Initial Data from the DELIVER Trial of DYNE-251 in Males with DMD Mutations Amenable to Exon 51 Skipping

Kevin Flanigan[1], Craig Campbell[2], Nicolas Deconinck[3], Liesbeth De Waele[4], Michelle Lorentzos[5], Han Phan[6], Perry Shieh[7], Chris Mix[8], Soma Ray[8], Dazhe Wang[8], Wildon Farwell[8], Ashish Dugar[8], Maria L. Naylor[8], Michela Guglieri[9], on behalf of the DELIVER study investigators

[1]Nationwide Children's Hospital, Columbus, OH, USA; [2]London Health Sciences Centre, London, Ontario, Canada; [3]Neuromuscular Reference Center UZ Gent, Gent, Belgium; [4]University Hospitals Leuven, Leuven, Belgium; [5]Children's Hospital at Westmead, Westmead, New South Wales, Australia; [6]Rare Disease Research, LLC, Atlanta, GA, USA; [7]University of California Los Angeles, Los Angeles, CA, USA; [8]Dyne Therapeutics, Inc., Waltham, MA, USA; [9]Royal Victoria Infirmary, Newcastle University, Newcastle-Upon-Tyne, UK

MDA Clinical and Scientific Conference, March 6, 2024

Disclosures

- Clinical trial support from Dyne, Avidity, Ultragenyx
- Advisor compensation from Apic Bio, Encoded, BioMarin, Locanabio, Sanofi
- Scientific advisory board for Armatus Bio

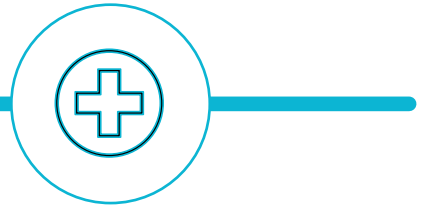
- DYNE-251 is an investigational medicine being evaluated in the ongoing DELIVER trial and has not received approval by FDA, EMA, or any other regulatory authorities.

DMD is a Devastating Disease with High Unmet Need Despite Approved Treatments

Presentation

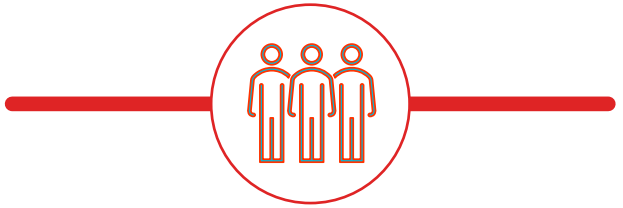
- Rare, X-linked, progressive disorder resulting from mutations in the *DMD* gene
- Affects 1 in 3,500 to 1 in 6,000 newborn boys
- Multisystem involvement with progressive muscle weakness and LoA
- Early death due to cardiorespiratory failure

Treatment



- Goal is to restore dystrophin expression to improve function
- Currently-approved therapies include PMOs (exons 51, 53, and 45) and gene therapy

Unmet Need



- Currently-approved exon 51-skipping therapy increases dystrophin production to <1%[1]
- Systemically-administered unconjugated PMOs can have limited delivery to muscle

Goal of Treatment: Increase Dystrophin Expression and Enable Effective Delivery to Muscle to Improve Function

DMD, Duchenne muscular dystrophy; LoA, loss of ambulation; PMO, phosphorodiamidate morpholino oligomer.

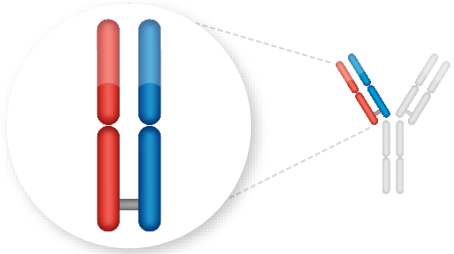
1. McDonald CM, et al. *J Neuromuscul Dis*. 2021;8:989-1001.

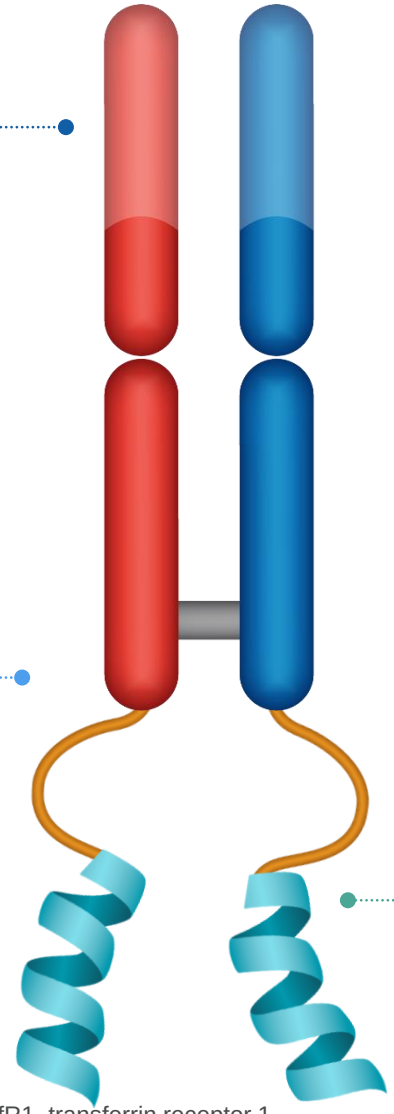
DELIVER

FORCE™ Platform-Based Oligonucleotide Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



