Safety and efficacy from the ongoing Phase 1/2 DELIVER trial of DYNE-251 in males with *DMD* mutations amenable to exon 51 skipping

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Disclosures

- Clinical trial support from Dyne Therapeutics, Avidity Biosciences, Ultragenyx
- Advisor compensation from Apic Bio, Encoded, BioMarin, Locanabio, Sanofi
- Scientific advisory board for Armatus Bio
- DYNE-251 is an investigational medicine being evaluated in the ongoing DELIVER trial and has not received approval by the FDA, EMA, or any other regulatory authorities

DELIVER

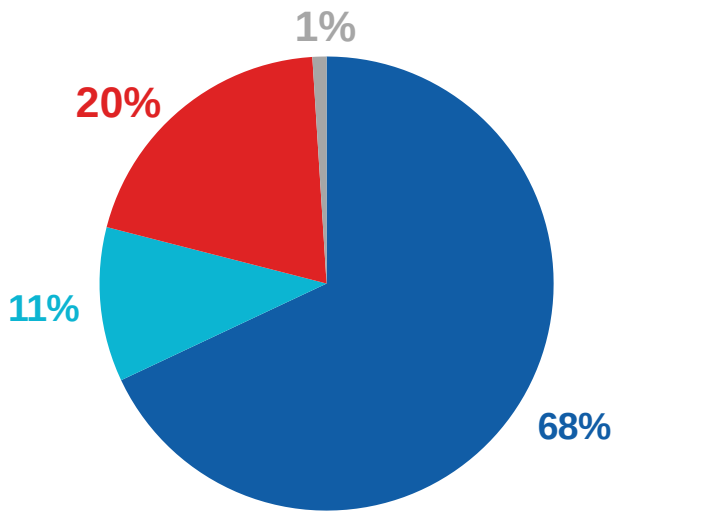
EMA, European Medicines Agency; FDA, Food and Drug Administration.

Goal of treatment in DMD is to increase dystrophin expression in key tissues to improve function

- DMD is caused by mutations in the *DMD* gene, which result in greatly reduced production of dystrophin protein, which is essential for muscle structure, function, and preservation[1–5]

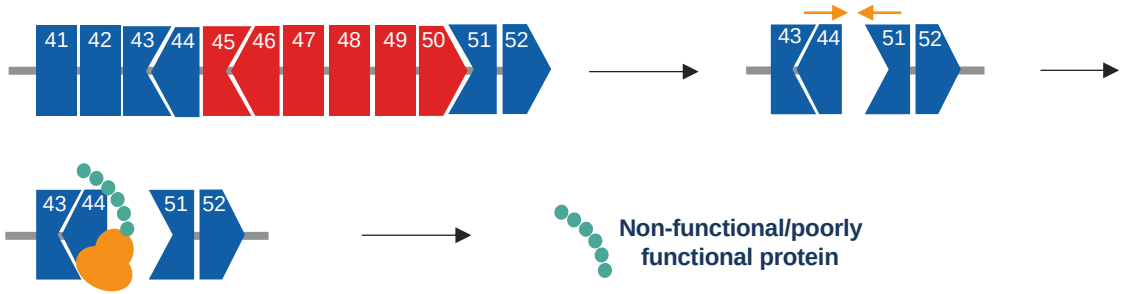
- PMO-induced exon skipping restores the *DMD* mRNA reading frame, leading to the production of internally shortened, near full-length, functional dystrophin protein[7,8]

Deletions account for more than two-thirds of DMD cases[6]

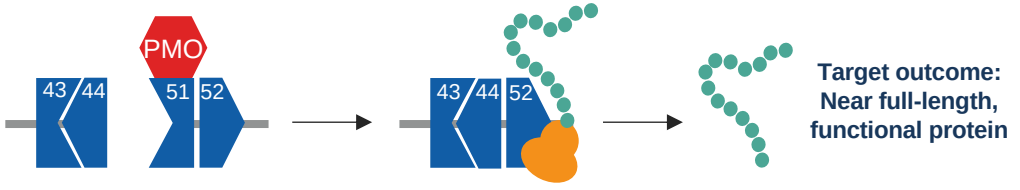


- Large deletions
- Large duplications
- Small mutations
- Mid intronic mutations

Exon 45–50 deletion disrupts reading frame



Skipping exon 51 with PMO restores reading frame



DMD, Duchenne muscular dystrophy; mRNA, messenger ribonucleic acid; PMO, phosphorodiamidate morpholino oligomer.

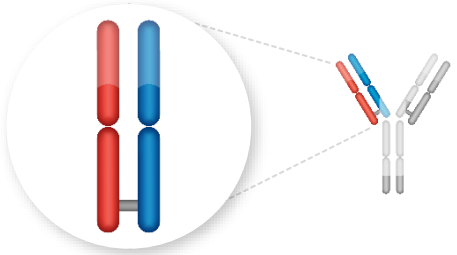
1. Claflin DR, Brooks SV. *Am J Physiol Cell Physiol.* 2008;294(2):C651–58; 2. Ervasti JM, Campbell KP. *J Cell Biol.* 1993;122(4):809–23;
3. Hoffman EP, et al. *Cell.* 1987;51(6):919–28; 4. de Feraudy Y, et al. *Ann Neurol.* 2021;89(2):280–92; 5. Ohlendieck K, et al. *Neurology.* 1993;43(4):795–800;
6. Bladen CL, et al. *Hum Mutat.* 2015;36(4):395–402; 7. Niks EH, Aartsma-Rus A. *Expert Opin Biol Ther.* 2017;17(2):225–36; 8. Nakamura A, et al. *J Hum Genet.* 2017;62(10):871–6.

