Safety and Efficacy of DYNE-251 in Males with *DMD* Mutations Amenable to Exon 51 Skipping

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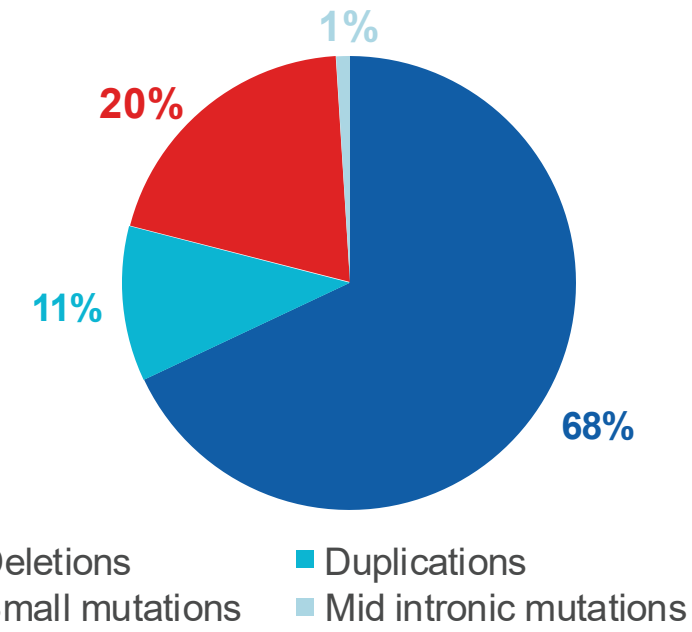
Disclosures

- I am a principal investigator on clinical trials sponsored by Antisense Therapeutics, Dyne Therapeutics, NS Pharma, Pfizer, PTC Therapeutics, and Sarepta Therapeutics.
- I have participated on advisory boards for Roche.
- DYNE-251 is an investigational medicine being evaluated in the ongoing DELIVER trial and has not received approval by FDA, EMA, or any other regulatory authorities.

DMD is Caused by Mutations in the *DMD* Gene

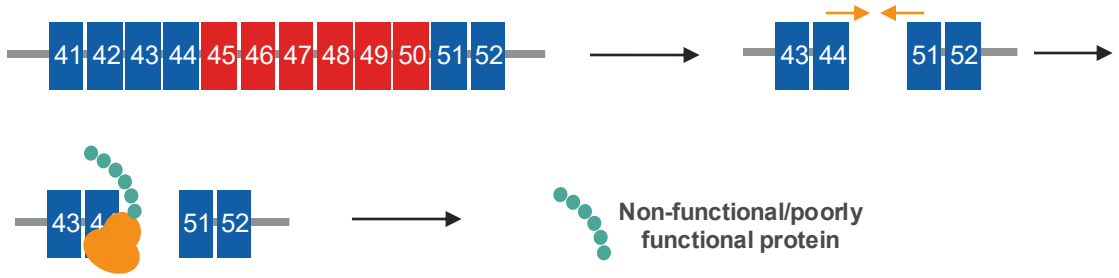
- DMD is caused by mutations in the *DMD* gene which result in greatly reduced production of dystrophin protein, essential for muscle structure, function, and preservation[1–5]

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

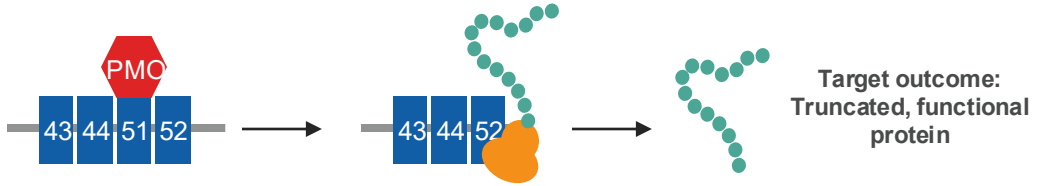


- PMO-induced exon skipping restores the *DMD* mRNA reading frame leading to the production of truncated, functional dystrophin protein[7,8]

Exon 45–50 deletion disrupts reading frame



Skipping exon 51 with PMO restores reading frame



DMD, Duchenne muscular dystrophy; PMO, phosphorodiamidate morpholino oligomer.

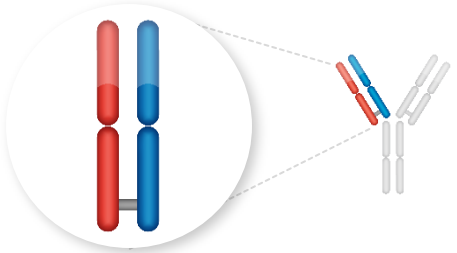
1. Claflin DR, Brooks SV. *Am J Physiol Cell Physiol* 2008;294:C651–58; 2. Ervasti JM, Campbell KP. *J Cell Biol* 1993;122:809–23;
3. Hoffman EP, et al. *Cell* 1987;51:919–28; 4. de Feraudy Y, et al. *Ann Neurol* 2021;89:280–92; 5. Ohlendieck K, et al. *Neurology* 1993;43:795–800;
6. Bladen CL, et al. *Hum Mutat* 2015;36:395–402; 7. Niks EH, Aartsma-Rus A. *Expert Opin Biol Ther* 2017;17:225–36; 8. Nakamura A. et al. *J Hum Genet* 2017;62:871–76.

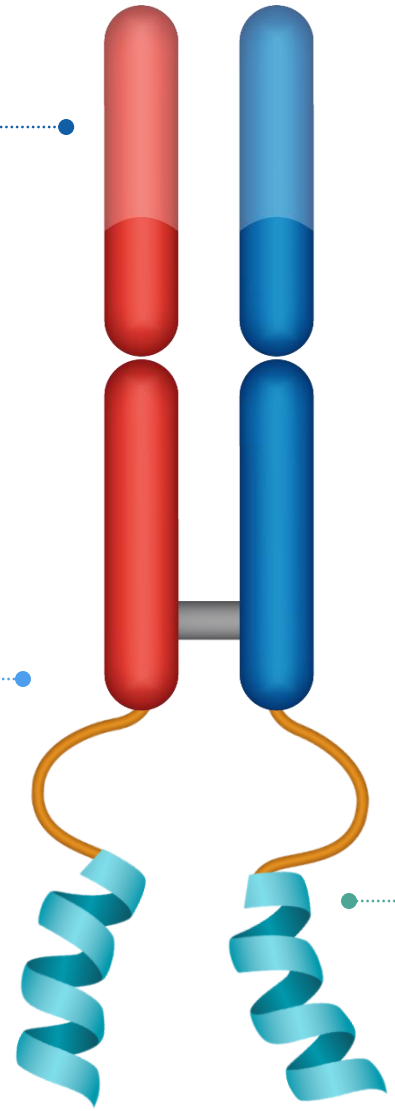
DELIVER

FORCE™ Platform-based Oligonucleotide Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