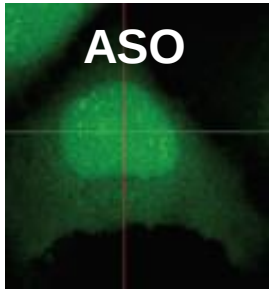


LINKER

Clinically validated, enables precise conjugation of multiple payloads to a single Fab

PAYLOAD

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



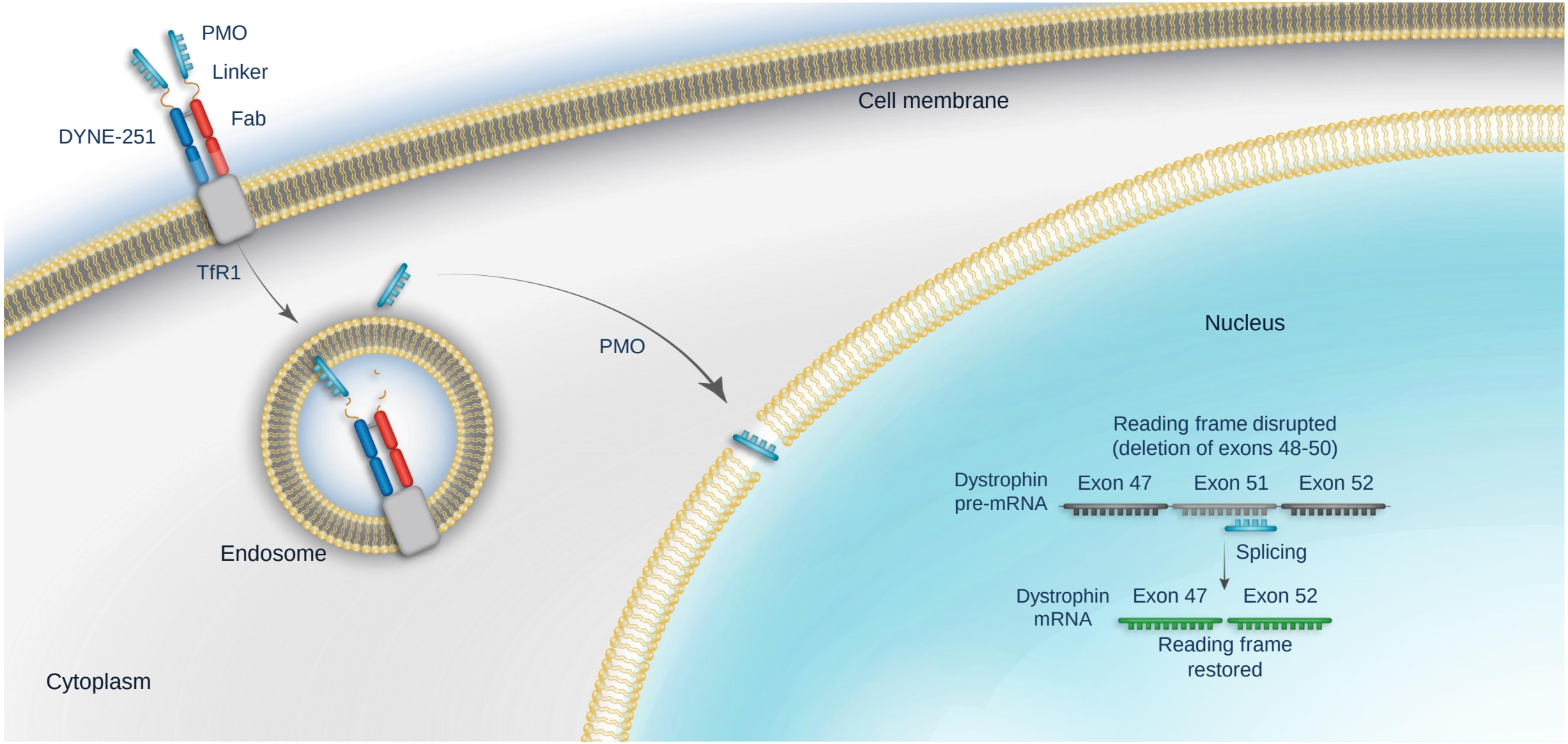
Nuclear localization

Cytoplasmic localization

ASO, antisense oligonucleotide; Fab, antigen-binding fragment; siRNA, small interfering RNA; TfR1, transferrin receptor 1.
Adapted from Ohrt T., et al. *Nucleic Acids Res* 2006;34:1369.

