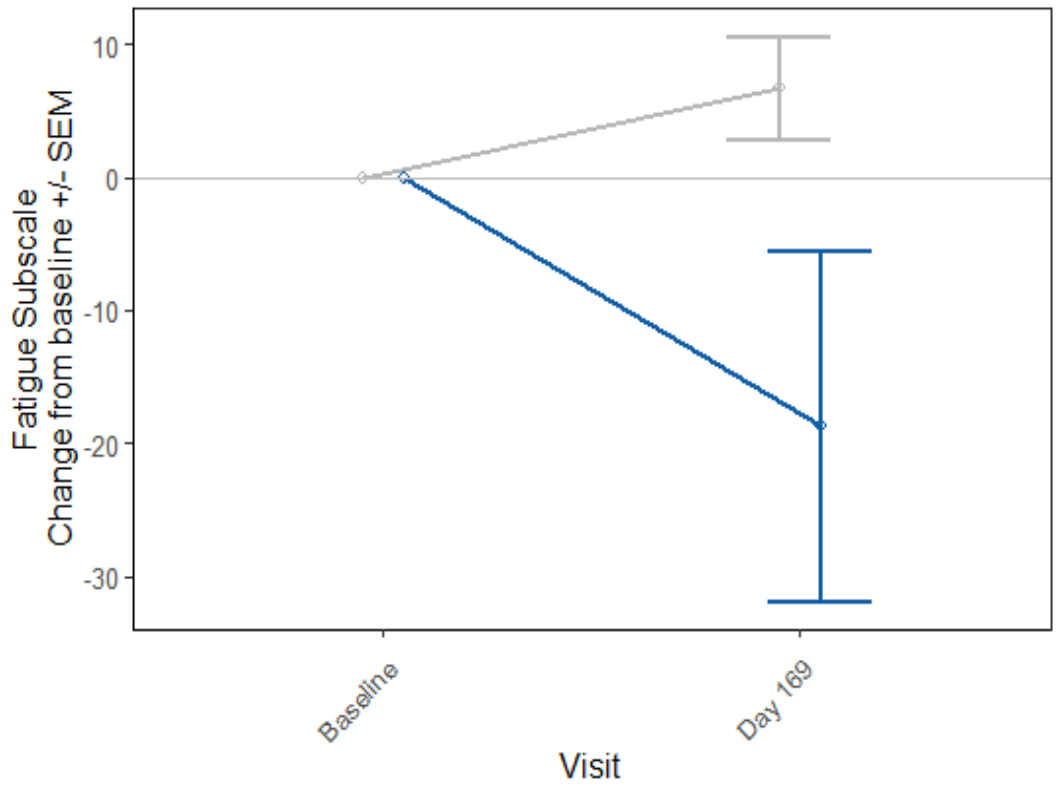
Patient Reported Outcomes Beginning to Show Effect at Lowest Dose in ACHIEVE

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.

Program

Opening remarks
Joshua Brumm, President & CEO

DYNE-101 ACHIEVE Trial Data
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on Myotonic Dystrophy Type 1 (DM1)
Valeria A. Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Professor of Neurology, University of Milan and a Principal Investigator for the ACHIEVE Trial

Q&A

PERSPECTIVES ON MYOTONIC DYSTROPHY TYPE 1

Valeria A Sansone, MD, PhD
Full Professor of Neurology, University of Milan
Neurorehabilitation Unit
Clinical and Scientific Director of the NEMO Center

Disclosures

I provide intellectual consultation in Advisory Boards/teaching activities for Biogen, Roche, Novartis, Dyne, Lupin, PTC, Santhera, Amylyx

Perspectives on Myotonic Dystrophy Type 1

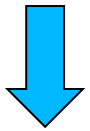
Overview

- Key elements of DM1
- Patient journey
- Unmet needs in DM1
- How is research addressing these?
  - What functional endpoints are most important?
  - What level of splicing matters?
  - What is clinically meaningful?
- How is the clinical development landscape evolving?

Prevalence

DM1 is the most frequent muscular dystrophy of adulthood

1:~~9~~000



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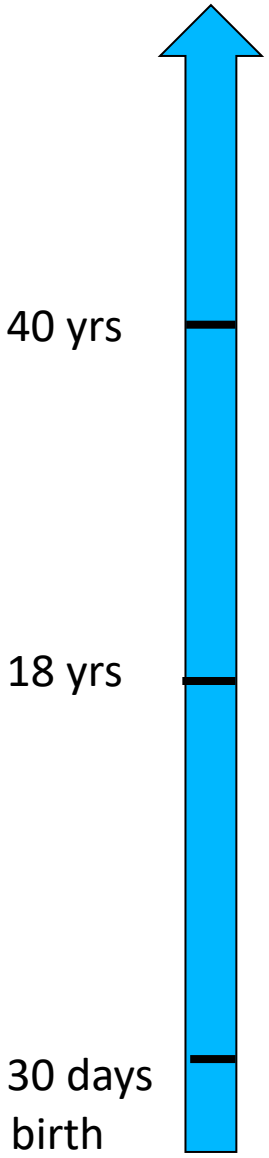
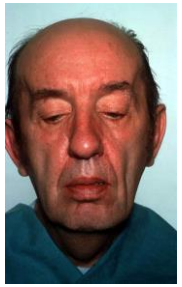
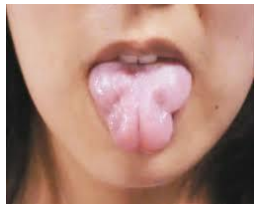
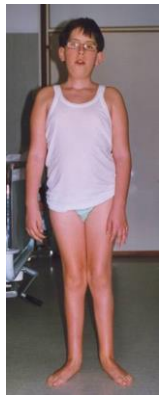
Nicholas Johnson
MDF meeting Philadelphia Sept. 2019

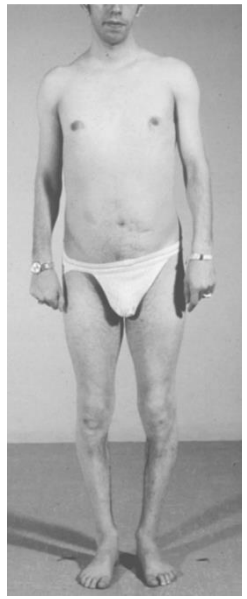
DM1: Onset At All Ages

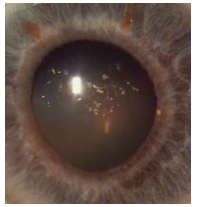








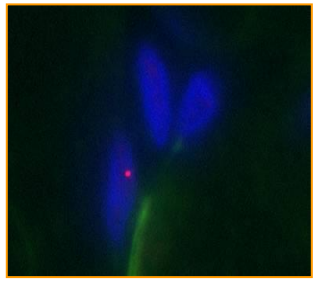




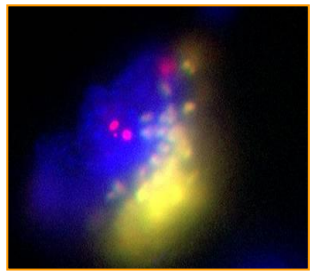
Myotonic Dystrophy is a spliceopathy
RNA-mediated toxic disease

expanded CTG repeat (DMPK)

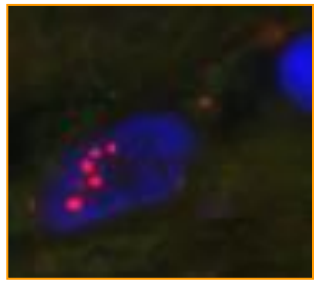
∧ expanded CUG repeat (RNA)



skeletal muscle

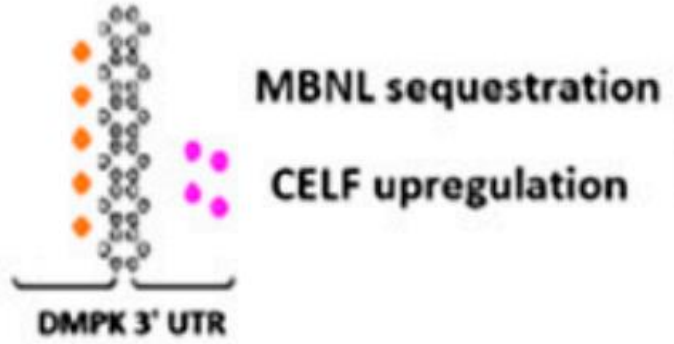


cortical neuron



heart

Kind courtesy of Charles Thornton



Patient journey

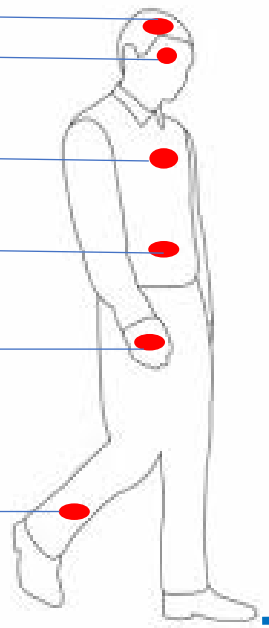
Frontal balding
Initial cataracts

Asymptomatic
AV block

GI problems

Fluctuating myotonia
Warm-up phenomenon

Stepping gait
L5 radiculopathy???



DIAGNOSTIC DELAY!!!
MULTIDISCIPLINARY CARE

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Diagnostic Odyssey of Patients with Myotonic Dystrophy

James E. Hilbert, MS[a], Tetsuo Ashizawa, MD[b], John W. Day, MD, PhD[c], Elizabeth A. Luebbe, MS[a], William B. Martens[a], Michael P. McDermott, PhD[a,d], Rabi Tawil, MD[a], Charles A. Thornton, MD[a], Richard T. Moxley III, MD[a], and the Registry Scientific Advisory Committee[*]

REVIEW OPEN ACCESS

Consensus-based care recommendations for adults with myotonic dystrophy type 1

Tetsuo Ashizawa, MD, Cynthia Gagnon, PhD, William J. Groh, MD, MPH, Laurie Gutmann, MD, Nicholas E. Johnson, MD, Giovanni Meola, MD, Richard Moxley III, MD, Shree Pandya, DPT, Mark T. Rogers, MD, Ericka Simpson, MD, Nathalie Angeard, PhD, Guillaume Bassez, MD, PhD, Kiera N. Berggren, MA, MS, Deepak Bhakta, MD, Marco Bozzali, MD, Ann Broderick, MD, MS, Janice L.B. Byrne, MD, Craig Campbell, MD, Edith Cup, PhD, John W. Day, MD, PhD, Elisa De Mattia, PT, Denis Duboc, MD, Tina Duong, MPT, PhDc, Katy Eichinger, PhD, Anne-Berit Ekstrom, MD, PhD, Baziel van Engelen, MD, PhD, Belen Esparis, MD, Bruno Eymard, MD, Marla Ferschl, MD, Shahinaz M. Gadalla, MD, PhD, Benjamin Gallais, PhD, Todd Goodglick, MD, Chad Heatwole, MD, James Hilbert, MS, Venessa Holland, MD, MPH, Marie Kierkegaard, PhD, Wilma J. Koopman, NP, PhD, Kari Lane, RD, Daphne Maas, PT, MSc, Ami Mankodi, MD, Katherine D. Mathews, MD, Darren G. Monckton, PhD, David Moser, PhD, Saman Nazarian, MD, PhD, Linda Nguyen, MD, Peg Nopoulos, MD, Richard Petty, MD, Janel Phetteplace, MS, Jack Puymirat, MD, PhD, Subha Raman, MD, Louis Richer, PhD, Elisabetta Roma, MD, Jacinda Sampson, MD, PhD, Valeria Sansone, MD, PhD, Benedikt Schoser, MD, Laurie Sterling, MS, Jeffrey Statland, MD, S.H. Subramony, MD, Cuixia Tian, MD, Careniña Trujillo, RN, MSN, Gordon Tomaselli, MD, Chris Turner, MD, PhD, Shannon Venance, MD, PhD, Aparajitha Verma, MD, Molly White, MA, and Stefan Winblad, PhD on behalf of the Myotonic Dystrophy Foundation

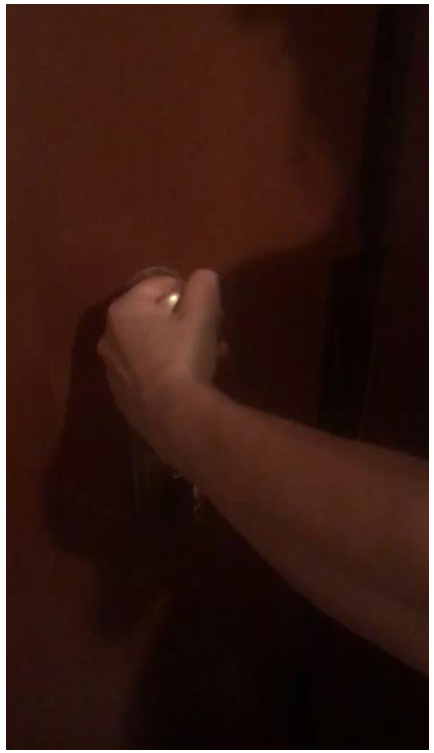
Correspondence
Dr. White
molly.white@myotonic.