DELIVER

FORCE™ platform-based therapeutics for neuromuscular diseases

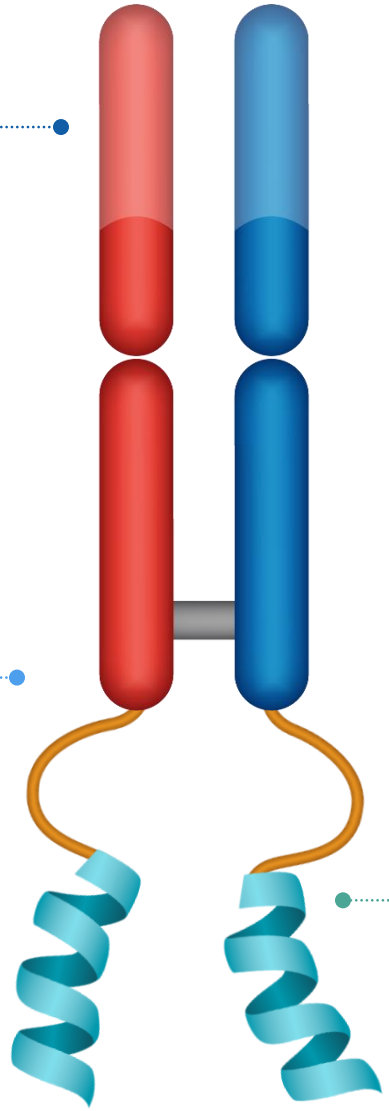
ANTIBODY

Proprietary Fab against TfR1 to enable targeted delivery to muscle and CNS



LINKER

Connects Fab and payload



PAYLOAD

Modularity enables rational selection of payload to target the genetic basis of disease (ASO, PMO, siRNA, enzyme)

ASO, antisense oligonucleotide; CNS, central nervous system; Fab, antigen-binding fragment; PMO, phosphorodiamidate morpholino oligomer; siRNA, small interfering RNA; TfR1, transferrin receptor 1.
Adapted from Ohrt T, et al. *Nucleic Acids Res.* 2006;34(5):1369.

DELIVER

DYNE-251 is designed to leverage TfR1 to deliver exon 51-skipping PMO to affected tissues in DMD

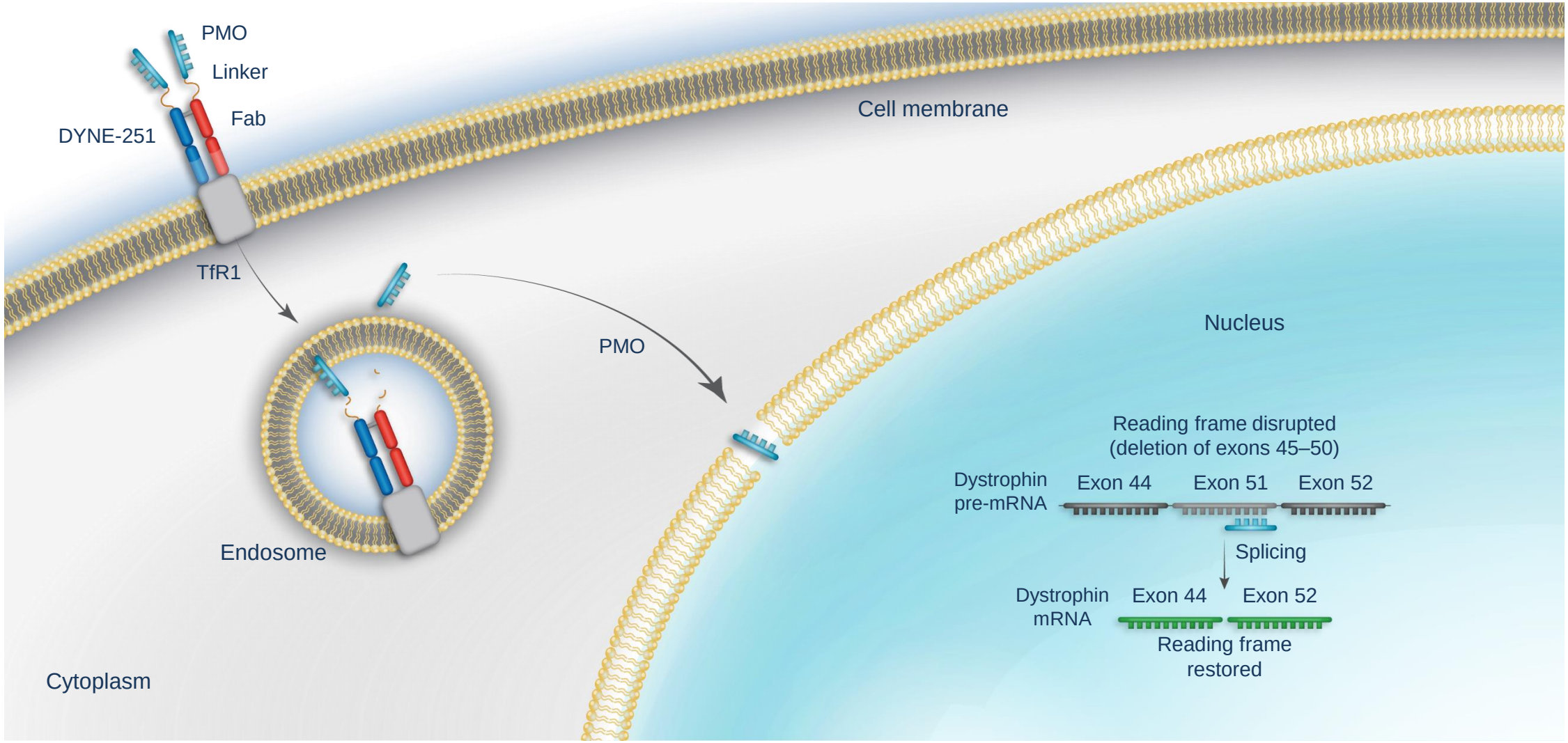


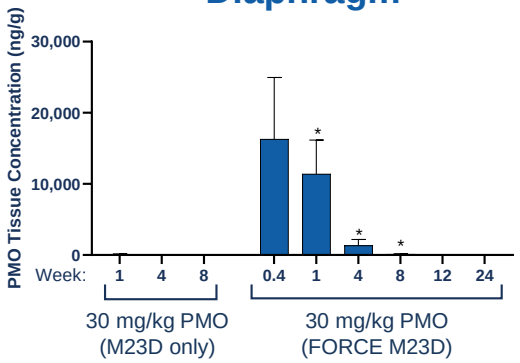
Image depicts intended mechanism of action of DYNE-251. Applicable to all *DMD* mutations amenable to skipping of exon 51.
DMD, Duchenne muscular dystrophy; Fab, antigen-binding fragment; PMO, phosphorodiamidate morpholino oligomer; TfR1, transferrin receptor 1.