DELIVER

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



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

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

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

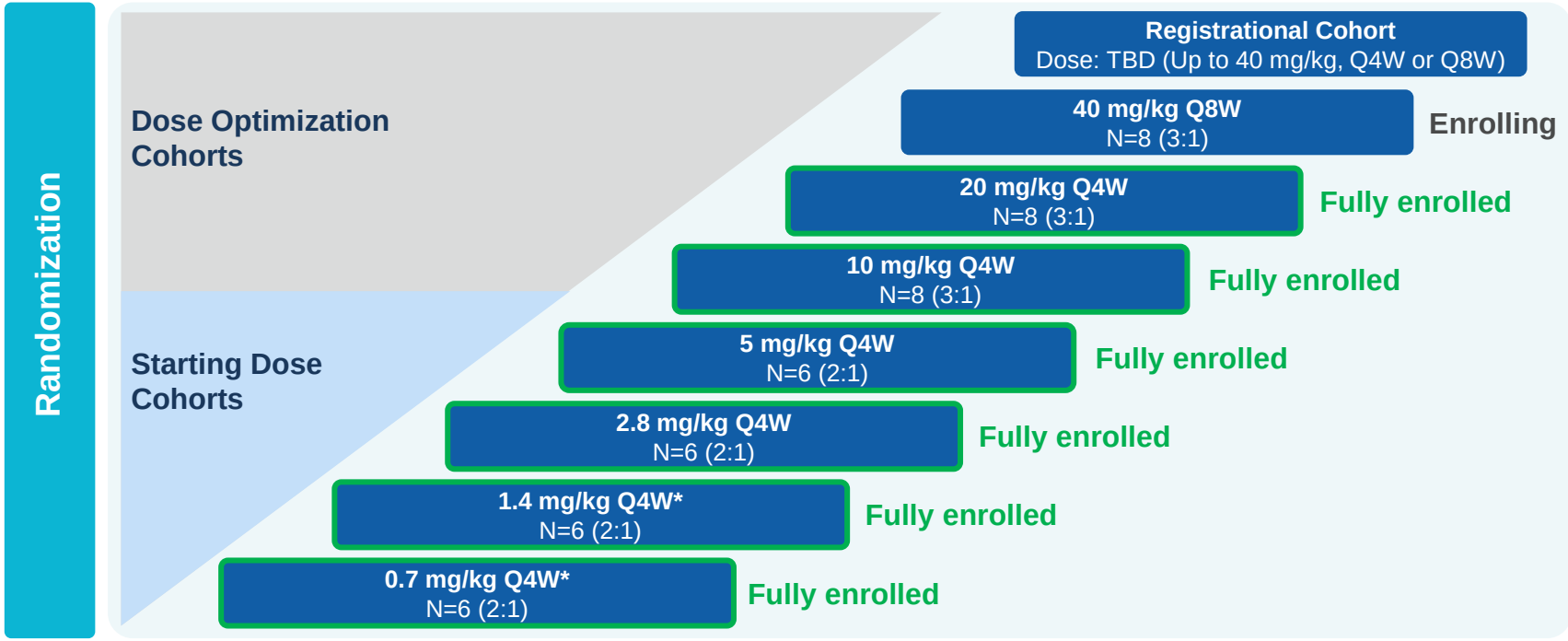
Stages of DELIVER

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

NSAA: North Star Ambulatory Assessment; PDPF: percent dystrophin-positive fibers.
For more information visit the DELIVER clinical trial posting on ClinicalTrials.gov ClinicalTrials.gov Identifier: NCT05524883 or clinicaltrialsregister.eu EudraCT Number: 2021-005478-24.

DELIVER Trial Design

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



MAD Study Details

- IV administration of DYNE-251 or placebo every 4 weeks or every 8 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

DMD, Duchenne muscular dystrophy; LTE, long-term extension; MAD, multiple ascending dose; OLE, open-label extension.
Doses provided refer to PMO component of DYNE-251. Cohorts randomized to active arm or placebo. Study protocol allows for dosing up to 40 mg/kg.
*Muscle biopsies taken at baseline and 24 weeks in 2.8 mg/kg Q4W cohort to 20 mg/kg Q4W cohort; muscle biopsies taken at baseline and 48 weeks in 40 mg/kg Q8W cohort; biopsies not taken in 0.7 mg/kg and 1.4 mg/kg cohorts.
For more information visit the DELIVER clinical trial posting on ClinicalTrials.gov ClinicalTrials.gov Identifier: NCT05524883 or clinicaltrialsregister.eu EudraCT Number: 2021-005478-24

DELIVER

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

BMI, body mass index; DMD, Duchenne muscular dystrophy; SD, standard deviation.
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

DYNE-251 Safety Profile 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	1.4mg/kg Q4W n=6	2.8mg/kg Q4W n=6	5mg/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