Neurology: Clinical Practice December 2018 vol. 8 no. 6 507-520 doi:10.1212/CPJ.0000000000000531

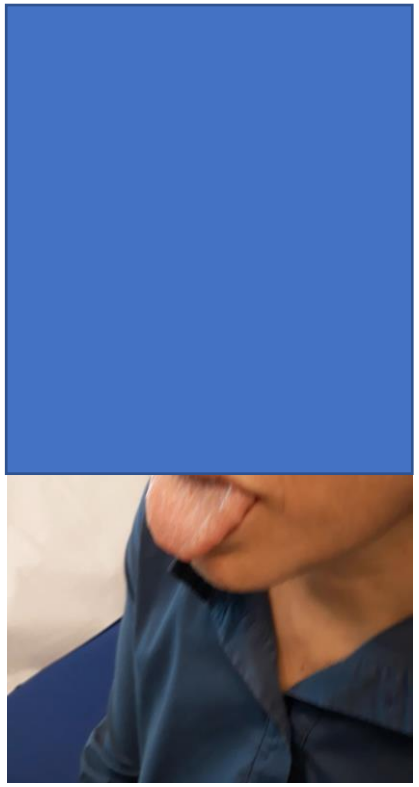
Burden Of Disease

Muscle weakness, fatiguability and myotonia

Stumbles, tripping and falls



Grip myotonia & distal hand impairment



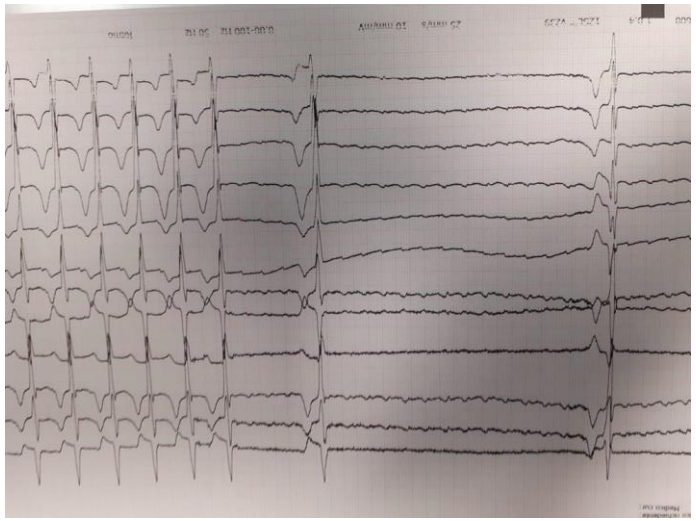
Tongue myotonia & Slurred speech

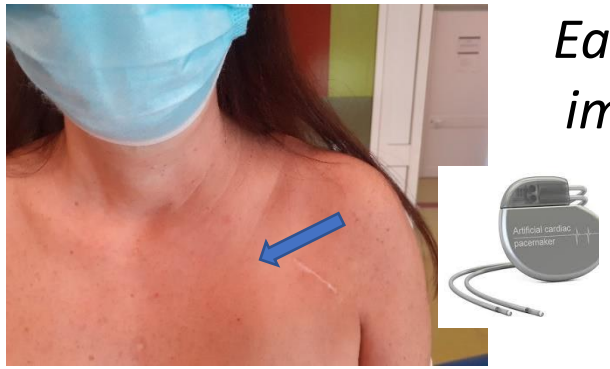
Burden Of Disease

Respiratory muscle weakness

Secretion management
Daytime hypoxia
Hypercapnia

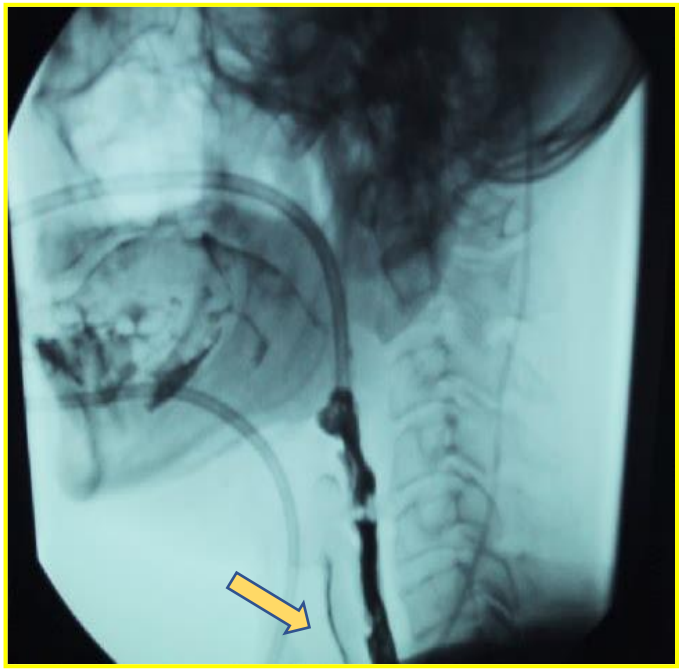
Cardiac arrhythmias





Early PM/ICD implantation

Smooth muscle involvement



Swallowing difficulties
GI symptoms

Burden Of Disease

Cognitive & behavioral abnormalities

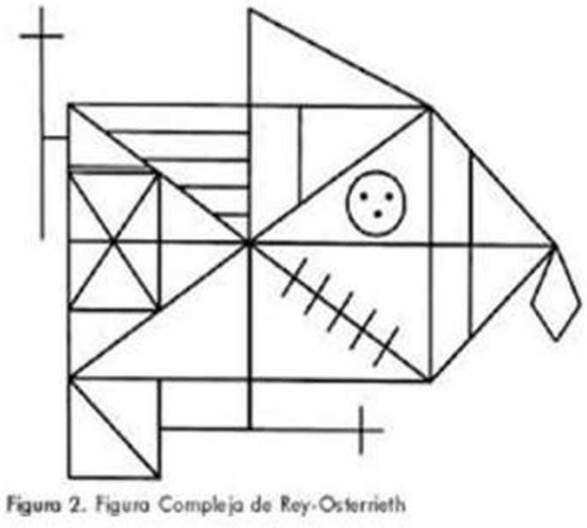
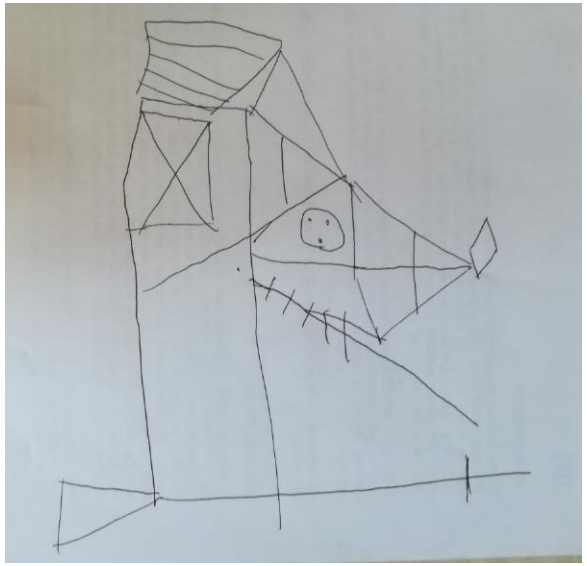


Figura 2. Figura Compleja de Rey-Osterrieth



Central fatigue, apathy,
frontal dysexecutive syndrome,
Excessive Daytime Sleepiness

Unmet needs

No Treatment!

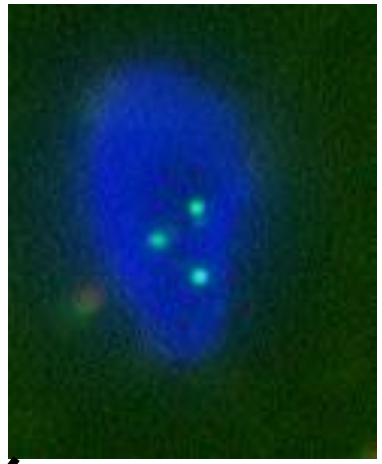
Unmet needs

Proof-of-concept of a potential drug

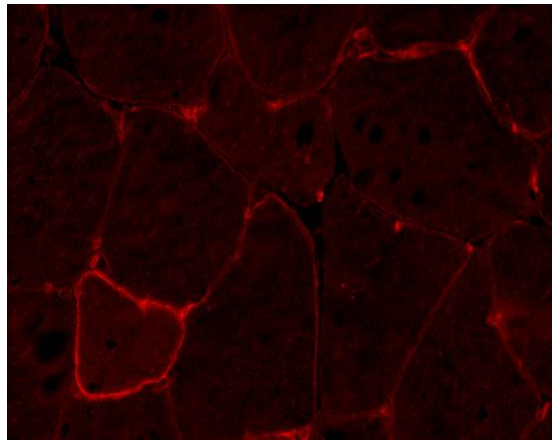
Improvement of myotonia

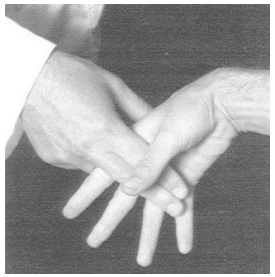
expanded CTG repeat
(DMPK)

expanded repeat
(DMPK RNA)



faulty regulation of
alternative splicing
(CLCN1)





myotonia

The FORCE Platform & Unmet needs

Preclinical Data

- **Correction of splicing** in the hTfR1/DMSXL mouse model observed in skeletal and cardiac muscle
- **Durable knockdown** of toxic human nuclear *DMPK* RNA in the hTfR1/DMSXL mouse model
- **Reversal of myotonia in HSA^{LR} Mouse Model**
- **Delivery to the CNS i**n hTfR1/DMSXL mice and NHPs
- **Robust effects** on skeletal, diaphragm, cardiac, smooth muscles and favorable safety profile in preclinical studies

Initial Data from ACHIEVE Trial of DYNE-101

- **Correction of splicing** approaching the 20-25% target level believed needed to drive functional benefits
- **Delivery to muscle tissue and** *DMPK* knockdown
- **Improvement in myotonia of almost 4 seconds** as measured by vHOT at a low dose
- **Early signs of impact on patient reported outcome (MDHI), including fatigue subscale.** Encouraging and important given the CNS manifestations in DM1
- **Favorable safety profile** and now dosing in higher cohorts

Conclusions

WHY ARE THESE ACHIEVE DATA IMPORTANT

- DM is the most frequent muscular dystrophy (1:3500 adults) with no approved therapies
- Very variable: very severe neonatal form to late onset forms
- Multiple organ involvement
- Very high patient and family burden, social impact, productivity
- Encouraging results at low doses:
  - Efficacy: improvement in myotonia
  - Splicing: nearing the 20-25% target level
  - Safety: favorable safety profile to date[1]