DELIVER

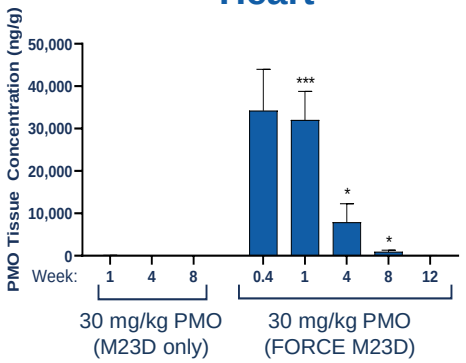
The FORCE platform drives broad PMO delivery and distribution in a *mdx* mouse model

PMO tissue concentration

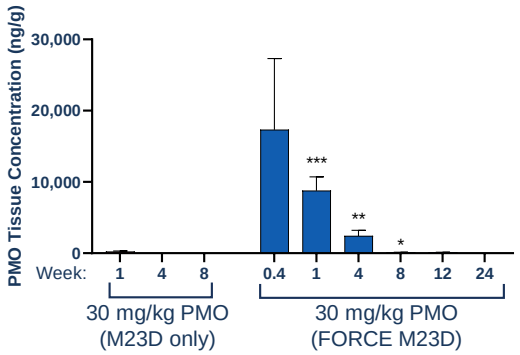
Diaphragm[1]



Heart[1]

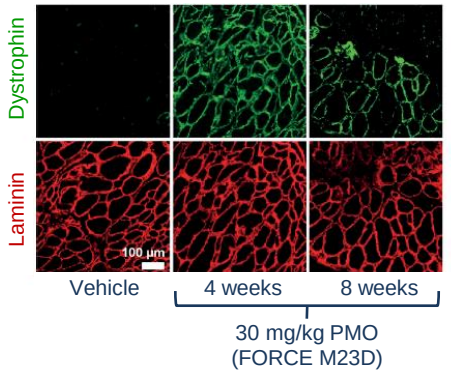


Quadriceps[1]

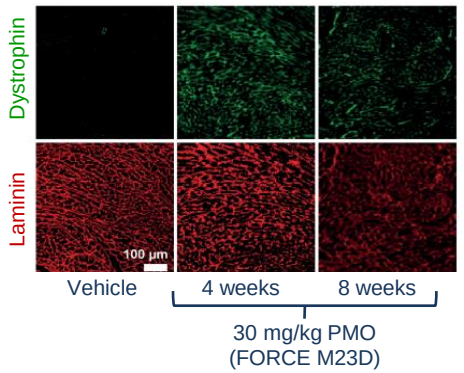


Dystrophin-positive myofibers

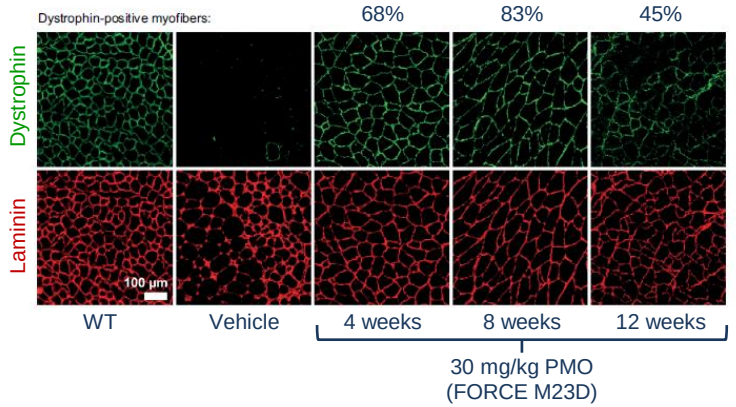
Diaphragm[1]



Heart[1]



Quadriceps[1]



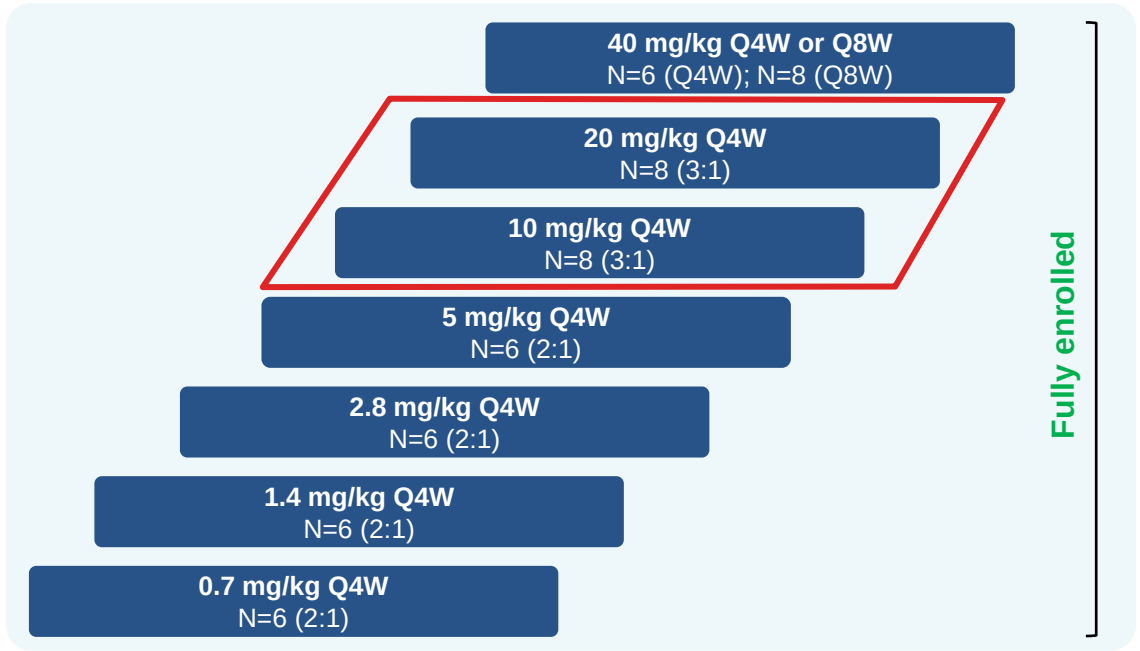
Note for the PMO data: 5-week-old *mdx* mice injected via tail vein. PMO exposure determined by hELISA. Data represent mean ± SD. *p<0.05, **p<0.01, ***p<0.0001.
hELISA, hybridization enzyme-linked immunosorbent assay; PMO, phosphorodiamidate morpholino oligomer; SD, standard deviation; WT, wild type.