- 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

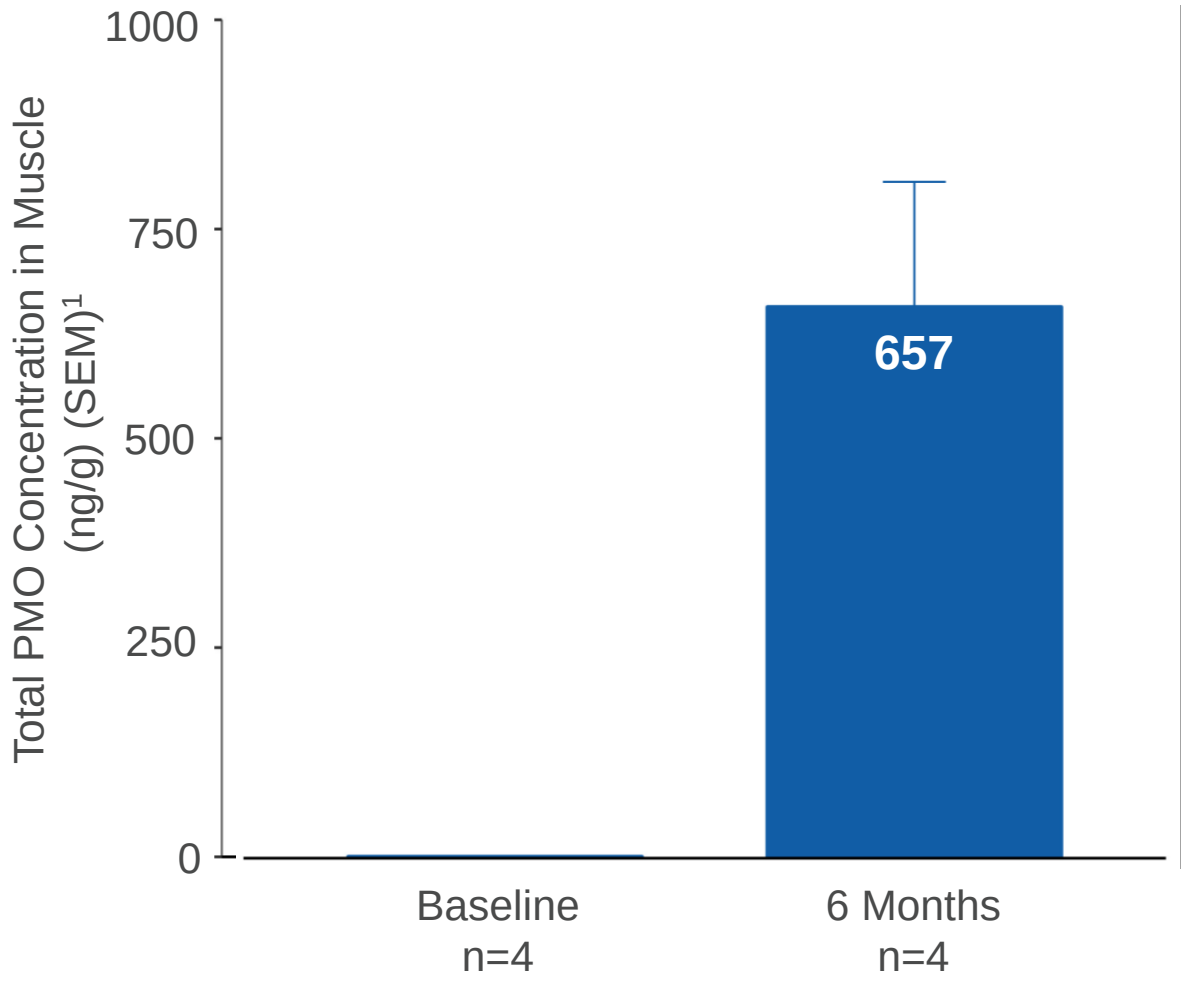
- No participants have demonstrated anemia or thrombocytopenia [2]
- No participants have demonstrated kidney injury[3]
- No participants have demonstrated clinically meaningful changes in electrolytes, including magnesium

AE, adverse event; Q4W, every 4 weeks dosing; Q8W, every 8 weeks dosing; TEAE, treatment-emergent adverse event.
* All cohorts combined. ** All infusion-related reactions have been mild or moderate in intensity; dosing has continued in all participants.
1. Data as of December 6, 2023; 2. Treatment emergent HGB or PLT persistently below LLN or reported AE. 3. Treatment emergent and persistently abnormal renal parameters or reported AE.
DYNE-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.