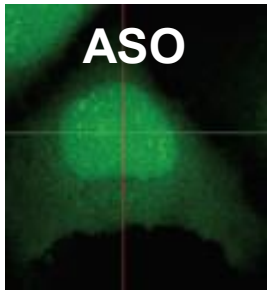


LINKER

Enables precise conjugation of multiple payloads to a single Fab

PAYLOAD

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



Nuclear localization

Cytoplasmic localization

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

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DYNE-251 is Designed to Leverage TfR1 to Deliver Exon 51-Skipping PMO to Affected Muscle in DMD

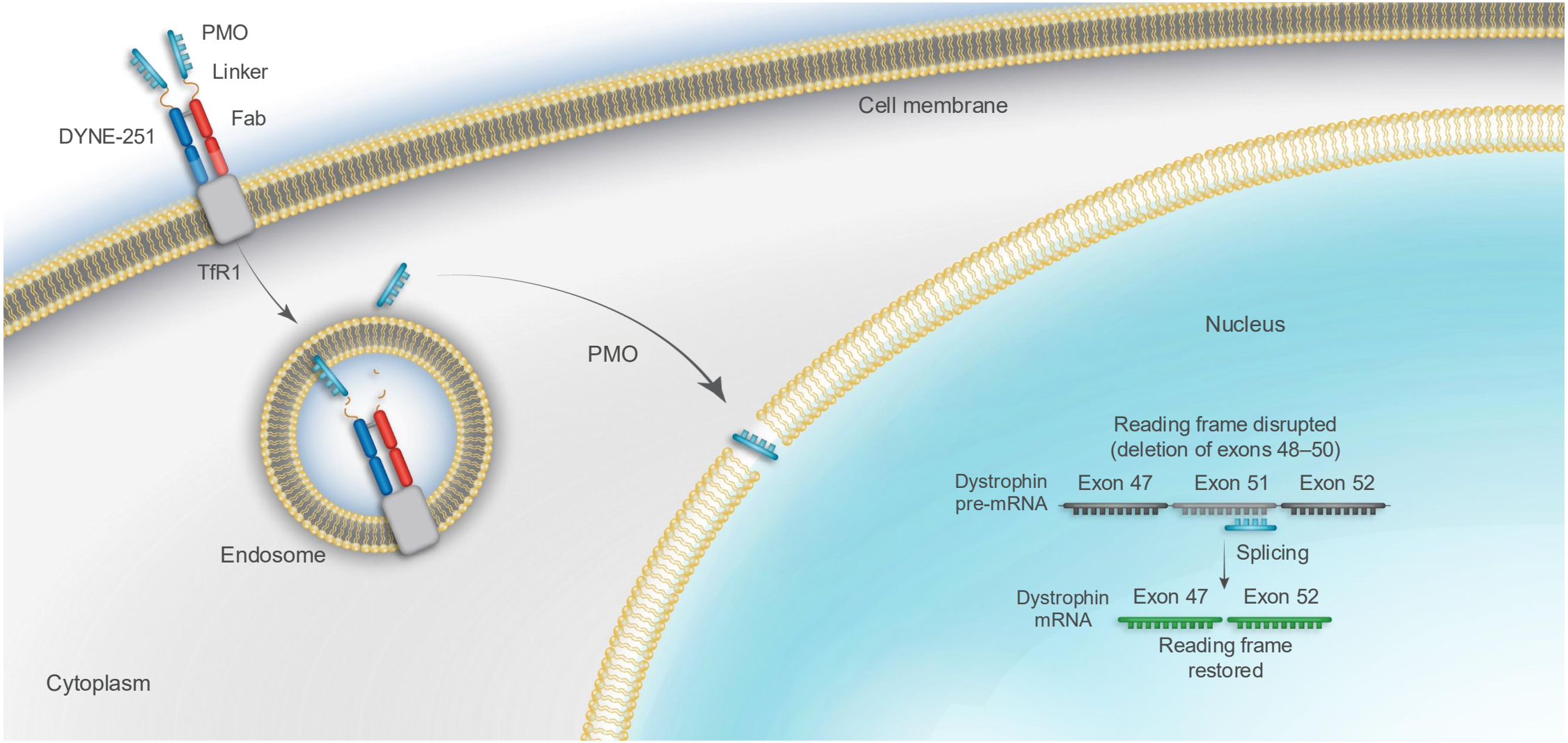


Image depicts intended mechanism of action of DYNE-251. Applicable to all DMD mutations amenable to skipping of exon 51.
Adapted from Desjardins CA, et al. *Nucleic Acids Res.* 2022;50(20):11401–11414.