1. Desjardins CA, et al. *Nucleic Acids Res.* 2022;50(20):11401–14.

DELIVER

DELIVER trial of DYNE-251 in males with *DMD* mutations amenable to exon 51 skipping

Placebo-controlled period (MAD cohorts)



Muscle biopsies at baseline and 24 weeks (except for 0.7 mg/kg and 1.4 mg/kg cohorts)

Transition to 20 mg/kg[1,2]

Open-label extension (OLE)

Long-term extension (LTE)

Population

- Ages 4–16 years
- Ambulant and non-ambulant

Primary endpoints

- Safety and tolerability
- Change from baseline in dystrophin levels by western blot

Select additional endpoints

- Pharmacokinetics
- Change from baseline of:
  - Exon 51 skipping levels
  - Muscle tissue PDPF
  - Multiple assessments of muscle function, including NSAA score, SV95C, and certain timed functional tests

Registrational dose and dose regimen selected at 20 mg/kg Q4W; registrational expansion cohort fully enrolled (N=32, 3:1 randomization)

Doses provided refer to PMO component of DYNE-251. Cohorts randomized to active arm or placebo.
1. Transition to 20 mg/kg dose started either in the placebo-controlled period or OLE for participants initiated at 40 mg/kg; 2. Transition to 20 mg/kg dose occurred at non-uniform times during OLE or LTE.
DMD, Duchenne muscular dystrophy; MAD, multiple ascending dose; NSAA, North Star Ambulatory Assessment; PDPF, percent dystrophin-positive fibers; PMO, phosphorodiamidate morpholino oligomer; Q4W, every 4 weeks; Q8W, every 8 weeks; SV95C, stride velocity 95th centile.

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DELIVER baseline participant characteristics: 10 mg/kg and 20 mg/kg cohorts

Mean (SD) or n (%)	10 mg/kg (N=8)	20 mg/kg (N=8)
Age (years)	6.6 (2.2)	8.1 (2.4)
BMI (kg/m^2)	18.3 (3.2)	18.6 (5.1)
Age of symptom onset (years)	2.8 (1.6)	2.9 (2.0)
Most recent corticosteroid dosing regimen, n (%)[1] Daily Other	 8 (100) 0 (0.0)	 8 (100) 0 (0.0)
Duration of corticosteroid treatment (years)[2]	1.6 (1.8)	2.0 (2.1)
Prior DMD therapy Eteplirsen Other	 1 (12.5) 1 (12.5)	 0 (0.0) 2 (25.0)
NSAA total score[3]	25.3 (6.40)	15.6 (5.09)
Time to rise from floor (sec)[3]	6.3 (5.60)	5.1 (2.28)
Timed 10-meter walk/run (sec)[3]	4.6 (1.86)	7.7 (3.84)
SV95C (m/sec)[3]	1.9 (0.45)	1.4 (0.47)

Note: DYNE-251 and placebo participants are reported together for baseline characteristics; 1. Most recent corticosteroid regimen refers to corticosteroid at baseline at time of randomization; 2. Cumulative duration of previous and most recent corticosteroid treatment at the time of randomization; 3. Ambulatory participants only.
BMI, body mass index; DMD, Duchenne muscular dystrophy; m, meter; NSAA, North Star Ambulatory Assessment; SD, standard deviation; sec, seconds; SV95C, stride velocity 95th centile.

DELIVER

DYNE-251 safety profile is consistent with expectations for the DMD population

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

TEAE category	Participants with ≥1 TEAE – n (%)								
	0.7 mg/kg Q4W N=6	1.4 mg/kg Q4W N=6	2.8 mg/kg Q4W N=6	5 mg/kg Q4W N=6	10 mg/kg Q4W N=8	20 mg/kg Q4W N=8	40 mg/kg Q8W N=8	40 mg/kg Q4W N=6	Overall N=54
Any TEAE	6 (100)	6 (100)	6 (100)	6 (100)	7 (87.5)	8 (100)	8 (100)	6 (100)	53 (98.1)
Any related TEAE	3 (50.0)	3 (50.0)	2 (33.3)	6 (100)	2 (25.0)	4 (50.0)	2 (25.0)	3 (50.0)	25 (46.3)
Any serious TEAE	0	0	1 (16.7)	0	0	1 (12.5)	2 (25.0)	3 (50.0)	7 (13.0)
Any serious related TEAE	0	0	0	0	0	0	0	2 (33.3)	2 (3.7)
Any TEAE leading to withdrawal from study	0	0	0	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0	0	0	0

Potentially related serious TEAEs

- Acute kidney injury; thrombocytopenia[2]
- Pancytopenia[3]

Most frequent TEAEs[4]

- Pyrexia (48%)
- Headache and vomiting (each 37%)
- Fall (35%)
- Nasopharyngitis (33%)
- Cough (26%)
- Infusion-related reaction[5] (24%)