DELIVER

DYNE-251 Drove Robust Delivery of PMO to Muscle

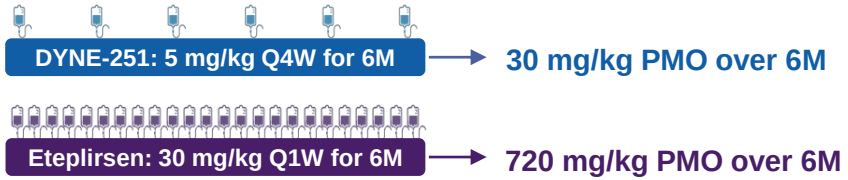
DYNE-251: 5 mg/kg Q4W for 6M

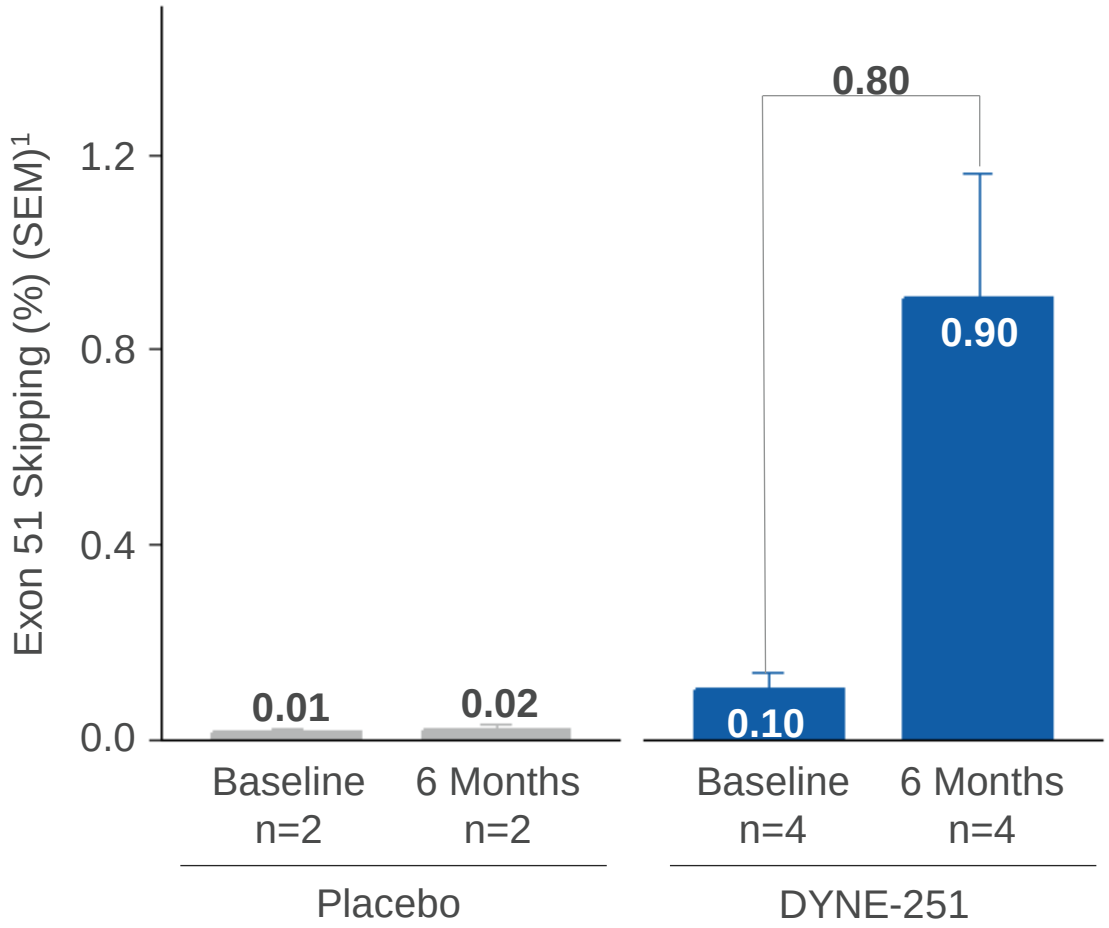


PMO, phosphorodiamidate morpholino oligomer.
1. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER.
DYNE-251 is an investigational medicine being evaluated in the ongoing DELIVER trial and has not received approval by FDA, EMA, or any other regulatory authorities.