1. Data as of December 6, 2023

Data So Far Support the ASO Approach

Transcriptional silencing

1. Inhibition of RNA polymerase co-factors
2. Small molecules that bind to GC-rich repeats

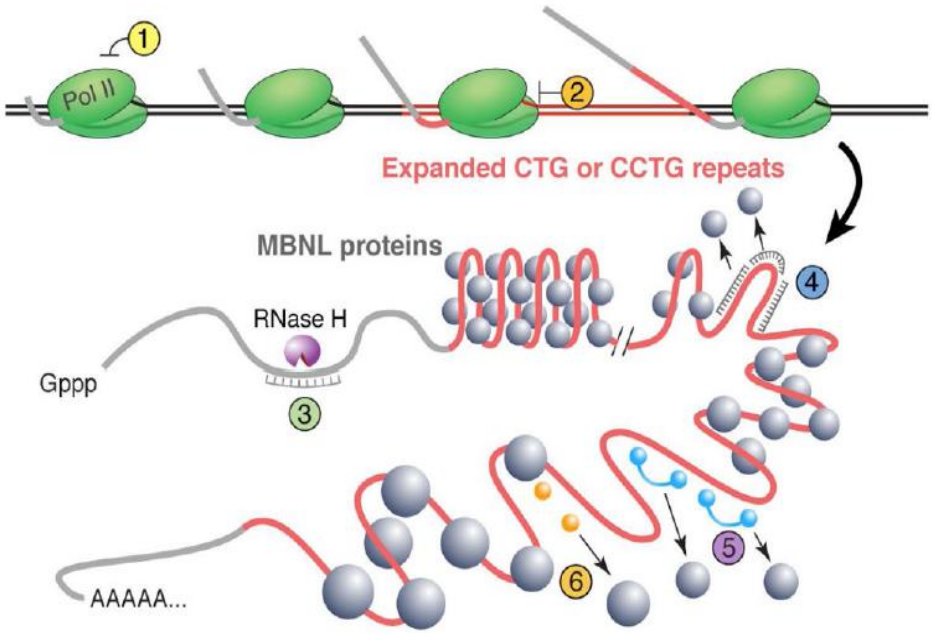
Post-transcriptional silencing

3. Antisense oligonucleotides
4. Small RNAs targeting CUG repeats

Inhibiting interactions between MBNL and toxic RNA

5. Small molecules - monomers and polymers
6. Peptides

Targeting pathways downstream of RNA toxicity



Thornton C et al. Curr Opin Genetics 2017

SMA & ALS experience

- Biomarker
- Safety profile
- Durability of action

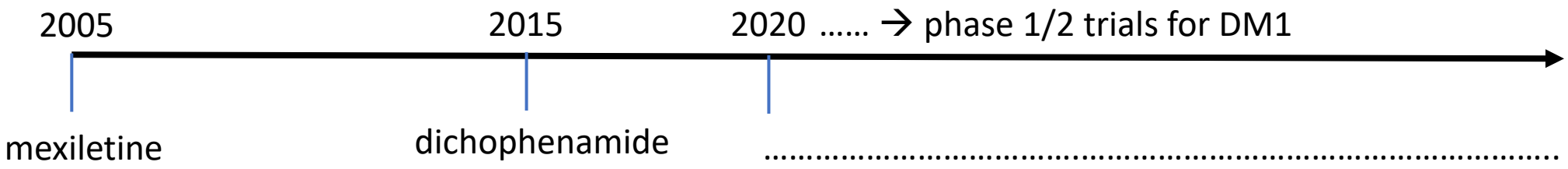
ASOs | **(EXP)n** | **SMALL MOL**

Conclusions

- ✓ PATIENTS are becoming more and more PROACTIVE
- ✓ DM1 experts are seeing patients with a different approach

Would this be a good candidate for the trial?
Would there be a clinically meaningful change?

- ✓ There is more hope for our patients



Program

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DYNE-101 ACHIEVE Trial Data
Wildon Farwell, M.D., MPH, Chief Medical Officer

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Q&A

Program

DYNE-251 DELIVER Trial Data
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on Duchenne Muscular Dystrophy (DMD)
Perry Shieh, M.D., Ph.D., Professor of Neurology and Pediatrics at the David Geffen School of Medicine at UCLA and a Neurologist at the Ronald Reagan UCLA Medical Center in Los Angeles and a Principal Investigator for the DELIVER Trial

Q&A

Closing remarks
Joshua Brumm, President & CEO

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**

DMD Community Has Urgent Need for Improved Treatment Options

“A potentially transformative treatment for me would be halting the progression of DMD and that would change everything for me and so many other people with it.

And because right now the progression of it, yeah, it's very tough. Great people are dying every day from it. It's always a big surprise, people die so suddenly from this. So, I think halting the progression would really change everything.”

Alan

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

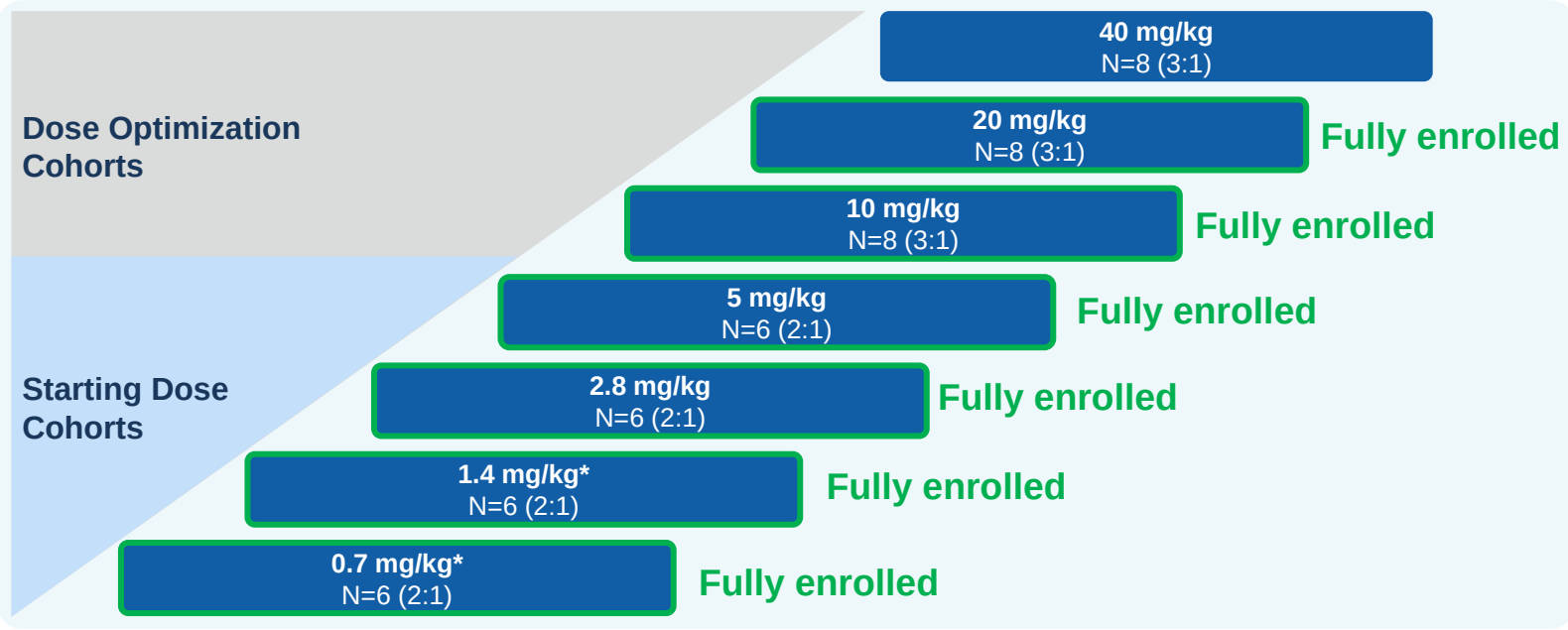
PDPF: percent dystrophin-positive fibers; NSAA: North Star Ambulatory Assessment

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

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

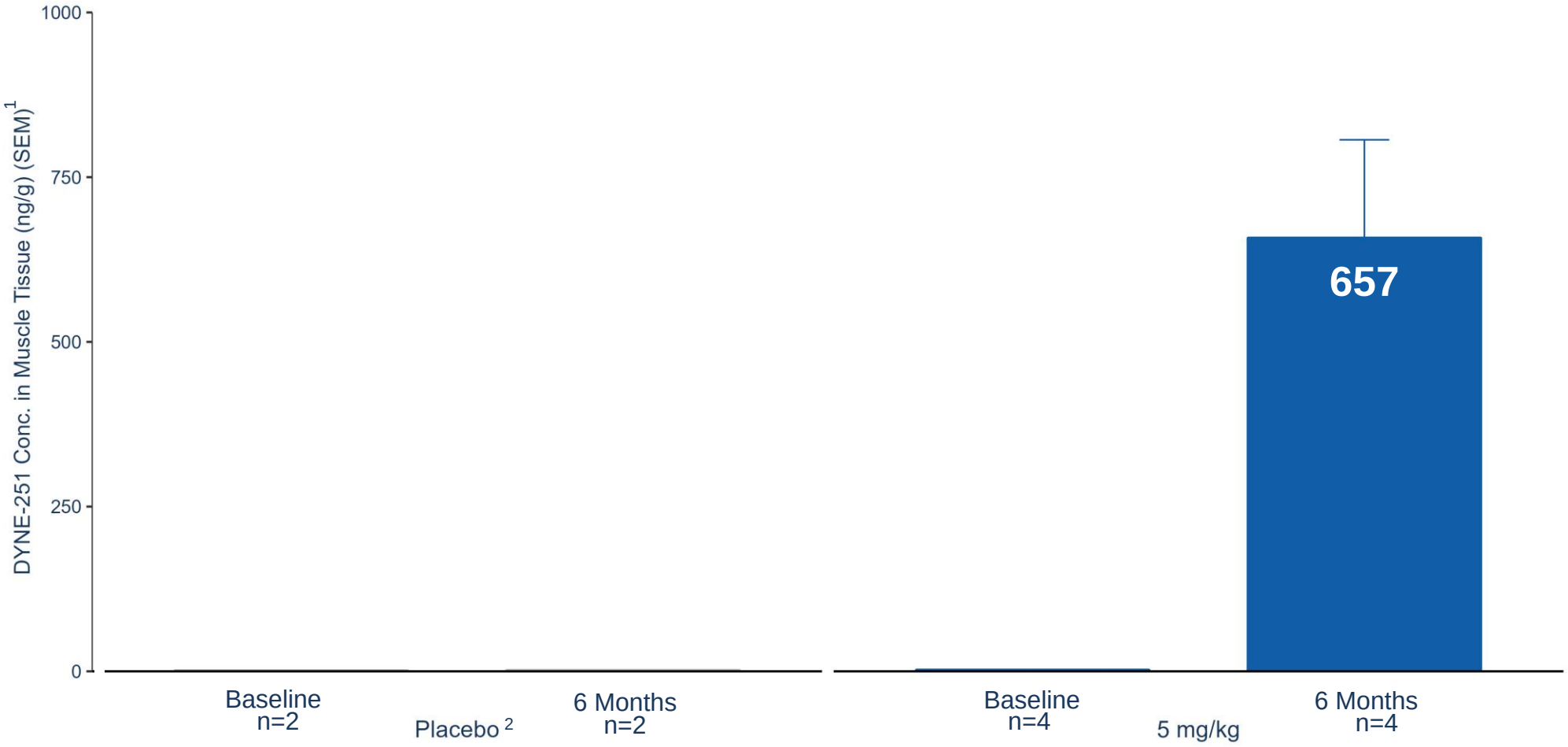
- No participants have demonstrated anemia or thrombocytopenia [3]
- No participants have demonstrated kidney injury[4]
- No participants have demonstrated clinically meaningful changes in electrolytes, including magnesium

* 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]