DELIVER

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

DELIVER

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

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

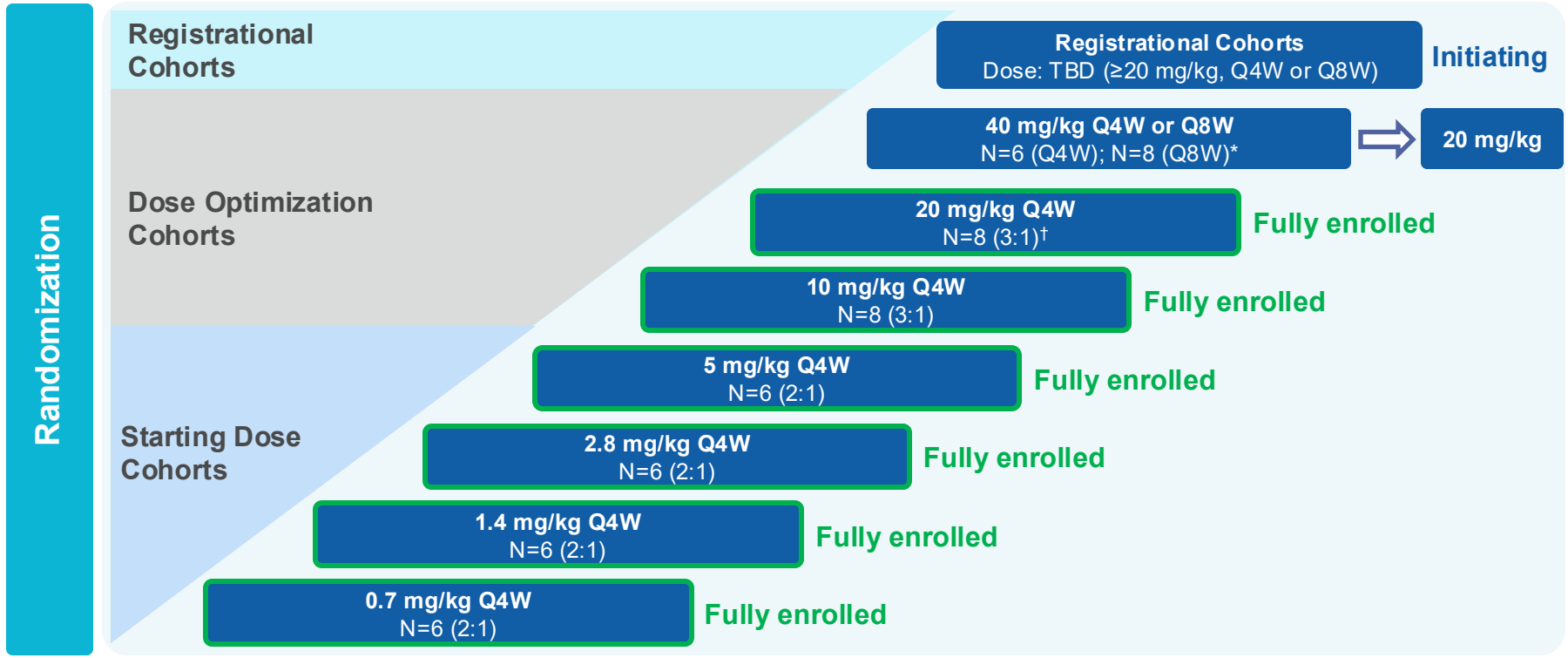
Stages of DELIVER

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

Additional endpoints include select secondary and exploratory endpoints.
NSAA: North Star Ambulatory Assessment; PDPF: percent dystrophin-positive fibers; SV95C, stride Velocity 95th Centile.
For more information visit the DELIVER clinical trial posting on ClinicalTrials.gov ClinicalTrials.gov Identifier: NCT05524883 or clinicaltrialsregister.eu EudraCT Number: 2021-005478-24.
De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225.

DELIVER Multiple Ascending Dose (MAD) Trial Design

Global, randomized, placebo-controlled stage evaluating administration of DYNE-251 in ambulant and non-ambulant male DMD patients with mutations amenable to exon 51 skipping therapy



MAD Study Details

- IV administration of DYNE-251 or placebo every 4 weeks or every 8 weeks
- Muscle biopsies: Baseline and 24 weeks‡
- 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

Doses provided refer to PMO component of DYNE-251. Cohorts randomized to active arm or placebo.
*14 participants who initiated at 40 mg/kg are now being dosed at 20 mg/kg following evaluation of the safety profile at 40 mg/kg. †All participants in DELIVER starting dose and dose optimization cohorts are currently receiving 20 mg/kg dose, including 32 participants who dose escalated following the placebo-controlled period from starting doses lower than 20 mg/kg. ‡Muscle biopsies taken at baseline and 24 weeks in 2.8 mg/kg Q4W cohort to 20 mg/kg Q4W cohort; biopsies not taken in 0.7 mg/kg and 1.4 mg/kg cohorts.
Q4W, every 4 weeks; Q8W, every 8 weeks; TBD, to be determined.
De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225.

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DELIVER Baseline Participant Characteristics: By Cohort

Mean (SD) or n (%)	0.7 mg/kg (N=6)	1.4 mg/kg (N=6)	2.8 mg/kg (N=6)	5 mg/kg (N=6)	10 mg/kg (N=8)	20 mg/kg (N=8)
Age (years)	10.8 (2.2)	8.0 (3.5)	10.7 (2.9)	8.3 (2.8)	6.6 (2.2)	8.1 (2.4)
BMI (kg/m^2)	19.5 (3.4)	18.6 (2.2)	22.6 (6.3)	20.9 (1.6)	18.3 (3.2)	18.6 (5.1)
Age of symptom onset (years)	3.7 (1.8)	4.5 (2.1)	2.8 (1.8)	3.7 (3.1)	2.8 (1.6)	2.9 (2.0)
Corticosteroid dosing regimen*						
Daily	4 (66.7%)	4 (66.7%)	5 (83.3%)	6 (100.0%)	8 (100.0%)	8 (100.0%)
Other	2 (33.3%)	3 (50.0%)	2 (33.3%)	0	0	2 (25.0%)
Prior DMD therapy						
Eteplirsen	4 (66.7%)	2 (33.3%)	5 (83.3%)	1 (16.7%)	1 (12.5%)	0
Other	2 (33.3%)	1 (16.7%)	0	0	1 (12.5%)	2 (25.0%)
NSAA total score†	22.2 (7.2)	22.8 (10.5)	20.3 (9.0)	21.0 (7.0)	25.3 (6.4)	15.6 (5.1)
10-meter run/walk (sec)†	6.1 (1.5)	6.3 (5.2)	6.9 (3.6)	5.1 (1.5)	4.6 (1.9)	7.7 (3.8)
Time rise from floor (sec)†	8.5 (4.0)	3.1 (0.3)	6.9 (4.9)	5.0 (2.6)	6.3 (5.6)	5.1 (2.3)
SV95C (m/sec)†	N/A	N/A	N/A	N/A	1.9 (0.5)	1.4 (0.5)

Note: Q4W and placebo arms are reported together for baseline characteristics. N/A: not applicable as data not collected.
*Historical corticosteroid regimen based on medical history; a participant can be counted in multiple categories. †Data exclude participants who were not able to complete the assessment.
BMI, body mass index; SD, standard deviation.
De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225.