DELIVER

DYNE-251, Dosed Monthly, Showed Increase in Percent Exon Skipping at 6 Months

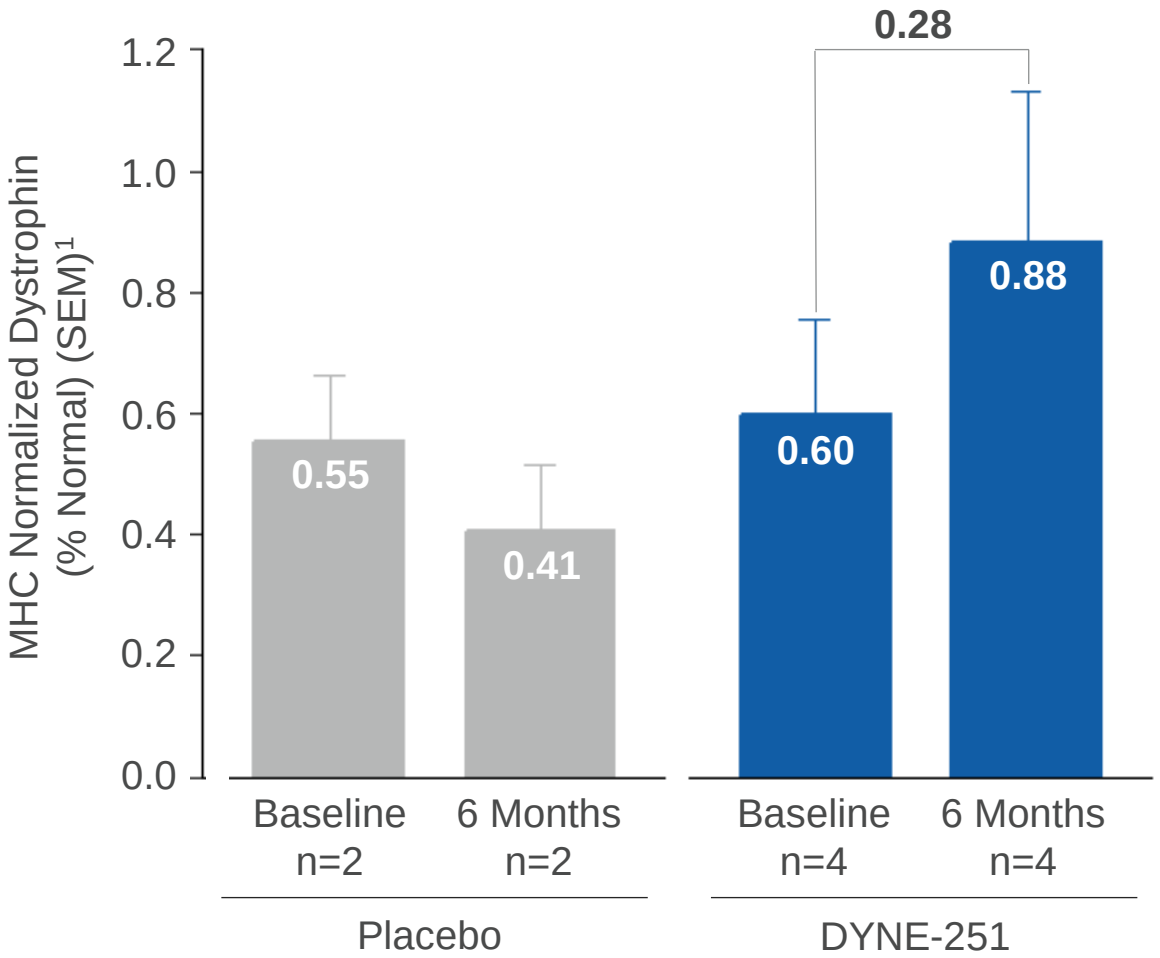




PMO, phosphorodiamidate morpholino oligomer; Q4W, every 4 weeks dosing; SEM, standard error of the mean.
1. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER and Week 24 for eteplirsen data; 2. No head-to-head trials have been conducted comparing DYNE-251 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 McDonald CM, et al. *J Neuromuscul Dis* 2021;8:989–1001.
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.

DELIVER

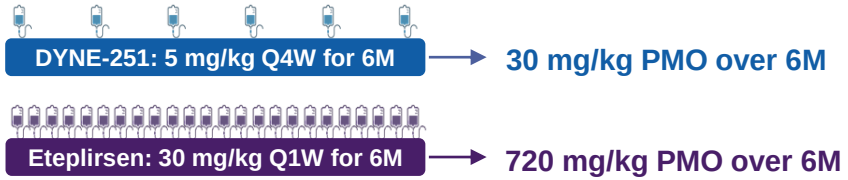
DYNE-251, Dosed Monthly, Showed Increase in Percent Dystrophin At 6 Months