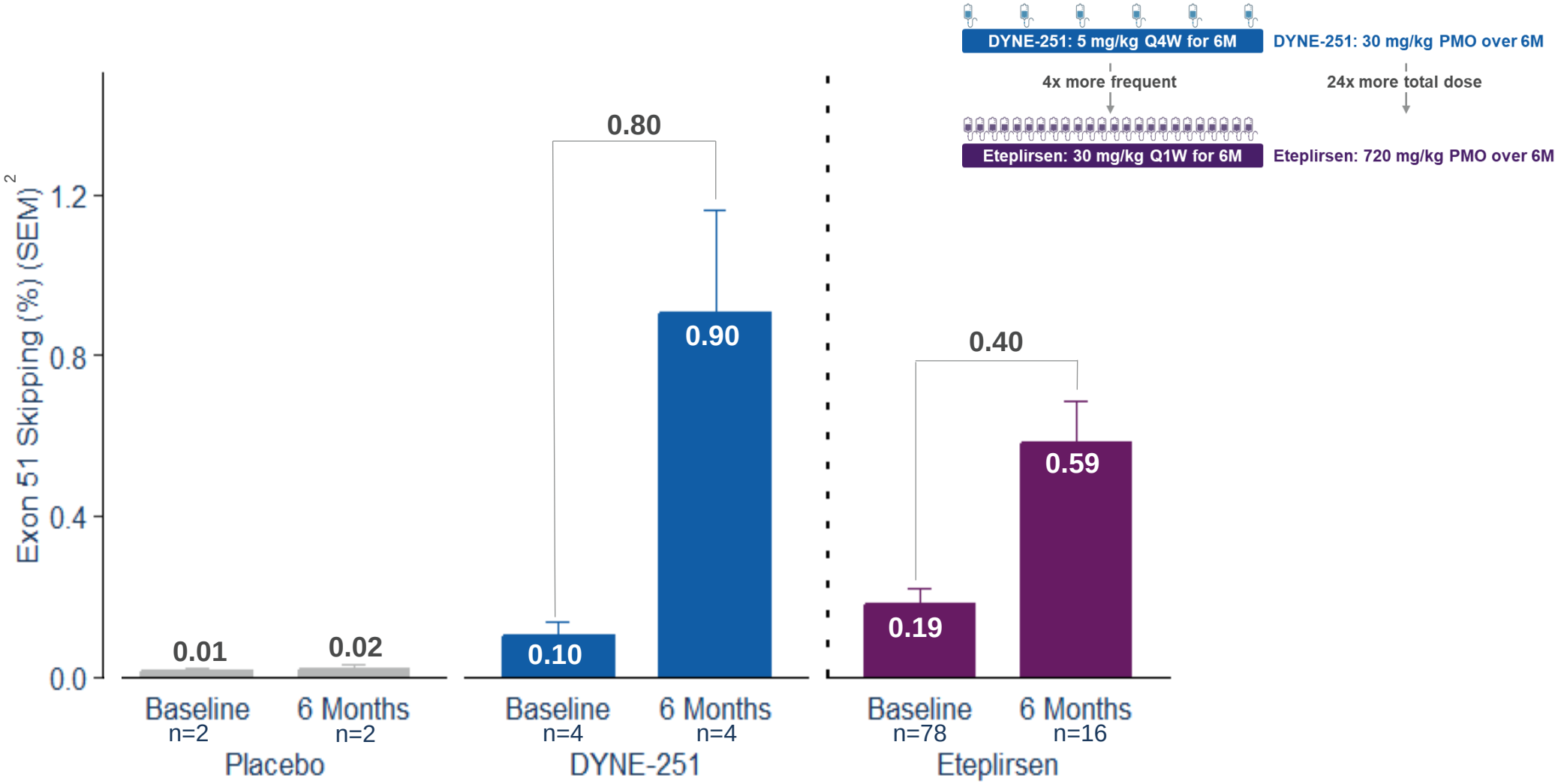
1. Data as of December 6, 2023; 2. Number of doses administered in DELIVER to date reflects doses administered across all study periods (MAD, OLE, LTE) in DELIVER; 3. Treatment emergent HGB or PLT persistently below LLN or reported AE. 4. Treatment emergent and persistently abnormal renal parameters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



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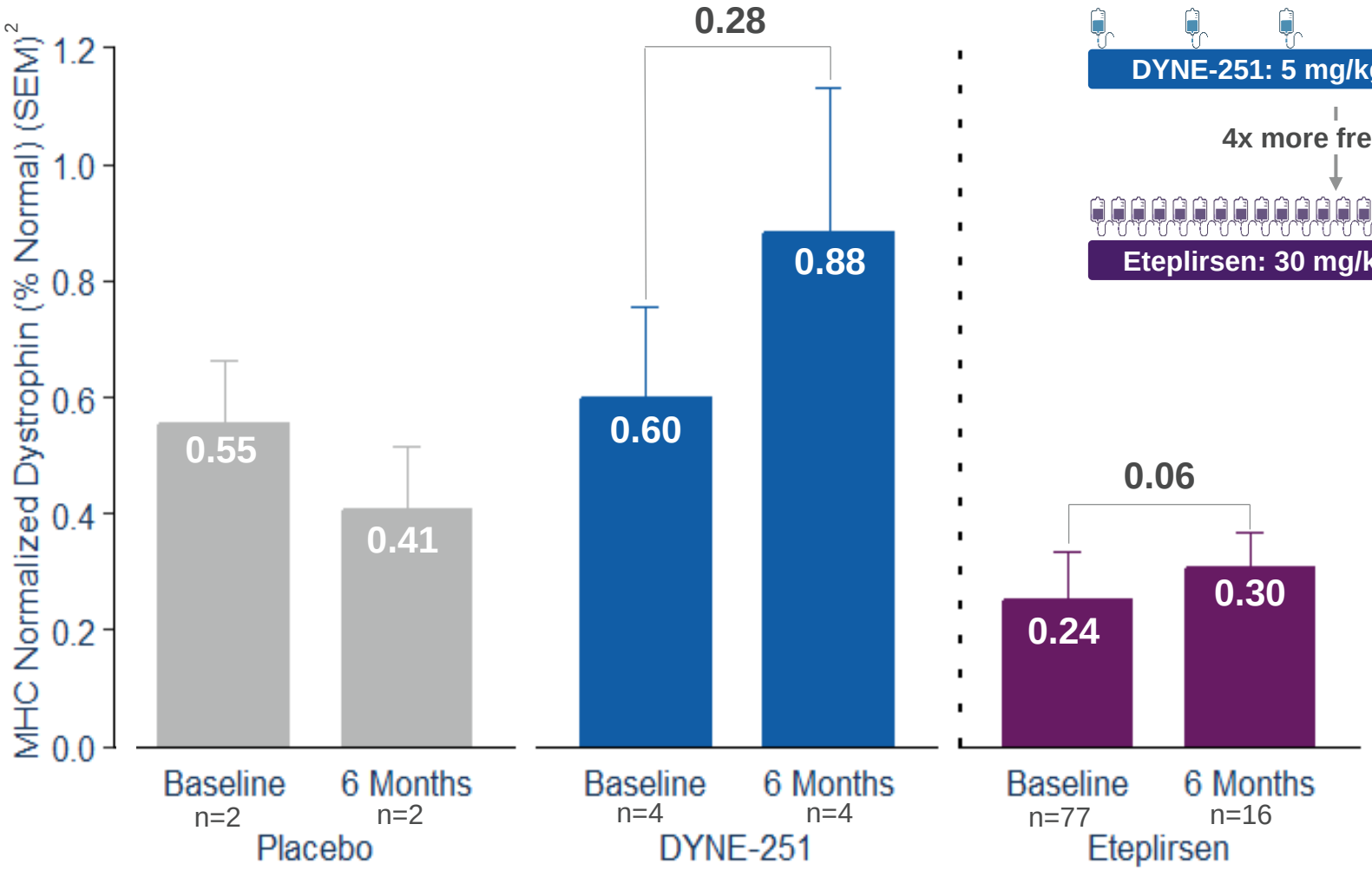
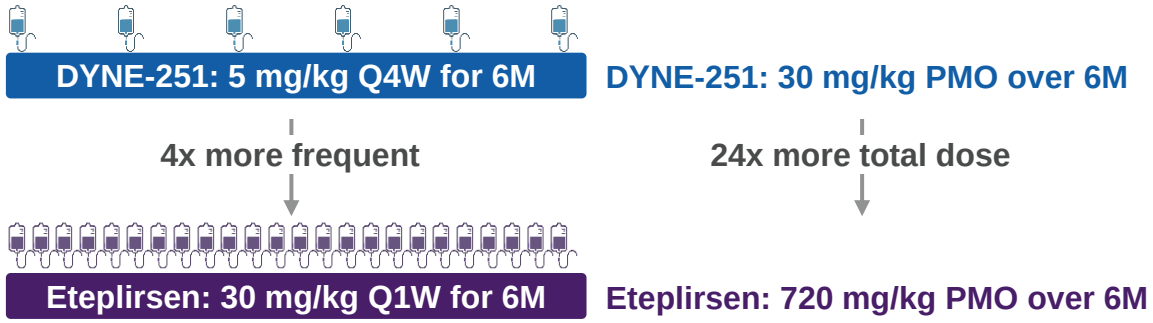
DYNE-251 Showed >2.5 Fold Higher Dystrophin at 6 Months than Eteplirsen Study with 24 Fold Lower PMO Dose Administered 4 Times Less Frequently [1]





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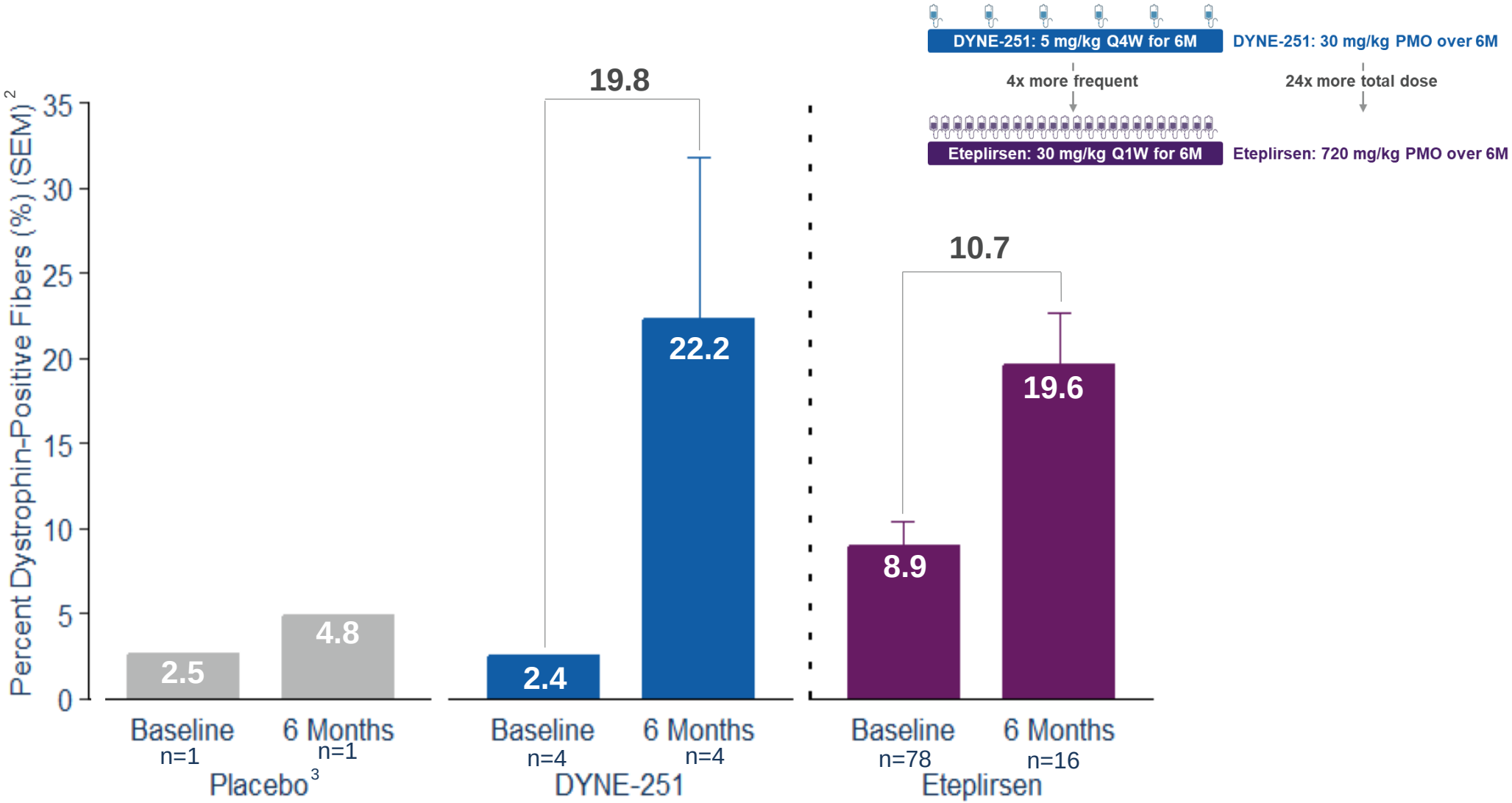
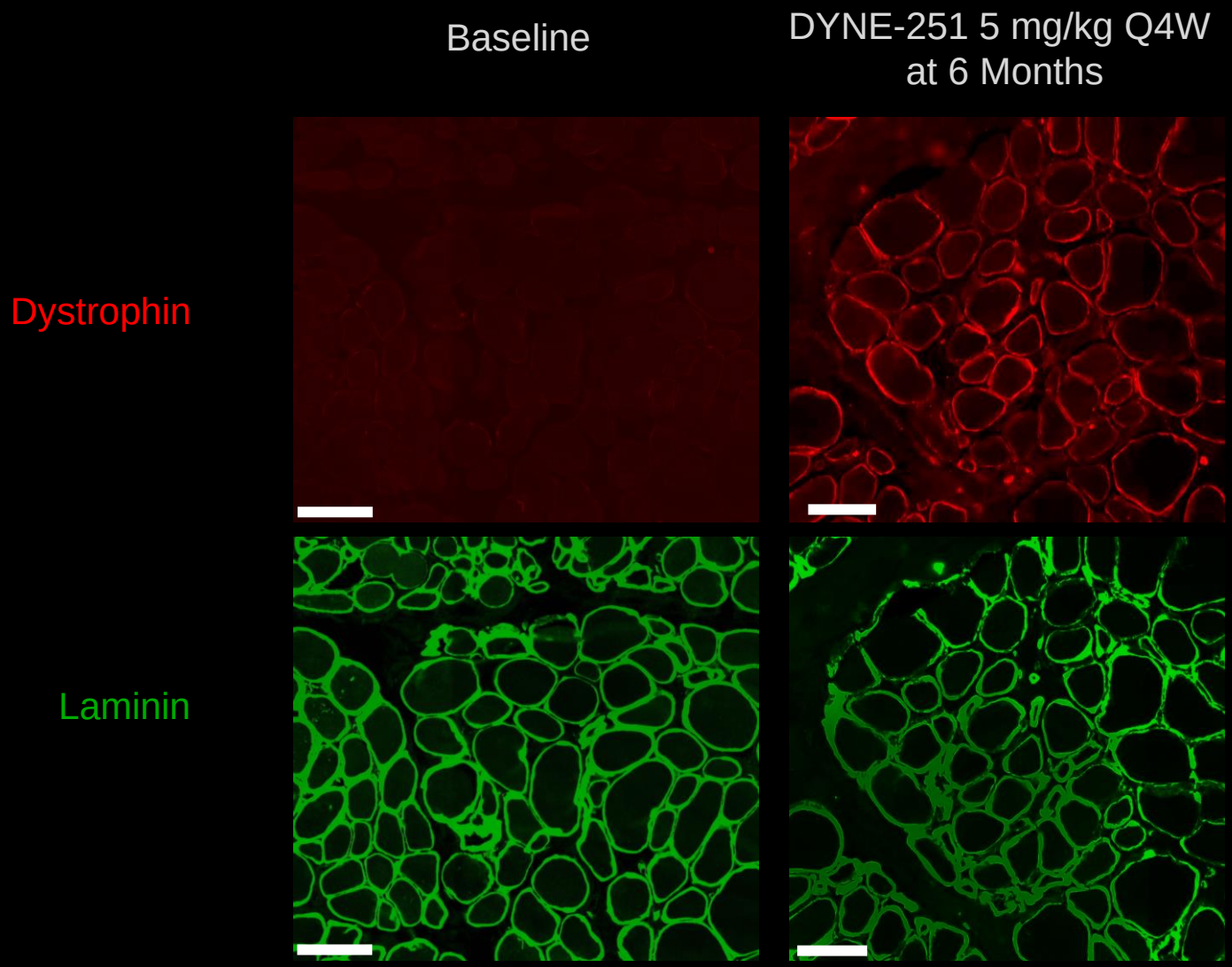
DYNE-251 Showed ~2 Fold Higher Change from Baseline in PDPF than Reported in Eteplirsen Study [1]