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DYNE-251 Safety Profile is Favorable to Date

Summary of Treatment-Emergent Adverse Events (TEAEs)*[1]

TEAE category, n (%)	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)	4 (67)	6 (100)	7 (88)	8 (100)	6 (75)	4 (67)	47 (87)
Any related TEAE	3 (50)	3 (50)	0	6 (100)	3 (38)	4 (50)	1 (13)	2 (33)	22 (41)
Any serious TEAE	0	0	1 (17)	0	0	1 (13)	2 (25)	2 (33)	6 (11)
Any serious related TEAE	0	0	0	0	0	0	0	2 (33)	2 (4)
Any TEAE leading to withdrawal	0	0	0	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0	0	0	0

Most TEAEs Were Mild Or Moderate in Intensity[1]

- 3 serious TEAEs potentially related to study drug in two participants
  - Acute kidney injury (1); thrombocytopenia (1)‡
  - Pancytopenia (1)§
  - No other participants have demonstrated persistent related anemia or thrombocytopenia
  - No other participants have demonstrated kidney injury
- 6 serious TEAEs unrelated to study drug
  - Dehydration due to gastroenteritis (1)
  - Femoral neck fracture (1); gastric volvulus (1)¶
  - Tibia fracture (1)
  - Febrile convulsion (1); pyrexia (1)¶
- Most common TEAEs (≥20% participant incidence)#
  - Pyrexia (32%)
  - Nasopharyngitis, headache, vomiting (each 26%)
  - Fall (26%)
  - Infusion-related reaction (20%)

Additional Safety Data[1]

- No participants have demonstrated clinically meaningful changes in electrolytes, including magnesium

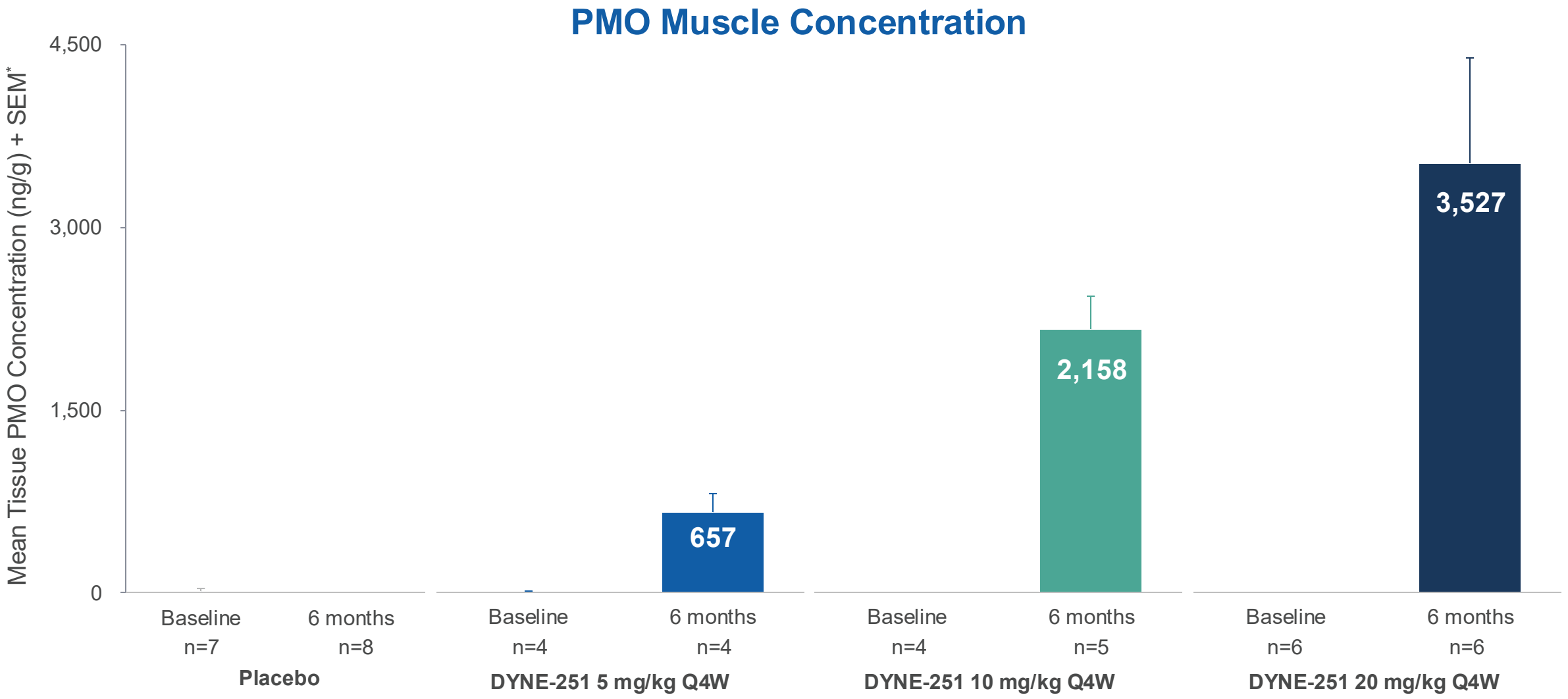
~675 doses administered to date representing over 50 patient-years of follow-up*[2]

*Data as of August 21, 2024; †14 participants initiated at 40 mg/kg who are now being dosed at 20 mg/kg following evaluation of the safety profile at 40 mg/kg; ‡Events have same day of onset in a single participant in the context of fever, hemolysis, diarrhea and positive blood in stool; together, these events are potentially consistent with hemolytic uremic syndrome with a potential infectious etiology; § Participant had a history of hemolytic anemia of unidentified etiology prior to enrolling in DELIVER. Presented with fever and tonsilitis; all symptoms resolved without therapeutic intervention; ¶Events occurred in same participant at different times; #All cohorts combined; preferred terms are reported.