Additional safety data

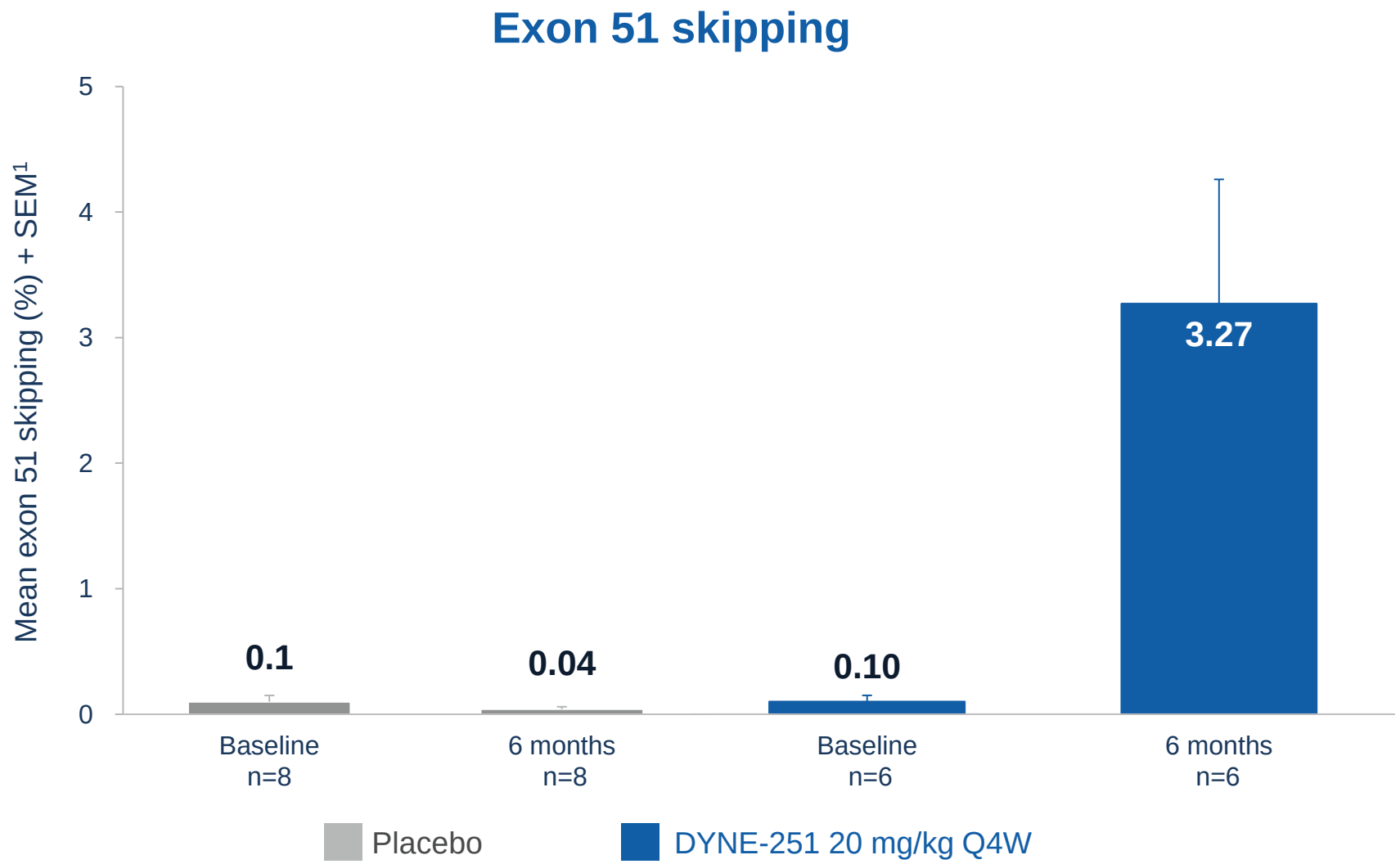
- Other than two participants with serious TEAEs in the 40 mg/kg Q4W cohort:
  - No participants have demonstrated persistent related anemia or thrombocytopenia
  - No participants have demonstrated kidney injury
- No participants have demonstrated clinically meaningful changes in electrolytes, including magnesium

970 doses of study drug administered to date over a period of 77.1 patient-years of follow-up[1]
546 doses of study drug at 20 mg/kg dose level administered to date[6]

1. Data as of February 7, 2025, all participants, placebo-controlled period, open-label period, long-term extension period; 2. Events have same day of onset in a single participant with a non-serious related TEAE of anemia in the context of fever, hemolysis, diarrhea, and positive blood in stool; together these events are consistent with hemolytic uremic syndrome with a possible infectious etiology; 3. Participant has a history of hemolytic anemia of unidentified etiology; presented with fever and tonsilitis; symptoms resolved without therapeutic intervention; 4. All cohorts combined; preferred terms are reported; 5. All infusion-related reactions have been mild or moderate in intensity; dosing has continued in all participants; 6. Data as of February 21, 2025.
Q4W, every 4 weeks; Q8W, every 8 weeks.

DELIVER

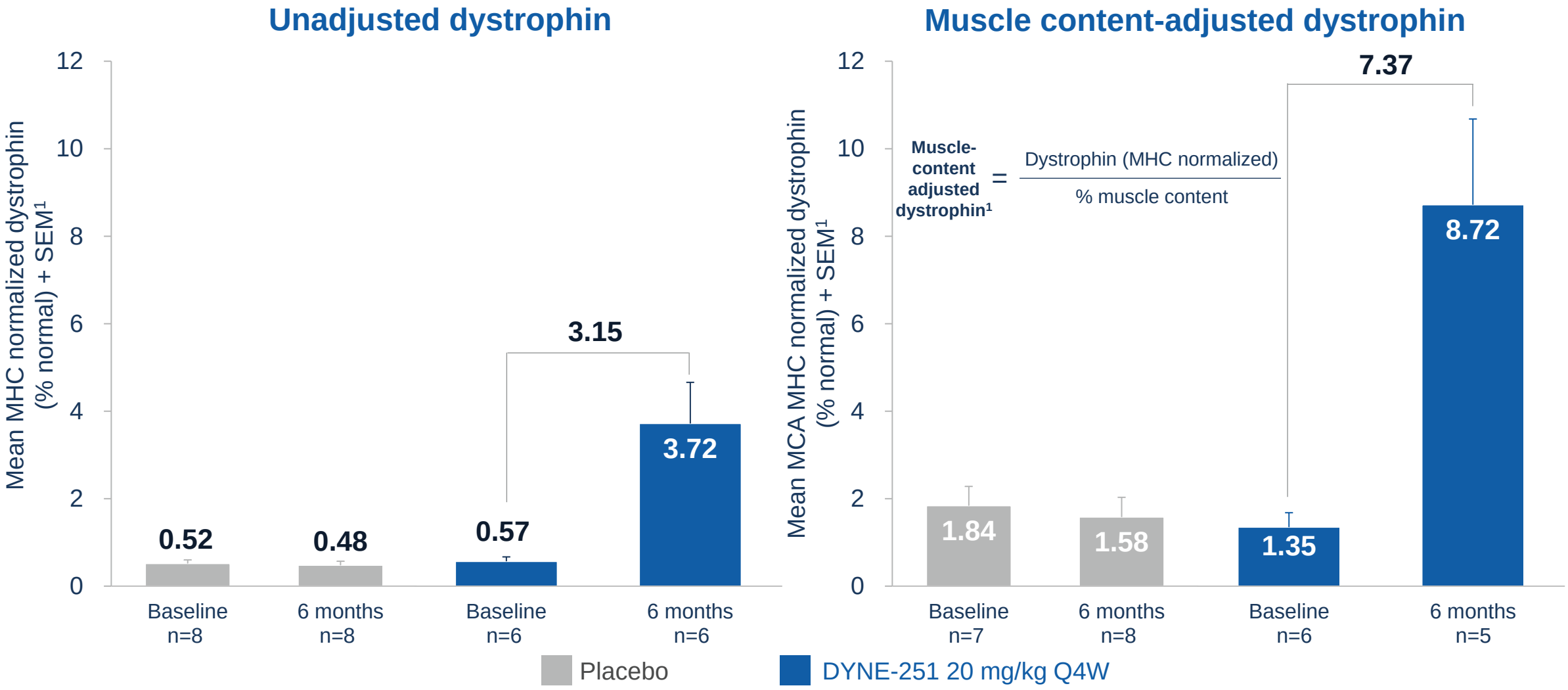
Robust exon 51 skipping with 20 mg/kg Q4W DYNE-251



1. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER.
PMO, phosphorodiamidate morpholino oligomer; Q4W, every 4 weeks; SEM, standard error of mean.