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. 3. PDPF data not available for 1 patient from placebo group.

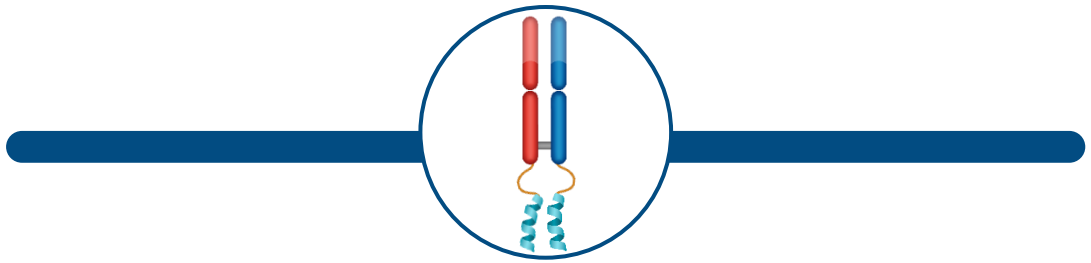
PDPF: Clear Improvement in Dystrophin Localization to Sarcolemma



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

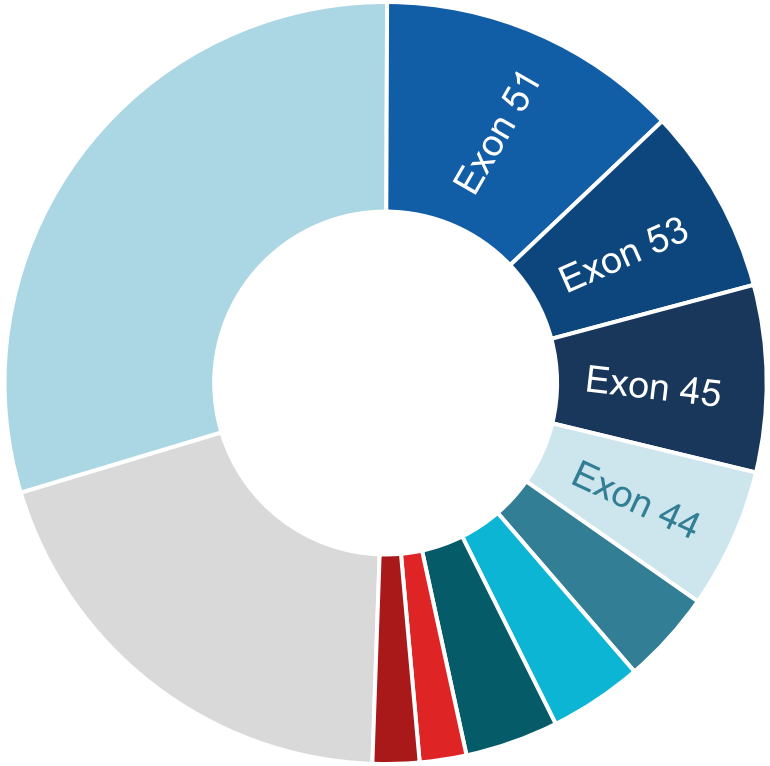
- Muscle delivery is the challenge
- Dyne founded to achieve targeted, receptor-mediated delivery to skeletal, cardiac and smooth muscle
  - Initial clinical data validates FORCE's targeted delivery to muscle
- Non-targeted delivery modalities face significant challenges, including an acceptable therapeutic 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

Dyne is Committed to Developing a Global DMD Franchise: Leading with DYNE-251, Payloads Identified for Exons 53, 45, 44

Approximately

80% of patients

have genotypes amenable to exon skipping



- Exon 51 – **13%**
- Exon 53 – **8%**
- Exon 45 – **8%**
- Exon 44 – **6%**
- Exon 50 – **4%**
- Exon 52 – **4%**
- Exon 43 – **4%**
- Exon 55 – **2%**
- Exon 8 – **2%**
- Other exon skips – **~30%**
- May not be amenable to exon skipping – **~20%**

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.

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.

Program

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Q&A

Closing remarks
Joshua Brumm, President & CEO

The DMD Treatment Landscape

Perry Shieh, M.D. Ph.D.

Professor of Neurology and Pediatrics

University of California, Los Angeles

Personal Disclosures

Contracted Research support from: Astellas Gene Therapies, Sarepta, Pfizer, Solid, Novartis, PTC Therapeutics, Biogen, Fulcrum, Reveragen, Sanofi, Santhera

Personal fees from: Dyne, Sarepta, Roche, Astellas Gene Therapies, Novarits, Argenx, Alexion, UCB, Catalyst, Biogen, Grifols, CSL Behring

Approved treatments for DMD

Current treatments for DMD:

- **Steroids** are part of the standard-of-care guidelines for the treatment of DMD
- There are currently **eight** approved **treatments**, **seven of which are available in the US.**

Non-sense readthrough

Ataluren (Translarna™; only available outside of the USA)

- Ambulatory; ≥2 years of age with a nonsense mutation

Exon skipping (PMO)

Eteplirsen (EXONDYS 51®)

- Exon 51 skipping eligible

Golodirsen (VYONDYS 53®)

- Exon 53 skipping eligible

Viltolarsen (Viltepso®)

- Exon 53 skipping eligible

Casimersen (AMONDYS 45™)

- Exon 45 skipping eligible

Corticosteroid

Deflazacort (Emflaza®)

- for DMD patients

Vamorolone (AGAMREE™)

- for DMD patients 2 years of age and older

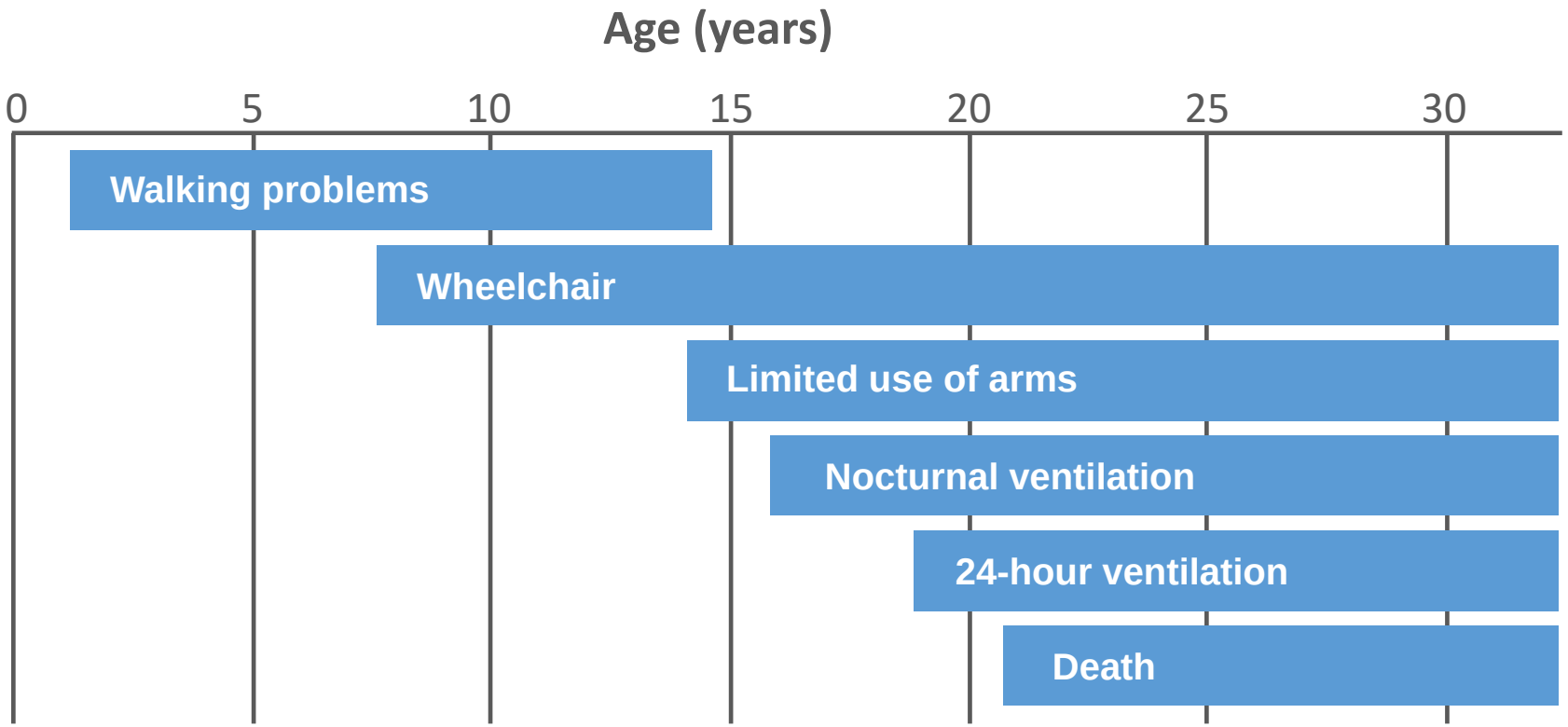
Gene therapy

Delandistrogene moxeparvovec (ELEVIDYS™)