1. De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225; 2. Dyne Corporate presentation. September 2024.

DELIVER

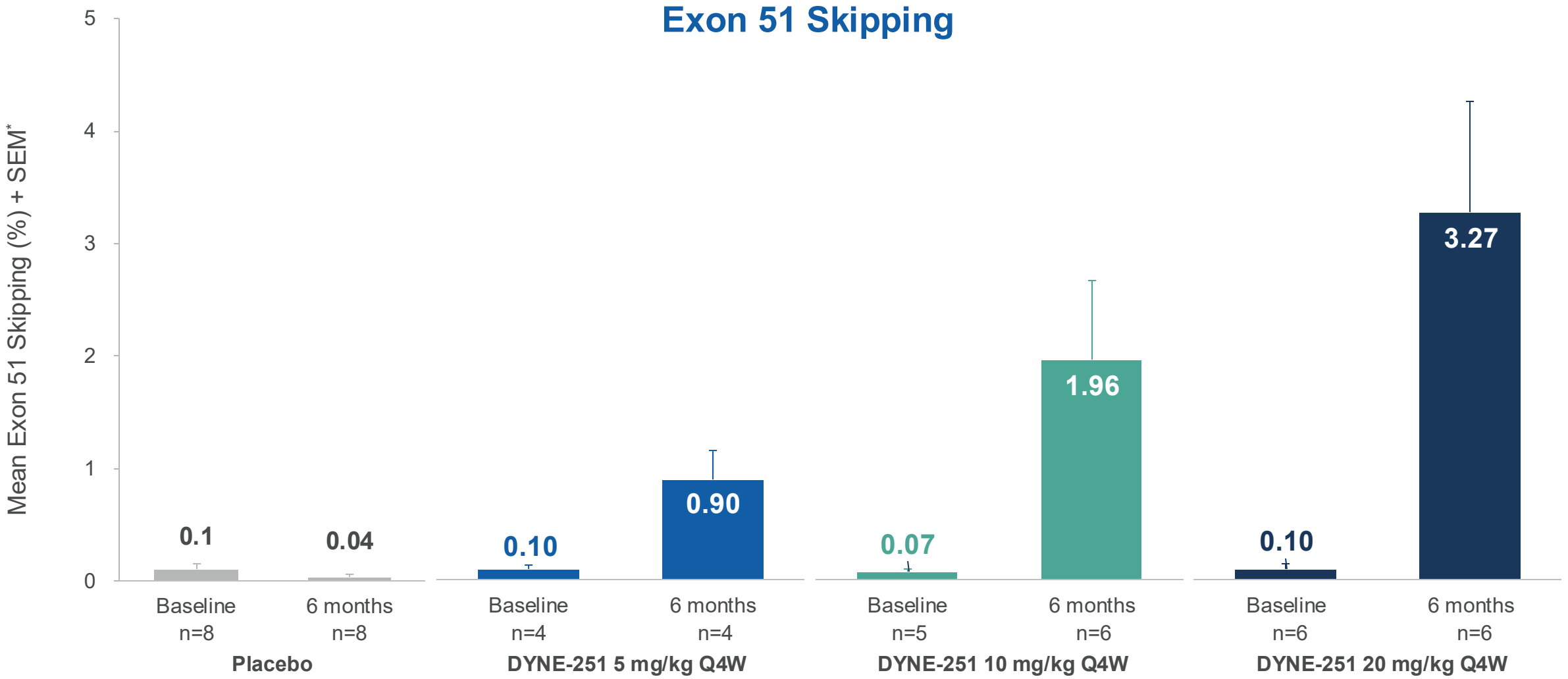
DYNE-251 Drove Dose-dependent Delivery of PMO to Muscle



*DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER.
SEM, standard error of mean.
De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225.

DELIVER

DYNE-251 Demonstrated Dose-dependent Exon Skipping

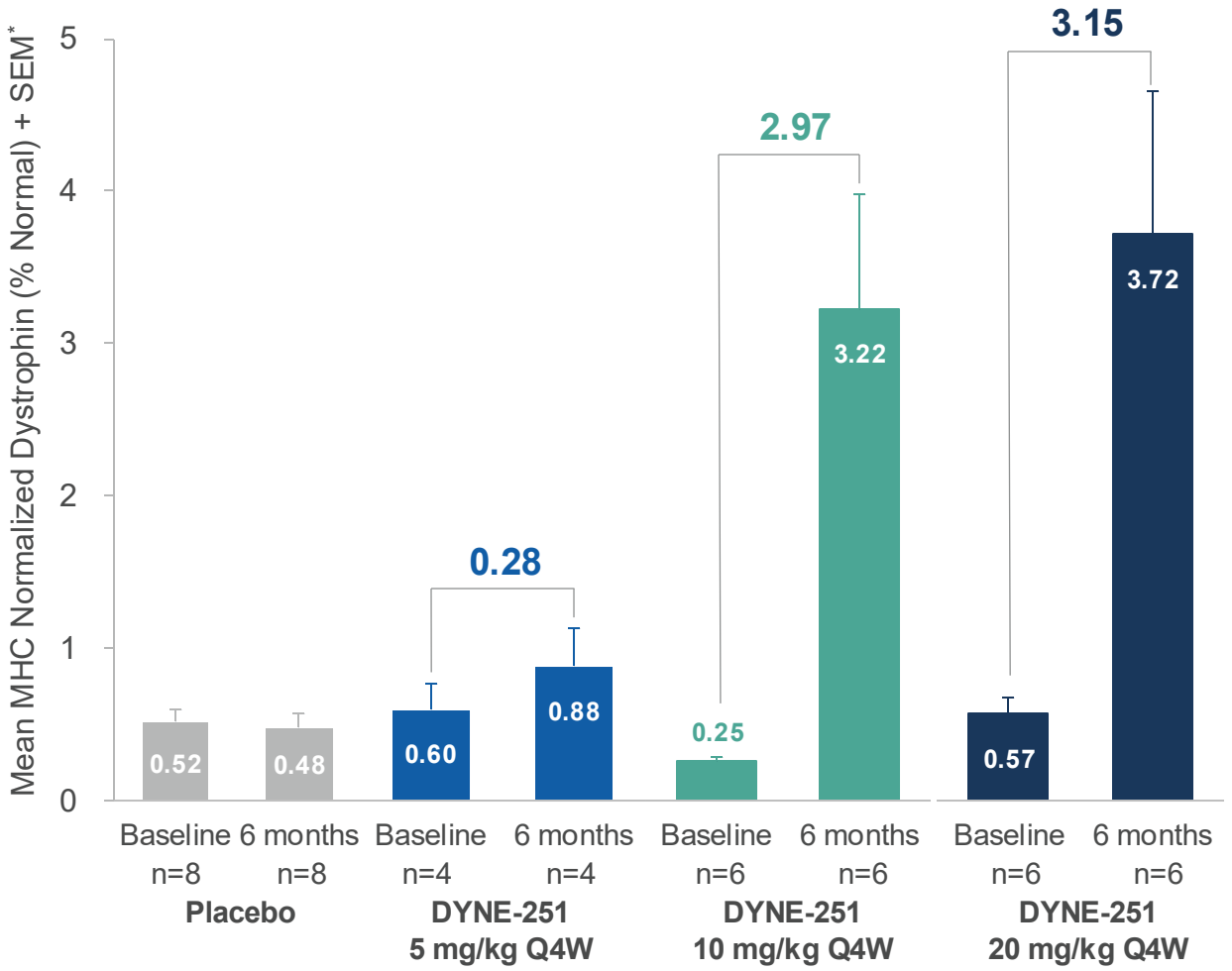


*DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER.
De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225.