DELIVER

DYNE-251 achieved robust dystrophin expression at 6 months



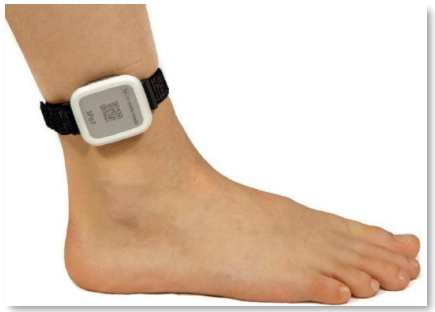
1. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER.
MCA, muscle content-adjusted; MHC, myosin heavy chain; Q4W, every 4 weeks; SEM, standard error of the mean.

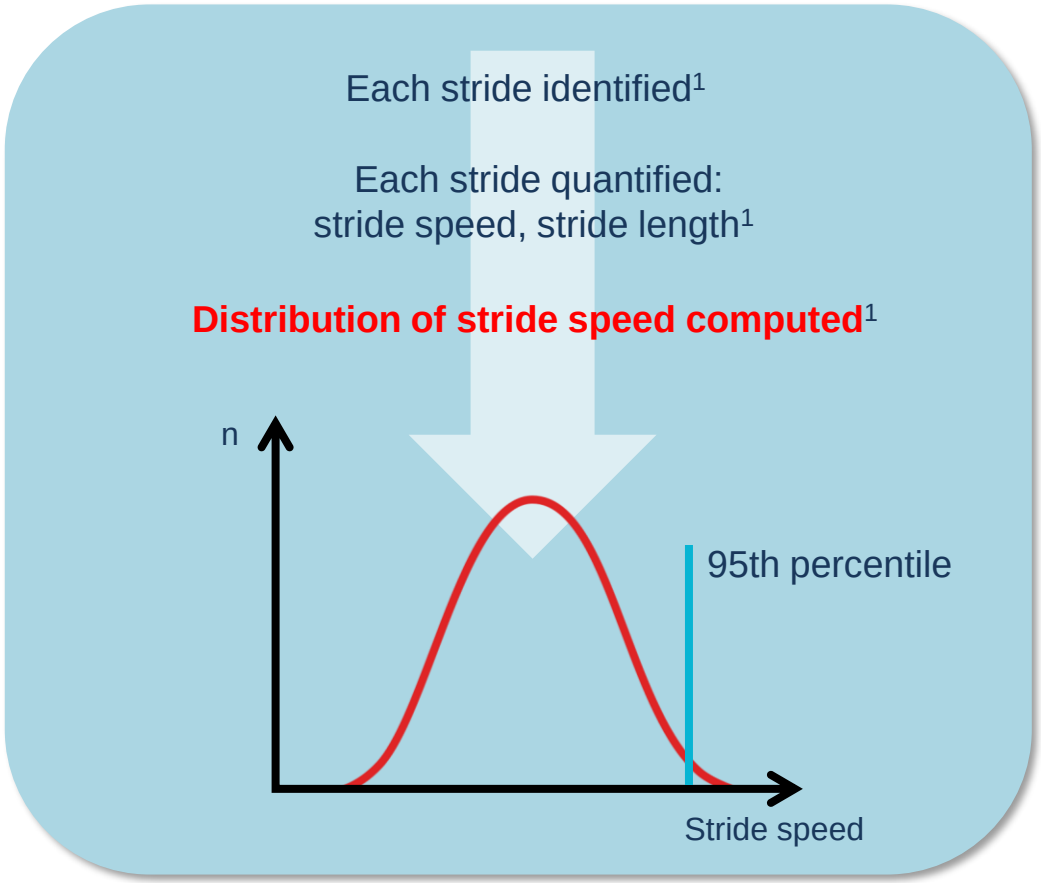
DELIVER

Stride velocity 95th centile (SV95C) is qualified as a digital primary endpoint by EMA in studies in boys with DMD ≥4 years old[1]

SV95C | A digital objective endpoint of ambulatory performance in patients' normal daily environment[1,2]

- Correlated with traditional hospital-based clinical outcomes (6MWT, NSAA, 4SC)[1,2]
- Demonstrated sensitivity to detect change over time in natural history, steroid-treated patients, and in clinical trials[1]
  - SV95C has greater sensitivity vs other function tests, i.e. can detect change earlier[1,3]
- Proposed SV95C MCID = 0.1 m/s (36 m in 6 min) corresponds to 6MWT MCID = 30 m[1,4,5]
- Continuously collects data over a period of time; minimally impacted by social, familial, or environmental factors[1,5]