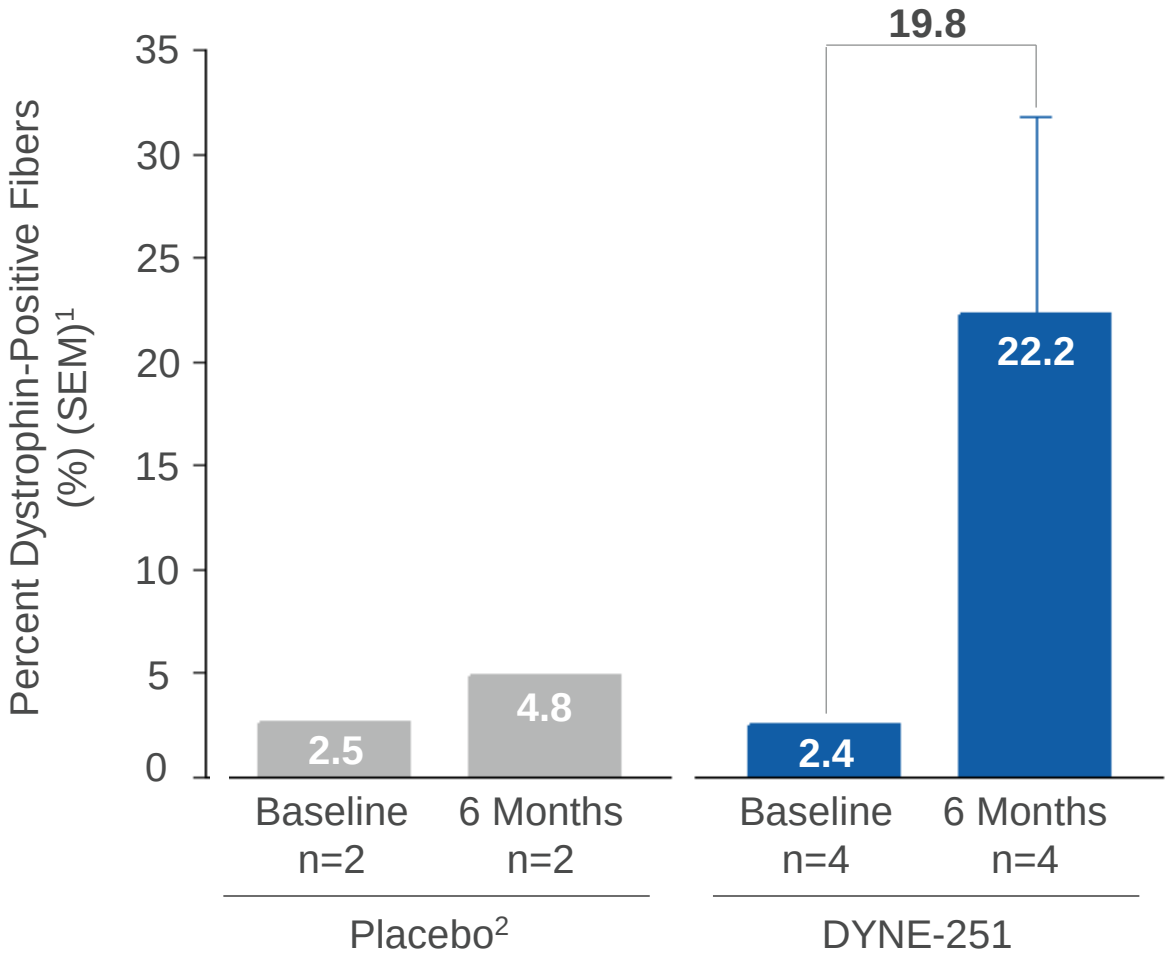


MHC, myosin heavy chain; PMO, phosphorodiamidate morpholino oligomer; Q4W, every 4 weeks dosing; SEM, standard error of the mean.
1. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER and Week 24 for eteplirsen data; 2. No head-to-head trials have been conducted 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 McDonald CM, et al. *J Neuromuscul Dis* 2021;8:989–1001.
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.

DELIVER

DYNE-251, Dosed Monthly, Showed Increase in Percent Dystrophin Positive Fibers (PDPF) At 6 Months





PDPF, percent dystrophin-positive fiber; PMO, phosphorodiamidate morpholino oligomer; Q4W, every 4 weeks dosing; SEM, standard error of the mean.

1. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER and Week 24 for eteplirsen data. 2. PDPF data not available for 1 patient from placebo group; 3. 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 McDonald CM, et al. *J Neuromuscul Dis* 2021;8:989–1001.

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.