- Ambulatory; 4–5 years of age with a *DMD* mutation*

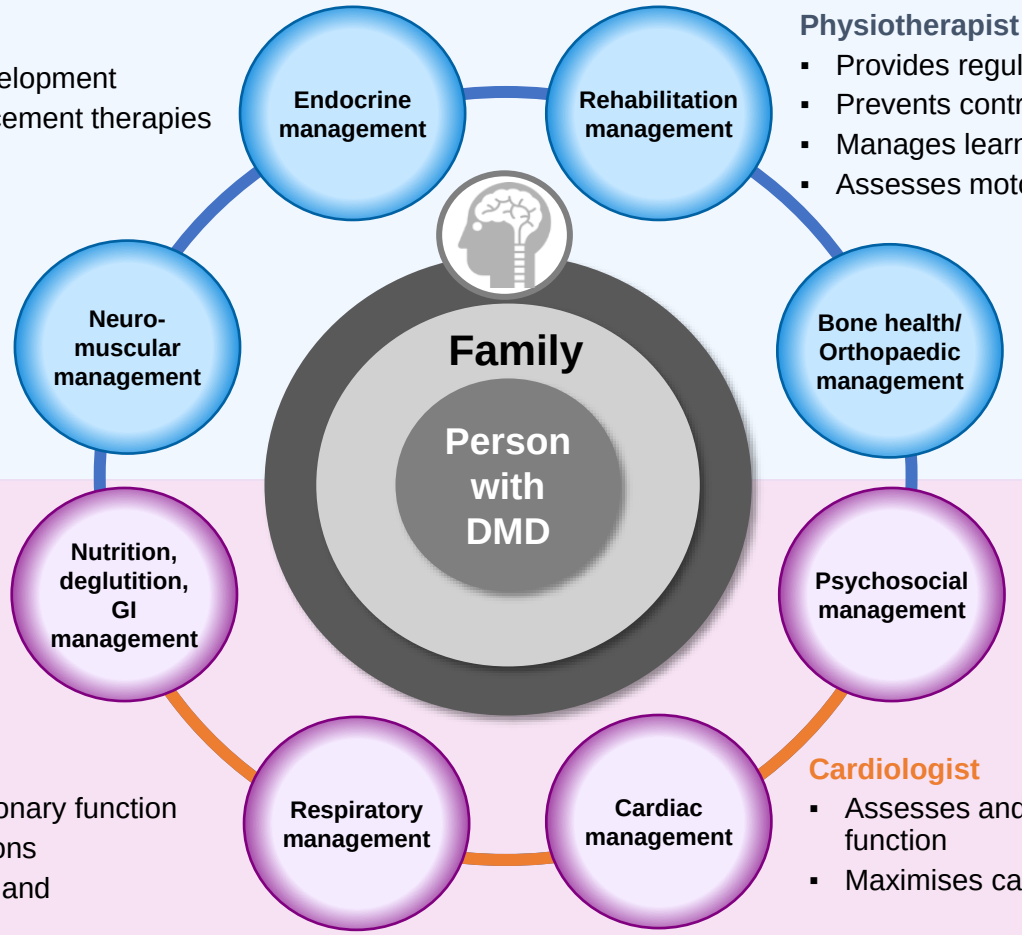
* Deletions within exons 8-9 are contraindicated

DMD: Progression of Disease[1,2]



*This representation of disease progression is an estimation; each patient will present differently based on individual disease trajectory or mutations.
DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment.
1. Aartsma-Rus A, et al. *J Med Genet.* 2016; 53:145–151; 2. Birnkrant DJ, et al. *Lancet Neurol.* 2018; 17:347–361; 3. Chen YW, et al. *Neurology*. 2005; 65:826–834; 4. Peverelli L, et al. *Neurology*. 2015; 85:1886–1893; 5. Lurio JG, et al. *Am Fam Physician.* 2015; 91:38–44; 6. Cyrulnik SE, et al. *J Pediatr*. 2007; 150:474–478; 7. Goemans N, et al. *Neuromuscul Disord.* 2013; 23:618–623; 8. Bushby K & Connor E. *Clin Investig (London).* 2011; 1:1217–1235; 9. Emery AEH. *Lancet*. 2002; 359:687–695; 10. Henricson EK, et al. *Muscle Nerve*. 2013; 48:55–67; 11. Muntoni F, et al. *PLoS One*. 2019; 14:e0221097.

Multidisciplinary care in DMD



Endocrinologist
- Monitors growth and development
- Provides hormone replacement therapies

Physiotherapist
- Provides regular physical, occupational and speech and language therapy
- Prevents contracture, deformity, falls and fractures
- Manages learning, attentional and sensory processing differences
- Assesses motor function using assessments such as the NSAA

Paediatric neurologist
- Provides use of new therapies, genetic counselling, education and individual/family support
- DMD-specific treatment prescribers

Orthopaedist
- Treats/monitors people with DMD for early indications of bone fragility
- Monitors for scoliosis
- Prescribes foot surgery

Nutritionist
- Diet monitoring and supplementation
- Input of feeding tube (gastrostomy/jejunal)

Mental health clinician
- Assesses the mental health of people with DMD and their family
- Provides neuropsychological evaluations/interventions for learning, emotional and behavioural problems

Pulmonologist
- Assesses/monitors pulmonary function
- Treats respiratory infections
- Provides assisted cough and nocturnal ventilation

Cardiologist
- Assesses and monitors cardiac function
- Maximises cardiac therapy

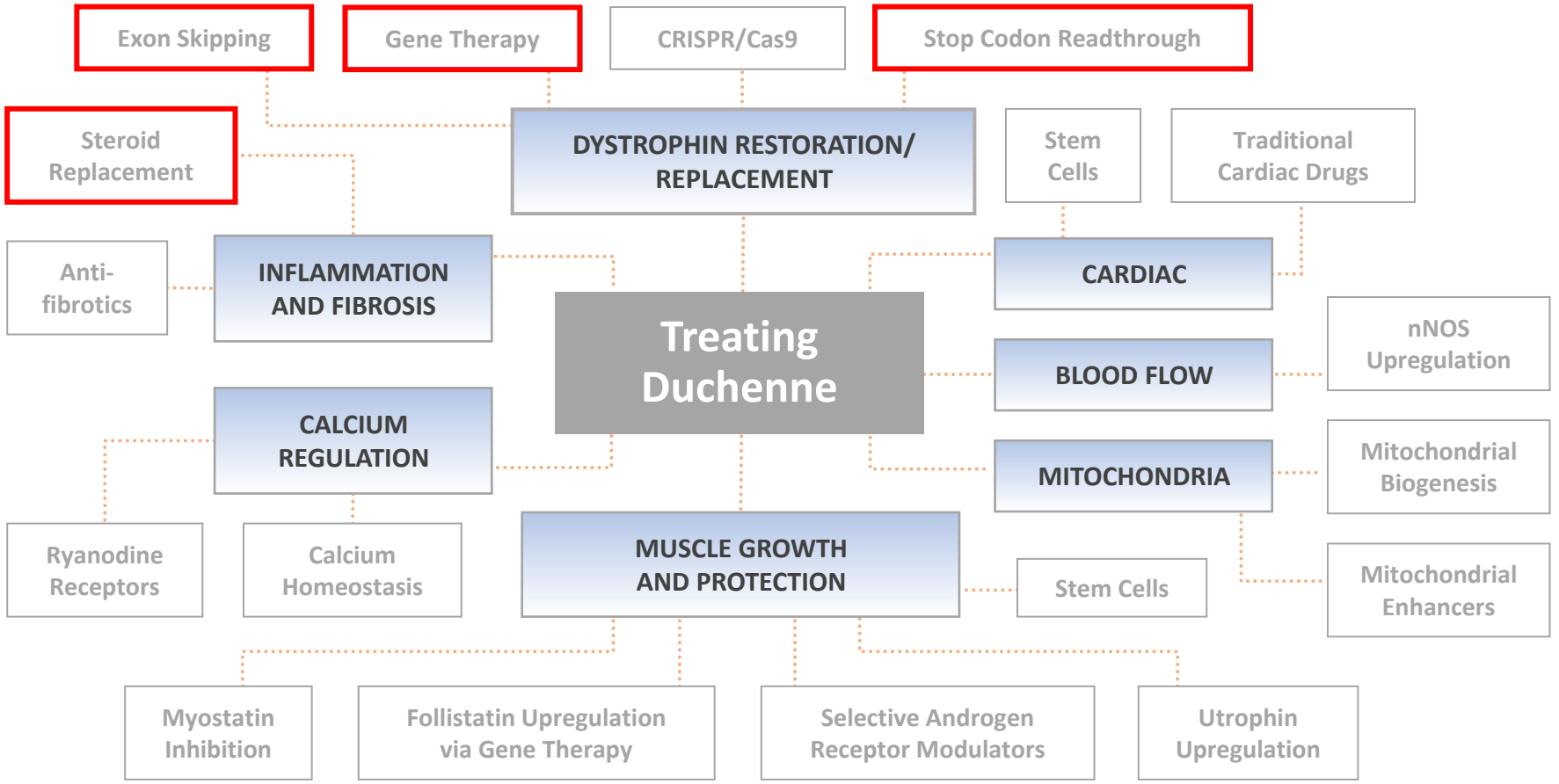
Management of other complications

Neuromuscular and skeletal management

DMD, Duchenne muscular dystrophy; GI, gastrointestinal; NSAA, North Star Ambulatory Assessment.

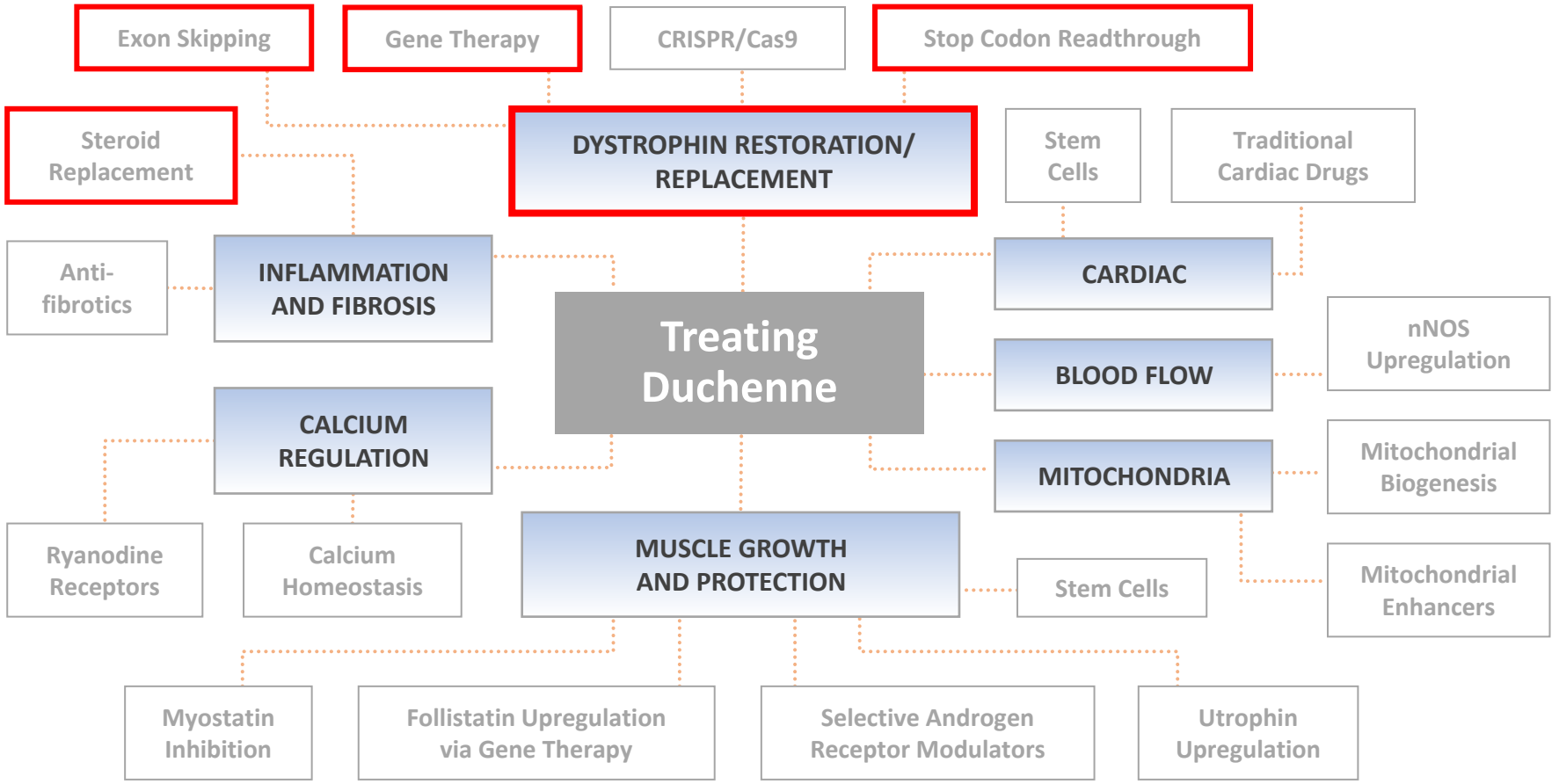
Birnkrant DJ, et al. *Lancet*. 2018; 17:251–267.