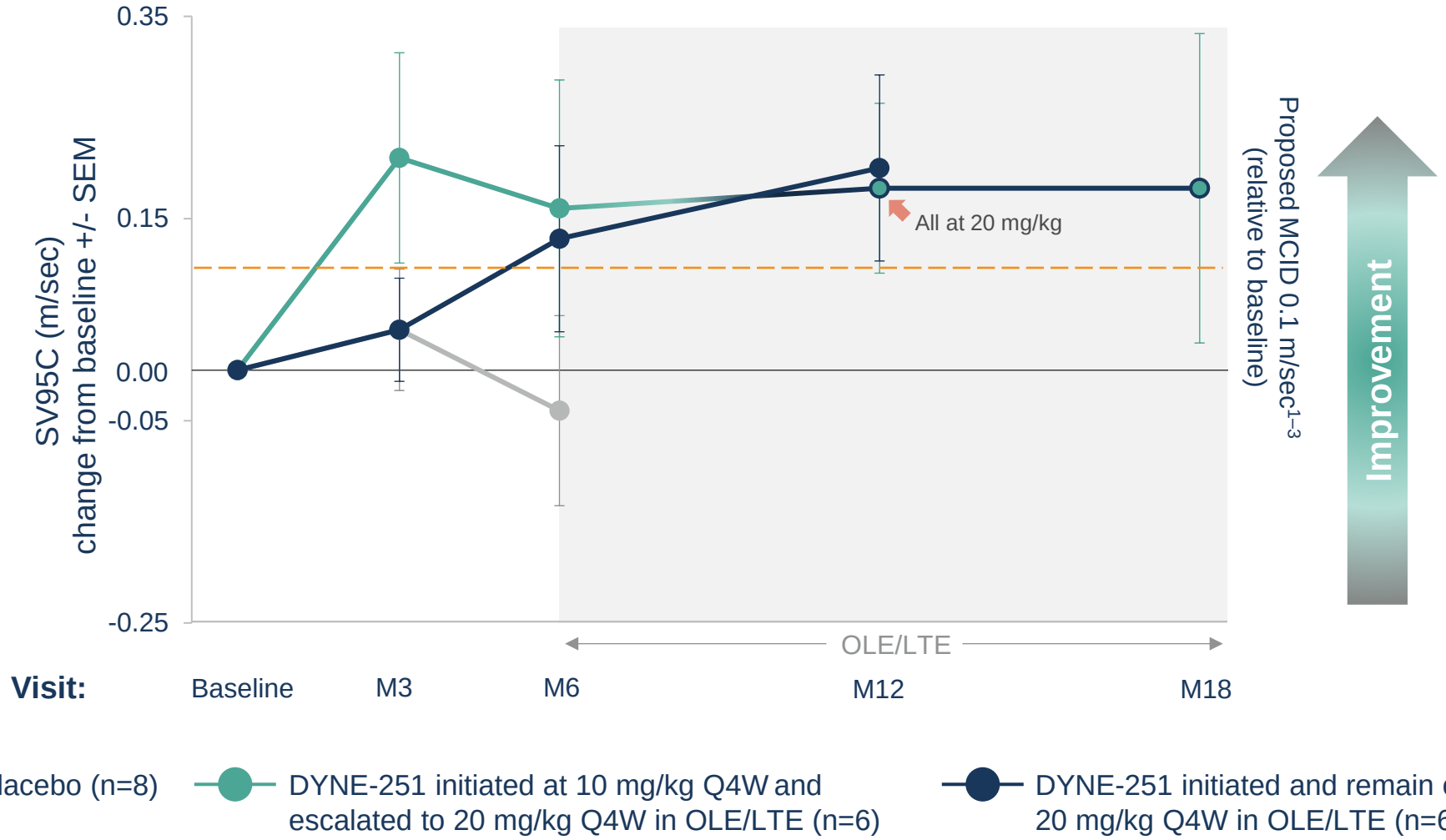
EMA, European Medicines Agency; DMD, Duchenne muscular dystrophy; MCID, minimal clinically important difference; 6MWT, 6-minute walk test; NSAA, North Star Ambulatory Assessment; 4SC, 4-stair climb.

1. EMA. Opinion on SV95C. July 2023. Accessed February 11, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-primary-endpoint-studies-ambulatory-duchenne-muscular-dystrophy-studies_en.pdf; 2. Servais L, et al. *Nat Med*. 2023;29(10):2391–2; 3. Servais L, et al. *Sci Rep*. 2024;14(1):29681; 4. McDonald CM, et al. *Muscle Nerve*. 2013;48(3):357–68; 5. EMA. Opinion on SV95C. April 2019. Accessed February 11, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular-dystrophy-measured-valid-and-suitable-wearable-device_en.pdf.

DELIVER

Early and sustained improvements in SV95C at 20 mg/kg DYNE-251

Robust improvement observed vs baseline through 18 months; proposed MCID achieved by 6 months

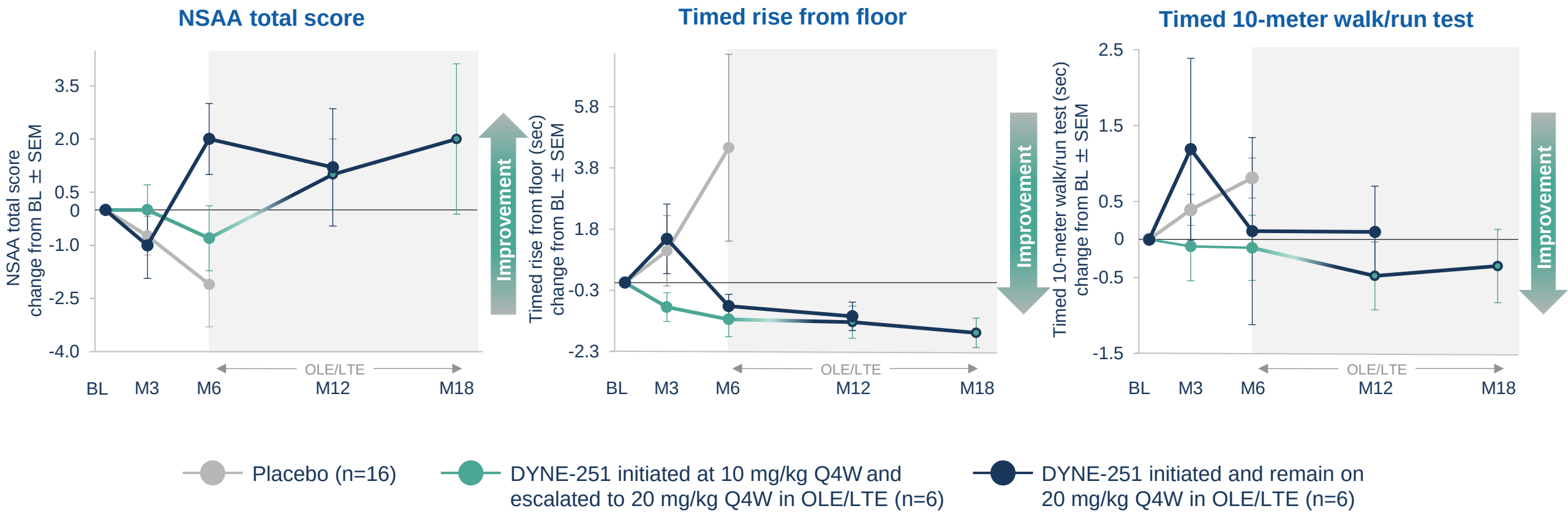


3 months = 85 days; 6 months = 169 days; 12 months = 337 days; 18 months = 505 days. LTE, long-term extension; m, meter; M, month; MCID, minimal clinically important difference; OLE, open-label extension; Q4W, every 4 weeks; sec, seconds; SEM, standard error of mean; SV95C, stride velocity 95th centile.