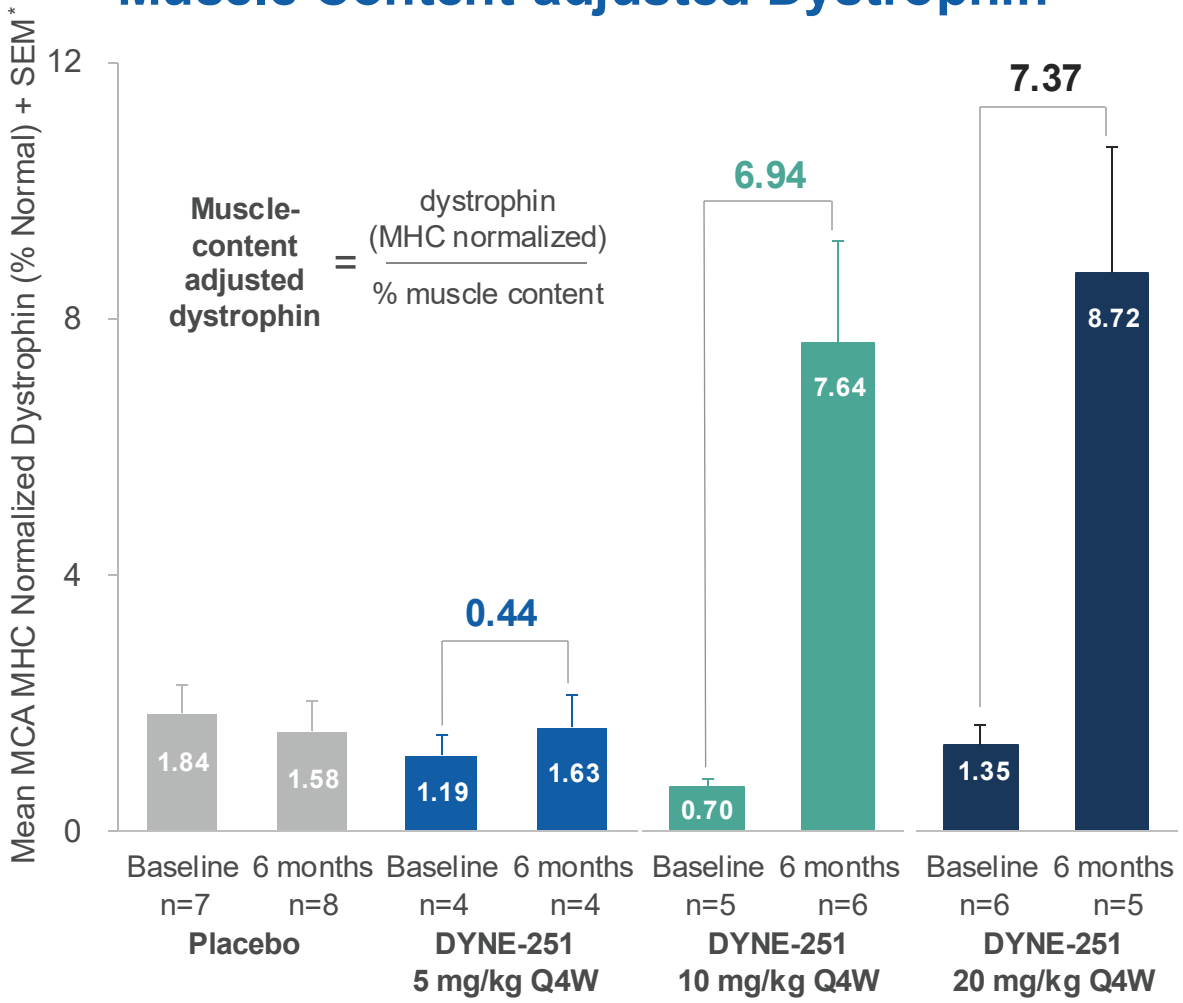
DELIVER

DYNE-251 20 mg/kg Q4W Achieved 3.7% and 8.7% Unadjusted and Muscle Content-adjusted Dystrophin, Respectively, at 6 Months

Unadjusted Dystrophin



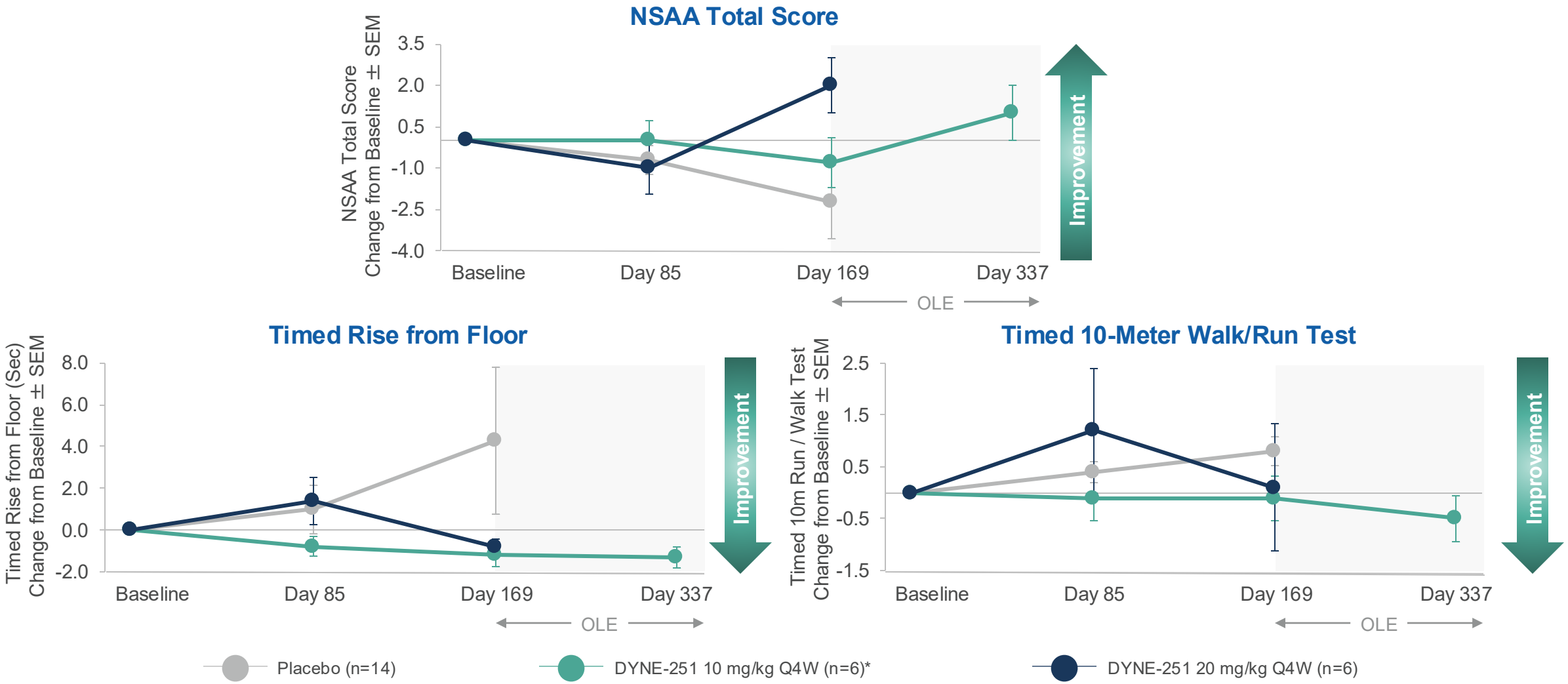
Muscle Content-adjusted Dystrophin



*DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER.
MCA, muscle content adjusted; MHC, myosin heavy chain.
De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225.