Strategies for disease modification in DMD



Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; nNOS, neuronal nitric oxide synthase.
Image adapted from Parent Project Muscular Dystrophy Website. New Duchenne Therapies in Development.
http://community.parentprojectmd.org/profiles/blogs/new-duchenne-therapies-in-development. Accessed April 5, 2019.

Strategies for disease modification in DMD



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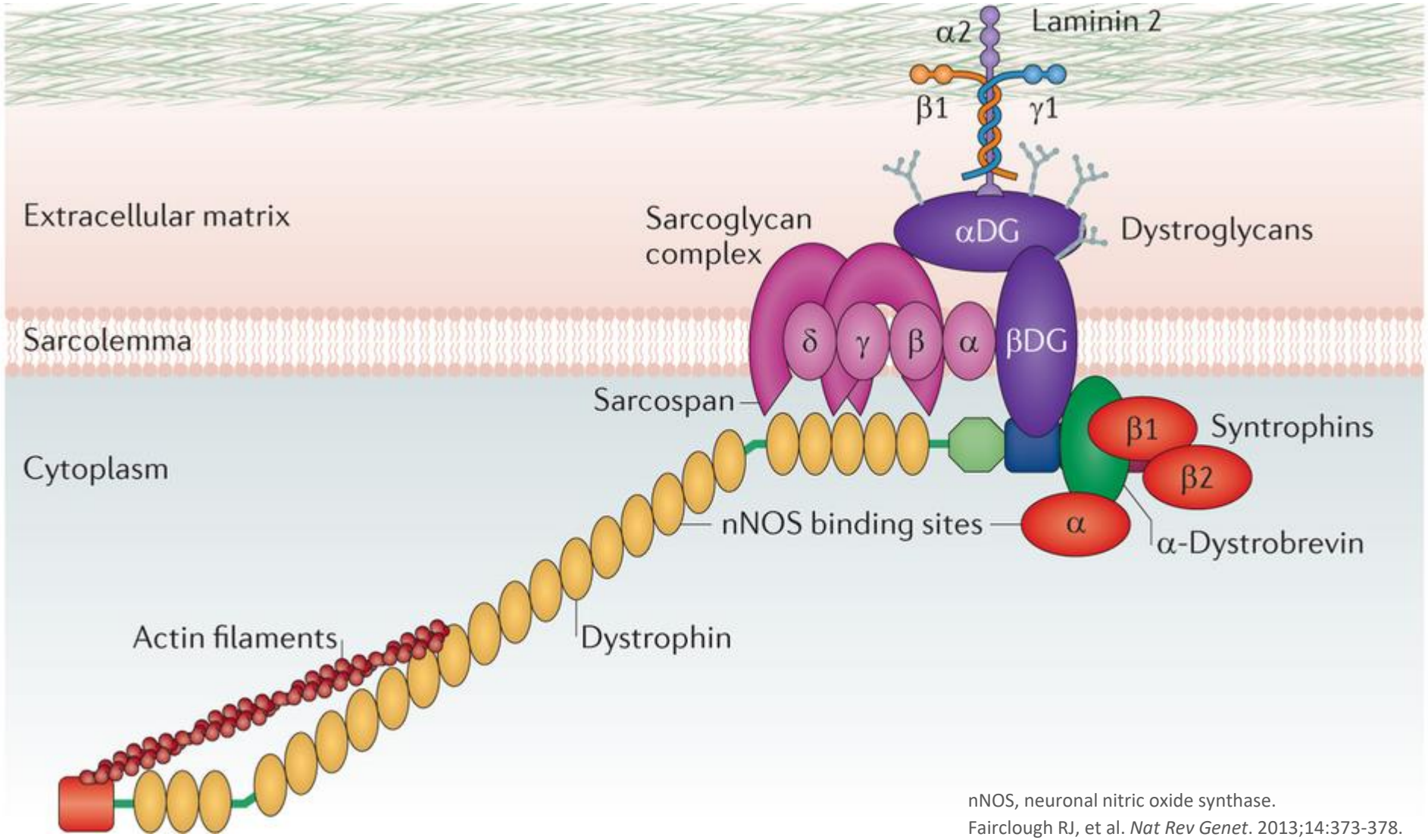
Dystrophin deficiency: the underlying cause of DMD

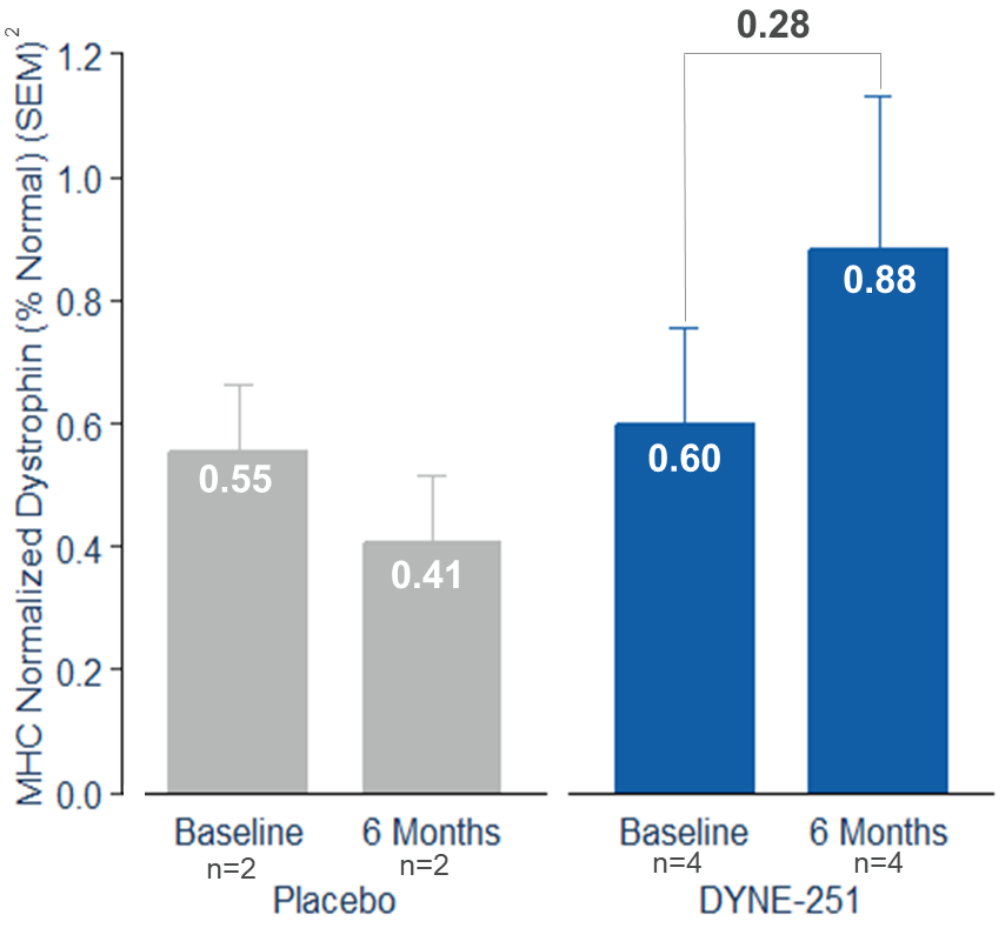


nNOS, neuronal nitric oxide synthase.

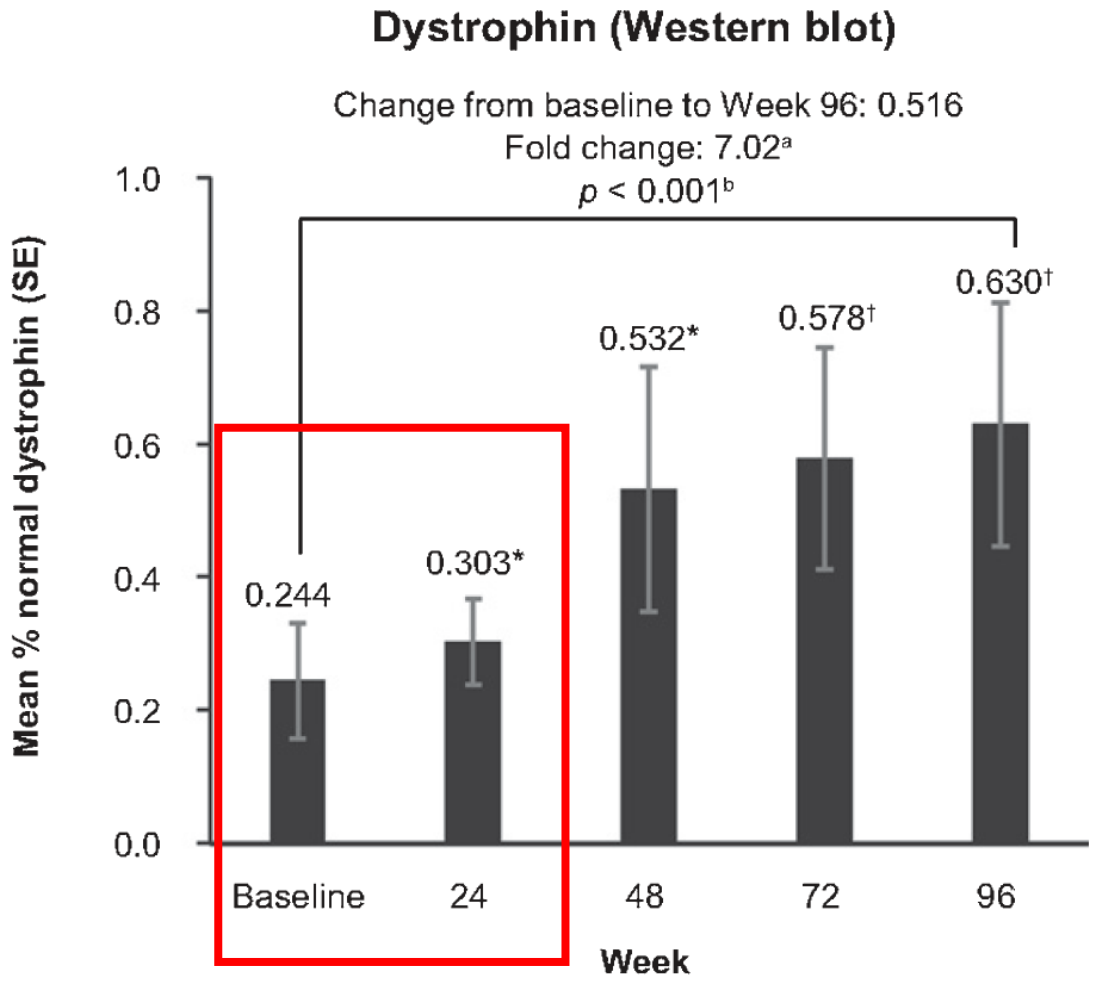
Fairclough RJ, et al. *Nat Rev Genet*. 2013;14:373-378.