1. EMA. Opinion on SV95C. July 2023. Accessed February 11, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-primary-endpoint-studies-ambulatory-duchenne-muscular-dystrophy-studies_en.pdf; 2. Servais L, et al. *Sci Rep.* 2024;14(1):29681; 3. EMA. Opinion on SV95C. April 2019. Accessed February 11, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular-dystrophy-measured-valid-and-suitable-wearable-device_en.pdf.

DELIVER

Long-term improvements vs baseline observed across multiple functional endpoints through 18 months



Placebo (n=16)

DYNE-251 initiated at 10 mg/kg Q4W and escalated to 20 mg/kg Q4W in OLE/LTE (n=6)

DYNE-251 initiated and remain on 20 mg/kg Q4W in OLE/LTE (n=6)

DELIVER

3 months = 85 days; 6 months = 169 days; 12 months = 337 days; 18 months = 505 days.
BL, baseline; LTE, long-term extension; m, meter; M, month; NSAA, North Star Ambulatory Assessment; OLE, open-label extension; Q4W, every 4 weeks; sec, seconds; SEM, standard error of mean.

Summary

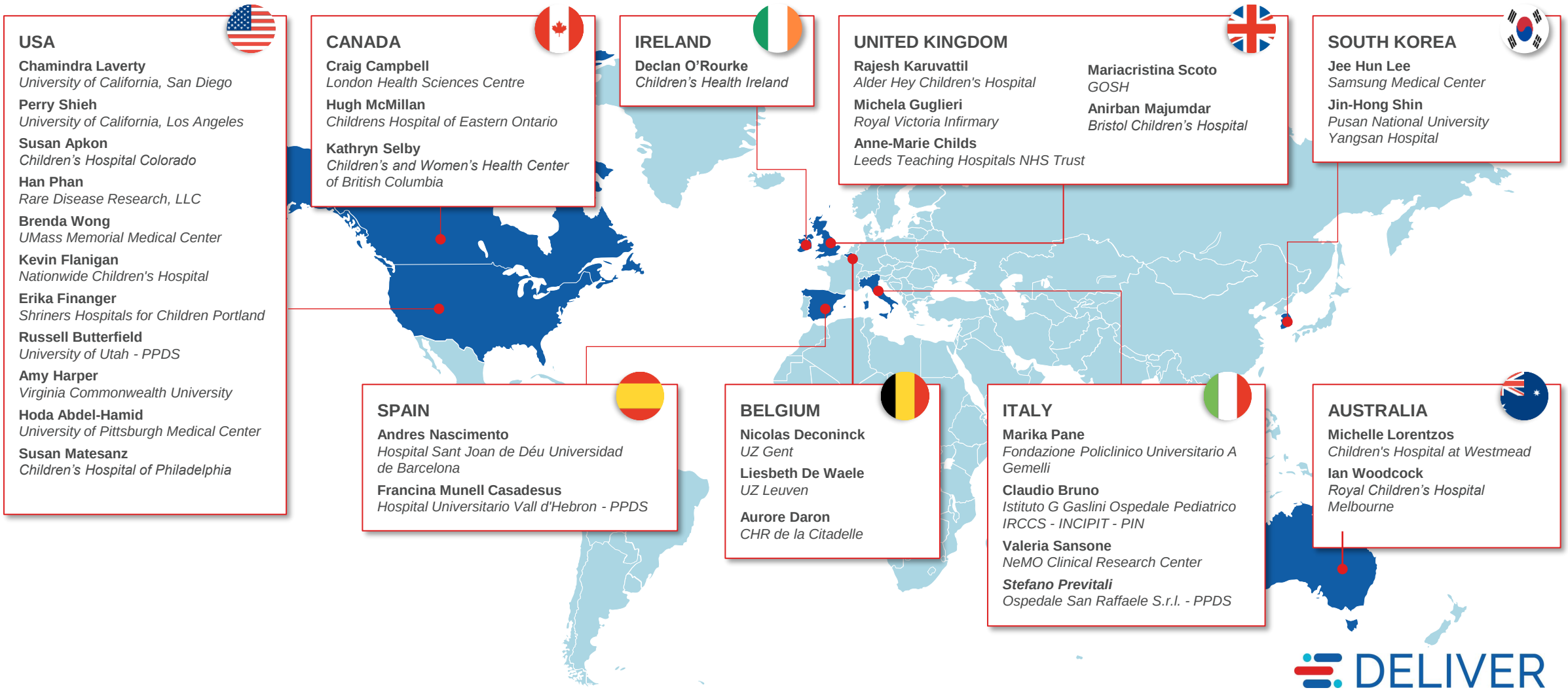
- **The safety profile of DYNE-251 is favorable to date**, with some participants on therapy for ~2.5 years[1]
- **Robust expression of near full-length dystrophin** following treatment with DYNE-251
- **Early and sustained benefit** of treatment with DYNE-251 consistently seen on clinical and real-world functional outcomes, including SV95C, NSAA, TTR, and 10MWR, through 18 months
  - Improvement vs baseline in SV95C, a reliable measure of continuous real-world function, demonstrated at the registrational dose level of 20 mg/kg Q4W
  - Proposed MCID for SV95C achieved by 6 months
- The registrational expansion cohort (20 mg/kg Q4W) of DELIVER (N=32) is **fully enrolled**
  - Data planned for late 2025[2]

10MWR, 10-meter walk/run test; MCID, minimal clinically important difference; NSAA, North Star Ambulatory Assessment; Q4W, every 4 weeks; SV95C, stride velocity 95th centile; TTR, time to rise.

1. Data as of February 7, 2025; 2. Dyne Therapeutics (February 27, 2025). Dyne Therapeutics Reports Fourth Quarter and Full Year 2024 Financial Results and Recent Business Highlights [Press Release]. https://investors.dyne-tx.com/news-releases/news-release-details/dyne-therapeutics-reports-fourth-quarter-and-full-year-2024.

Acknowledgments

DELIVER participants and their families



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DELIVER

For more information visit the DELIVER clinical trial posting on ClinicalTrials.gov. ClinicalTrials.gov Identifier: NCT05524883 or clinicaltrialsregister.eu EudraCT Number: 2021-005478-24.