DELIVER

DYNE-251 Demonstrated Improvements Across Multiple Functional Endpoints in Multiple Cohorts



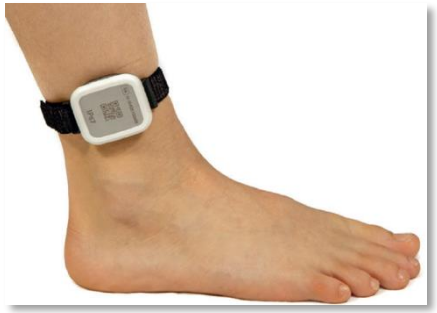
*During the OLE, all participants in 10 mg/kg cohort were dose escalated to 20 mg/kg Q4W regimen.
sec, seconds.
De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225.

DELIVER

Stride Velocity 95th Centile (SV95C) is Qualified as a Digital Primary Endpoint by EMA in Studies on Boys with DMD ≥4 Years Old[1]

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

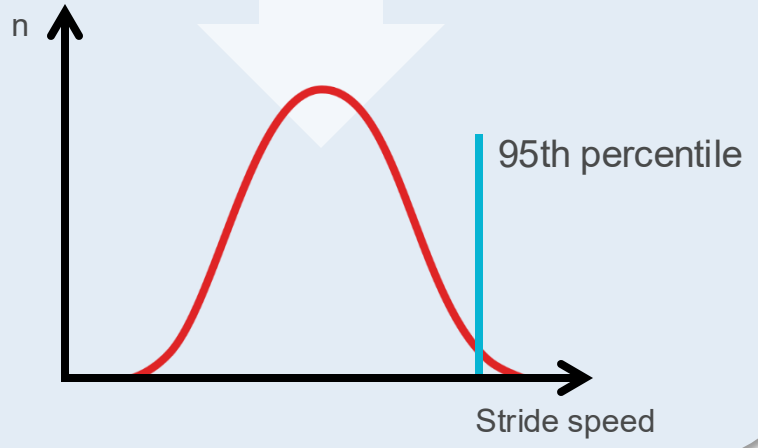
- Demonstrated sensitivity to detect change over time in natural history, steroid-treated patients, and in clinical trials[1]
- Correlated with traditional hospital-based clinical outcomes (6MWT, NSAA, 4SC)[1,2]
- SV95C MCID = 0.1 m/s (36 m in 6 min) corresponds to 6MWT MCID = 30 m[1,3,4]
- Minimally impacted by social, familial or environmental factors[1,4]



Each stride identified[1]

Each stride quantified:
Stride speed, stride length[1]

Distribution of stride speed computed[1]

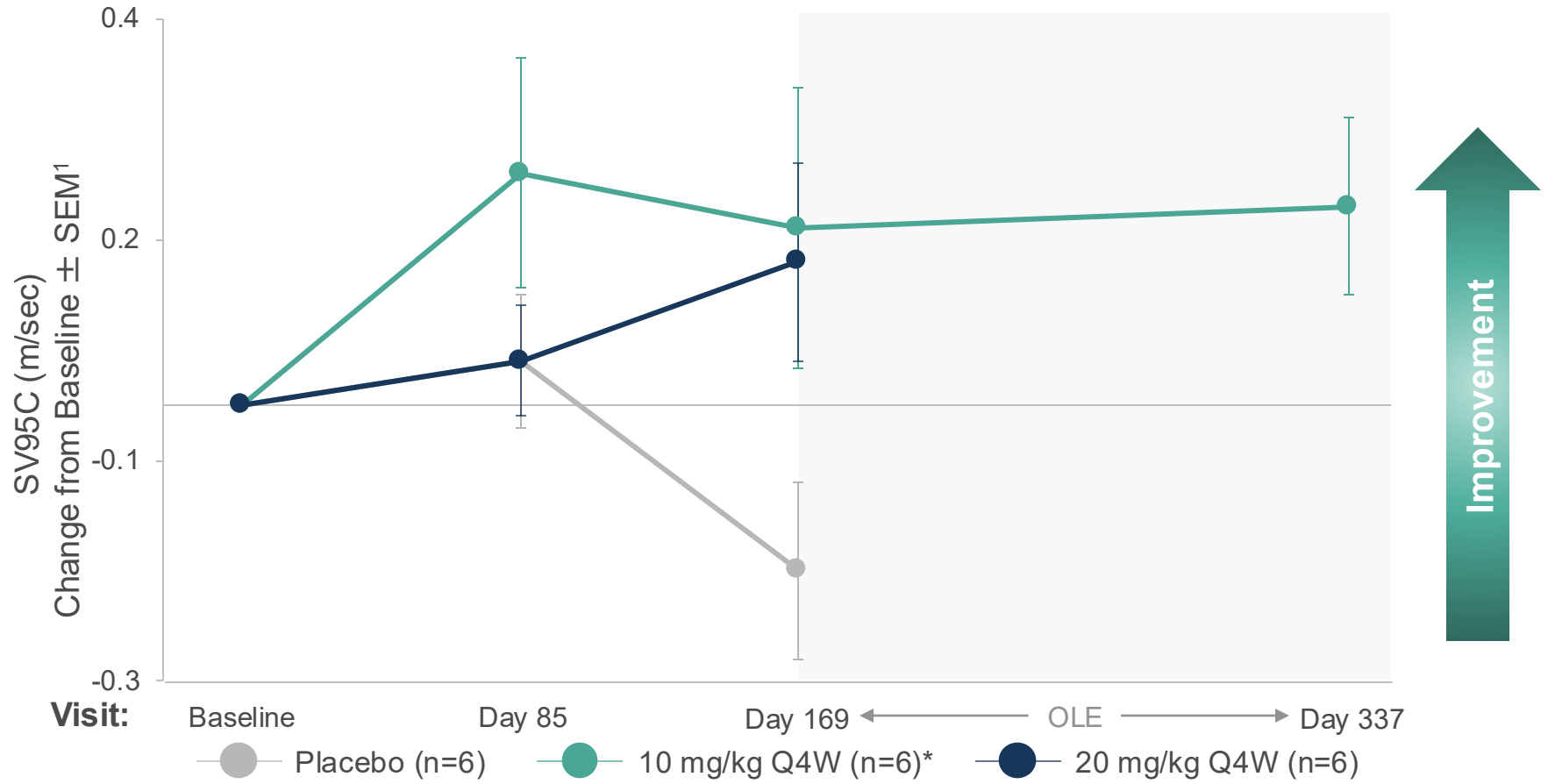


EMA, European Medicines Agency; 6MWT, 6-minute Walk Test; 4SC, 4 Stair Climb; MCID, Minimal Clinically Important Difference; min, minute.