Dystrophin Quantification – Western blot

DELIVER Data



PROMOVI Data



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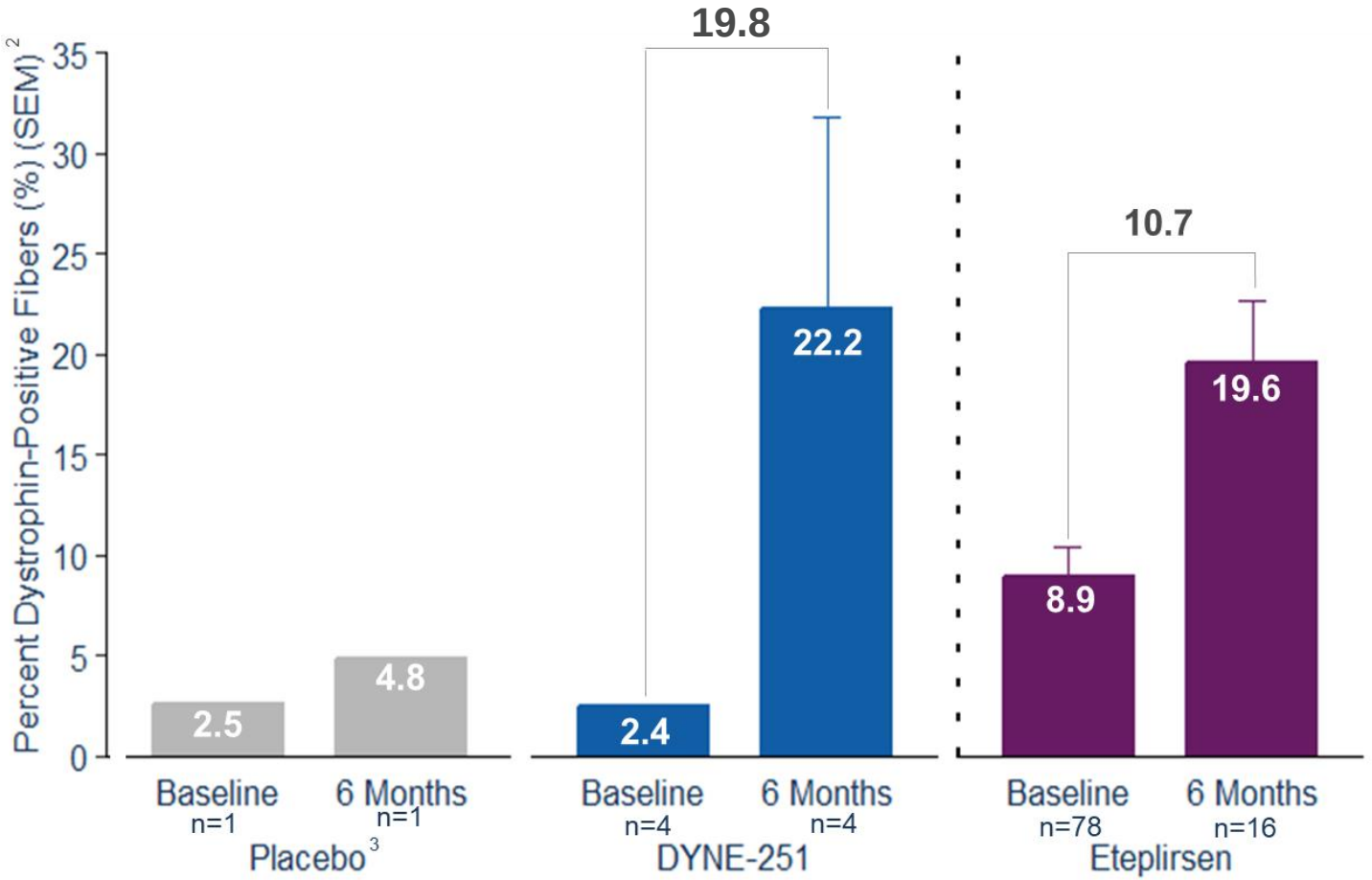
Dystrophin Quantification – Percent Dystrophin Positive Fibers (PDPF)



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A “Miniaturized” Dystrophin Found in Nature

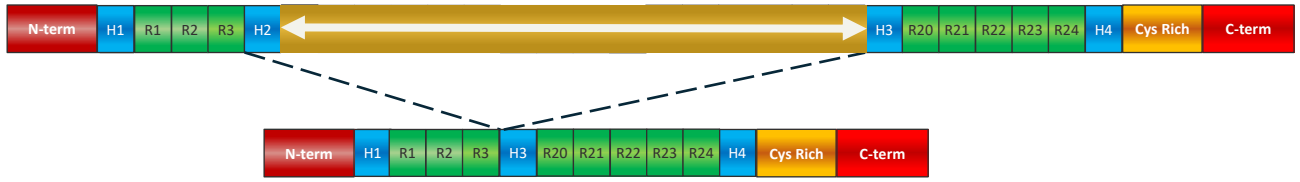
Very Mild Case of Becker Muscular Dystrophy Was Missing Exons 17-48 (46% of the coding region)

LETTERS TO NATURE

Very mild muscular dystrophy associated with the deletion of 46% of dystrophin

S. B. England*, L. V. B. Nicholson†, M. A. Johnson†, S. M. Forrest*, D. R. Love*, E. E. Zubrzycka-Gaarn‡, D. E. Bulman‡, J. B. Harris§ & K. E. Davies*‖

- 61-year-old ambulatory patient with Becker muscular dystrophy
- Deletion of exons 17-48, resulting in loss of 46% of coding region



“Mini”-dystrophin[2]

1. England SB et al. *Nature*. 1990;343:180-182. 2. Wells DJ et al. *Hum Mol Genet*. 1995;4:1245-1250.

Gene therapy: Microdystrophins

Delandistrogene moxeparvovec[1,2]
(Sarepta/Roche)

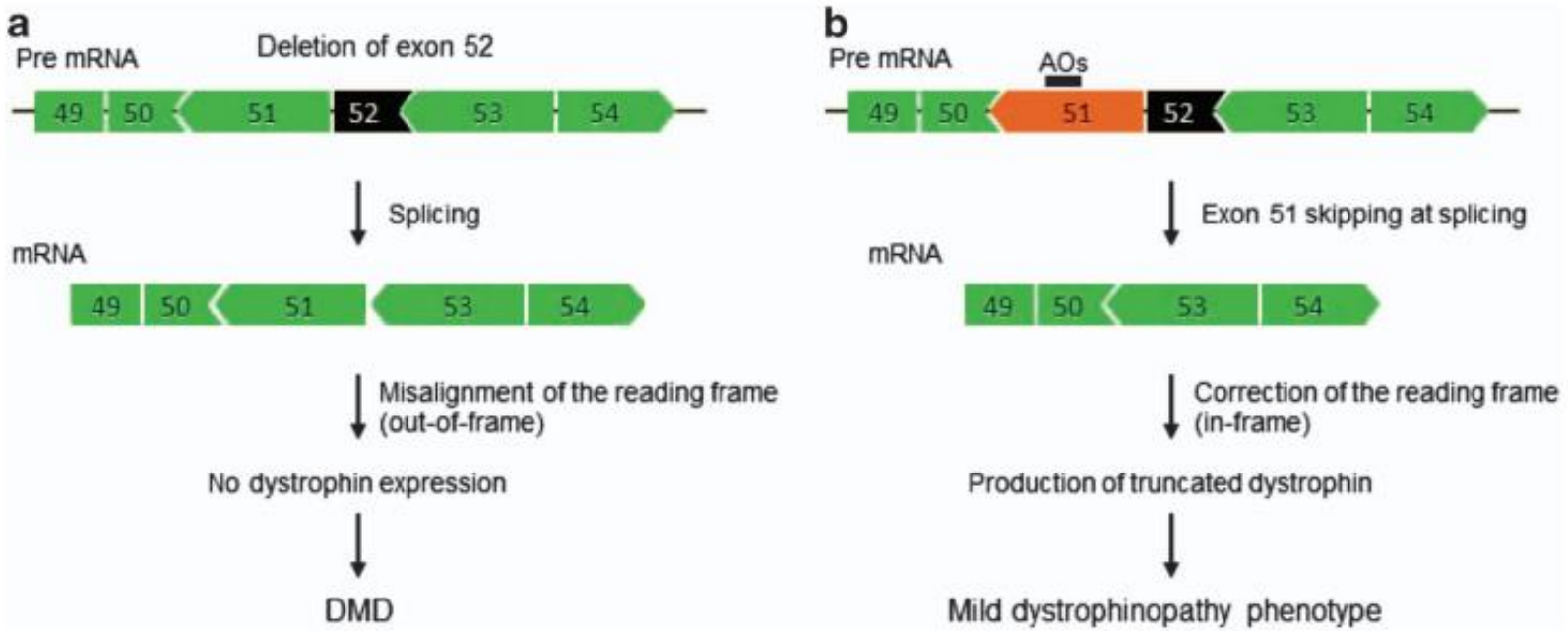
SGT-003[1,2]
(Solid Biosciences)

Fordadistrogene movaparvovec[2]
(Pfizer)

GNT-0004[3]
(Genethon)

RGX-202[4]
(REGENXBIO)

Exon 51 skipping therapy



Nakamura A, et al, Journal of Human Genetics, 2017

Exon 51 skipping

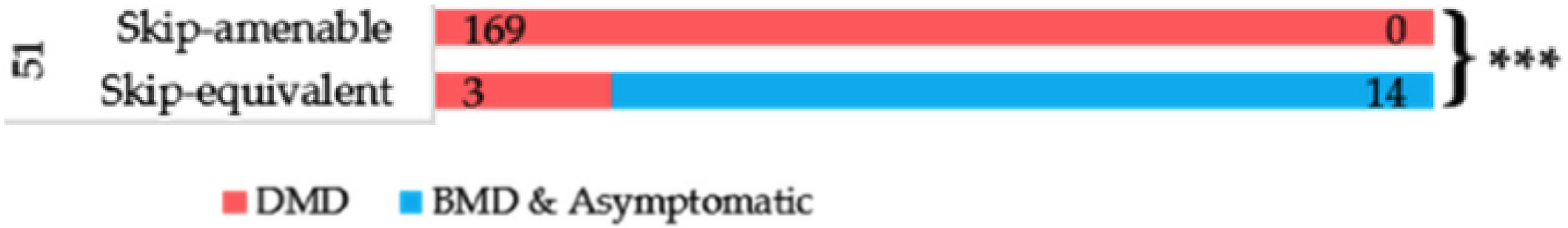
Mutation	**Skipped Dystrophin Product (in-frame)**
Deletion 45-50	Deletion 45-51
Deletion 48-50	Deletion 48-51
Deletion 49-50	Deletion 49-51
Deletion 52	Deletion 51-52
Deletion 50	Deletion 50-51

Bladen CL, et al. *Hum Mutat.* 2015;36(4):395-402.

Potential therapeutic effect of exon skipping is proven in nature

Meta-analysis - phenotype of

- Exon skipping amenable patients
- Patients with in-frame deletions representing the skipped product



Anwar S et al. *J Pers Med* 2021 11:46

Safety Profile of DYNE-251 in Context

- Appears to have a favorable safety profile to date[1] through the current dose level of 20 mg/kg
  - In the placebo-controlled period most treatment-emergent adverse events were mild or moderate in intensity
- It will be important for next generation therapies to have a wide therapeutic index and in the setting of chronic administration of therapy
- The safety of gene therapy in the older population is untested

1. Data as of December 6, 2023

Conclusions

- Despite advances, there remains a significant unmet need in the treatment of DMD
- Despite our optimism with gene therapy, questions of regarding durability and microdystrophin function remain
- An exon skipping therapy with improved delivery to muscle would likely be a treatment of choice for the appropriate subset of patients
- The data to date for DYNE-251, indicates increased dystrophin expression in the muscle of patients treated with a lower dose and frequency of treatment than with eteplirsen
  - Potential to reach transformational dystrophin levels with higher dose and more time on therapy

Program

DYNE-251 DELIVER Trial Data
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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

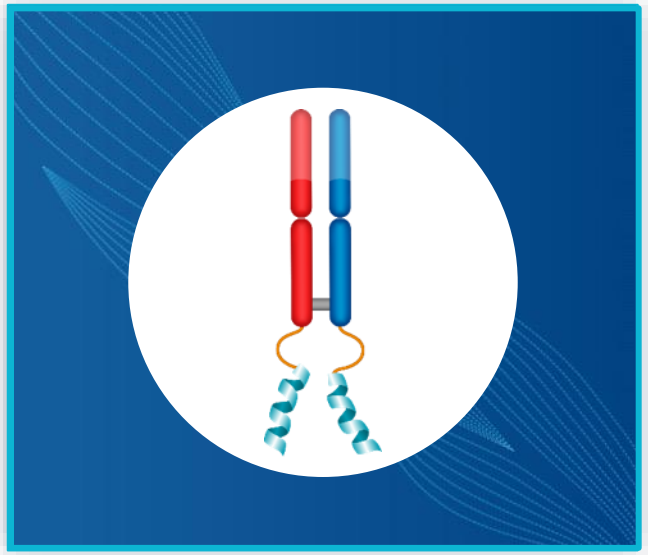
Favorable Safety & Tolerability Supporting Dose Escalation

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

Building the World's Leading Muscle Disease Company

Win in DM1, DMD, FSHD



Own Muscle Delivery & Leverage FORCE

Dynamo Culture

ACHIEVE

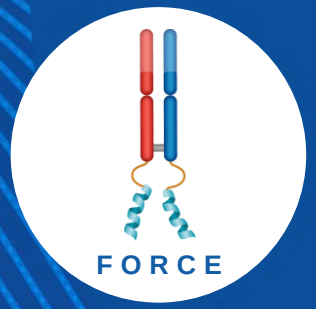
Dyne® THERAPEUTICS

DELIVER

Achieving the Promise of

FORCE

to Deliver for Patients



ACHIEVE & DELIVER CLINICAL DATA UPDATE | JANUARY 3, 2024