1. EMA Qualification Opinion. July 2023. Accessed October 1, 2024. 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):2391–2392; 3. McDonald CM, et al. *Muscle Nerve.* 2013;48(3):357–368; 4. EMA Qualification Opinion. April 2019. Accessed October 1, 2024. 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

DYNE-251 Drove Clinically Meaningful Improvements in Stride Velocity 95th Centile



The change from baseline in SV95C met the published MCID by the EMA†1,2

*During the OLE, all participants in 10 mg/kg cohort were dose escalated to 20 mg/kg Q4W regimen. †MCID as defined by EMA in its qualification opinion for SV95C as primary endpoint in studies in ambulatory DMD studies. MCID, minimal clinically important difference.

*During the OLE, all participants in 10 mg/kg cohort were dose escalated to 20 mg/kg Q4W regimen. †MCID as defined by EMA in its qualification opinion for SV95C as primary endpoint in studies in ambulatory DMD studies.

1. De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225; 2. EMA. Opinion on SV95C. Accessed October 1, 2024. https://www.ema.europa.eu/en/documents/scientificguideline/qualification-opinion-stride-velocity-95th-centile-primary-endpoint-studies-ambulatoryduchenne-muscular-dystrophy-studies_en.pdf.

DELIVER

Summary

- **DYNE-251** is designed to deliver an **exon 51 skipping PMO** to muscles via TfR1[1–3]
- The Phase 1/2 **DELIVER** trial is an ongoing, randomized, placebo-controlled global trial of DYNE-251 in ambulant and non-ambulant males with DMD with mutations amenable to exon 51 skipping therapy[3]
  - DYNE-251 exhibited **dose-dependent delivery to muscle** and exon skipping, showing **3.7% unadjusted dystrophin** levels and **8.7% muscle content-adjusted** levels after 6 months at 20 mg/kg Q4W
  - DYNE-251 showed trends in **improvement in functional outcomes**, including NSAA and SV95C, at 6 months at both 10 and 20 mg/kg Q4W and at 12 months with 10 mg/kg Q4W
  - DYNE-251 has demonstrated a **favorable safety profile** to date*

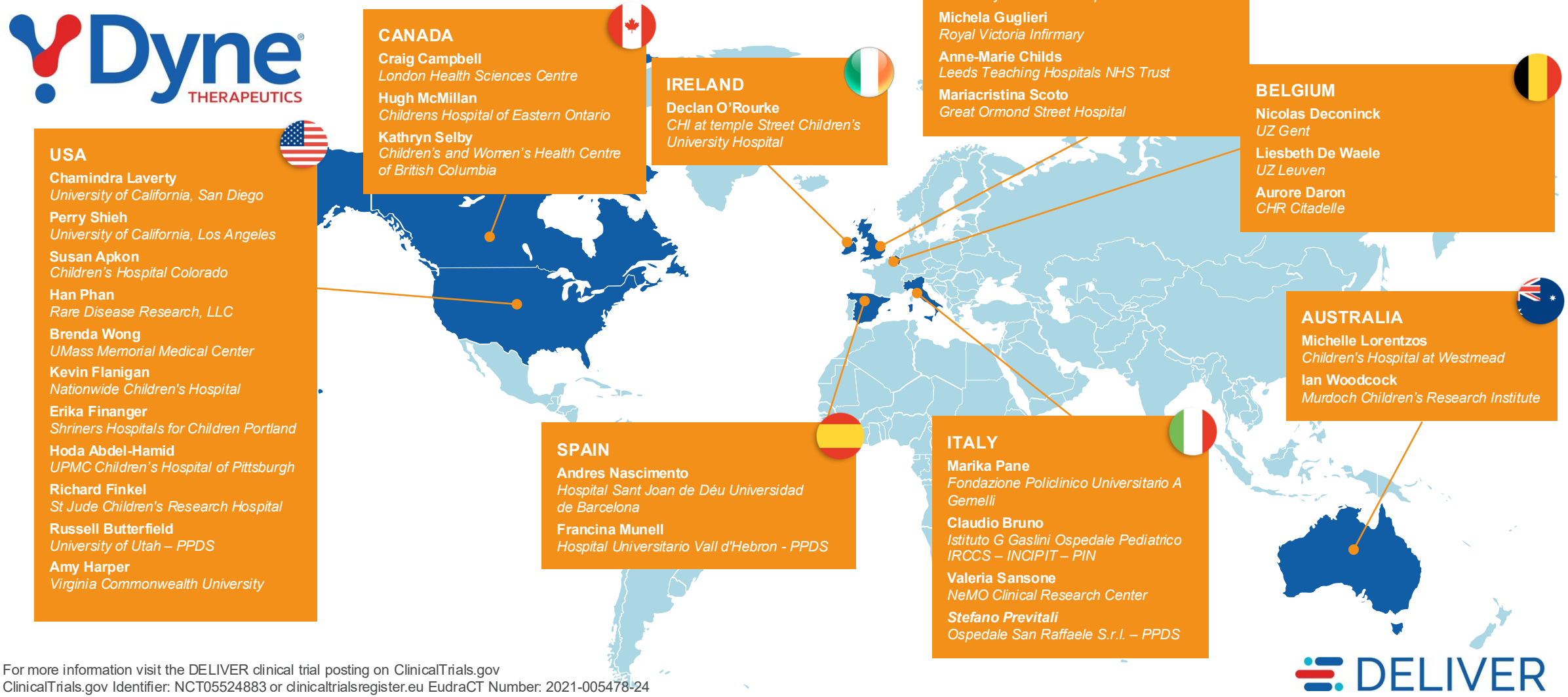
*Data as of August 21, 2024.

1. Desjardins CA, et al. *Nucleic Acids Res.* 2022;50(20):11401–11414; 2. Zanotti S. Presentation at the 26th American Society of Gene and Cell Therapy Annual Meeting Annual Meeting. May 17, 2023. Los Angeles, USA. Abstract 82; 3. De Waele L, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 225.

DELIVER

Acknowledgements

DELIVER participants and their families



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