DELIVER

Summary

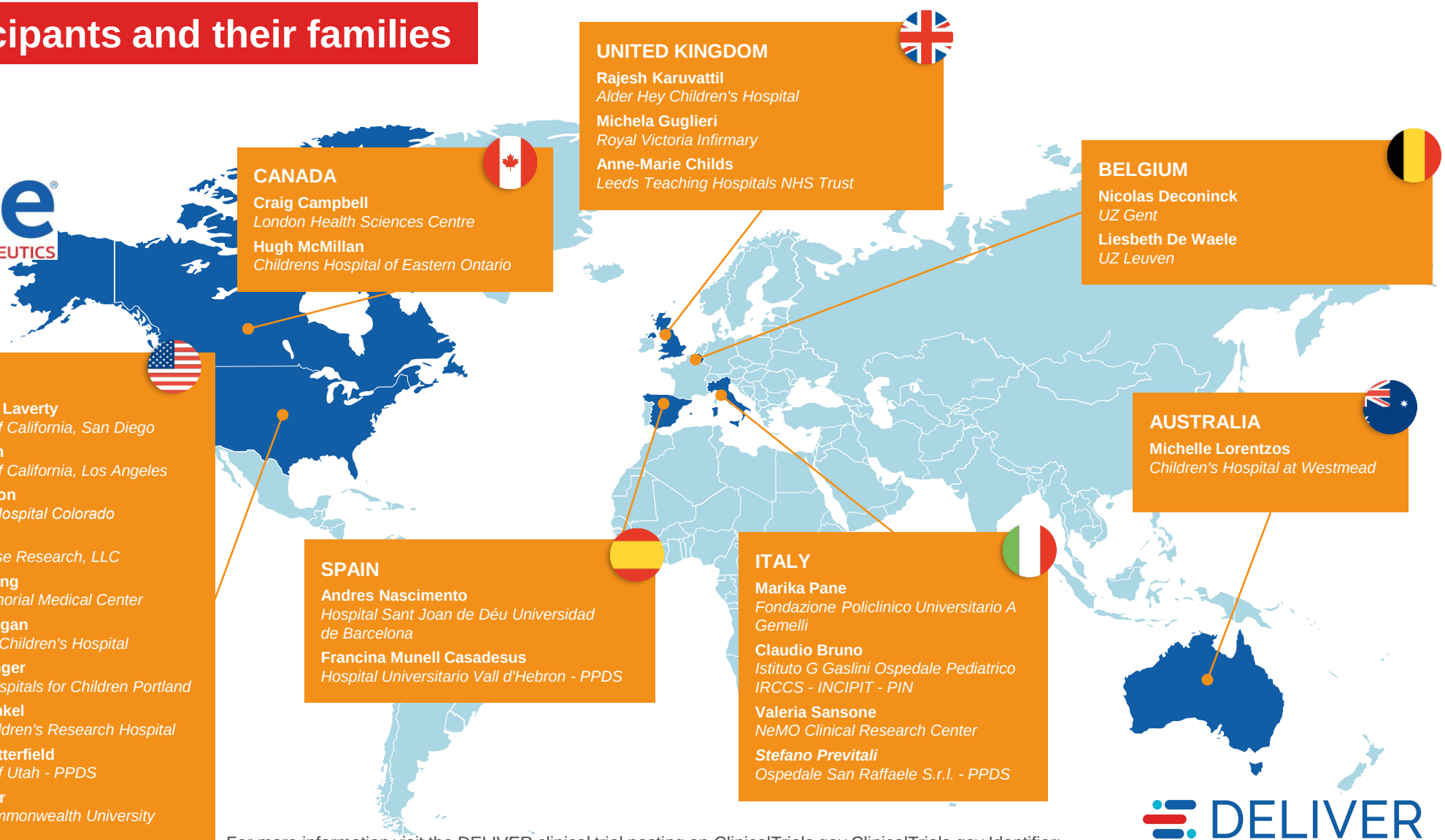
- DYNE-251 consists of an exon 51-skipping PMO conjugated to a TfR1-targeting Fab designed to deliver increased levels of PMO to muscles.
  - DYNE-251 leverages TfR1 biology to enable receptor-mediated muscle delivery.
- DELIVER is an ongoing, randomized, placebo-controlled global trial of DYNE-251 in ambulant and non-ambulant male DMD patients with mutations amenable to exon 51 skipping therapy.
- The safety profile of DYNE-251 is favorable to date[1], with the majority of TEAEs reported as mild or moderate.
  - The trial is fully enrolled through the 20 mg/kg cohort and favorable safety profile has supported dosing up to 40 mg/kg.
- In participants treated with 5 mg/kg (PMO equivalent) DYNE-251, initial data show levels of exon skipping, dystrophin, and PDPF increased at 6 months vs. baseline.
- These initial data support the continued clinical development of DYNE-251 for the treatment of DMD.

DMD, Duchenne muscular dystrophy; MAD, multiple ascending dose; PDPF, percent dystrophin-positive fiber; PMO, phosphorodiamidate morpholino oligomer; TfR1, transferrin receptor 1.
1. Data as of December 6, 2023.
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.

DELIVER

Acknowledgements

DELIVER participants and their families



USA
Chamindra Laverty
University of California, San Diego
Perry Shieh
University of California, Los Angeles
Susan Apkon
Children's Hospital Colorado
Han Phan
Rare Disease Research, LLC
Brenda Wong
UMass Memorial Medical Center
Kevin Flanigan
Nationwide Children's Hospital
Erika Finanger
Shriners Hospitals for Children Portland
Richard Finkel
St Jude Children's Research Hospital
Russell Butterfield
University of Utah - PPDS
Amy Harper
Virginia Commonwealth University

CANADA
Craig Campbell
London Health Sciences Centre
Hugh McMillan
Childrens Hospital of Eastern Ontario

UNITED KINGDOM
Rajesh Karuvattil
Alder Hey Children's Hospital
Michela Guglieri
Royal Victoria Infirmary
Anne-Marie Childs
Leeds Teaching Hospitals NHS Trust

BELGIUM
Nicolas Deconinck
UZ Gent
Liesbeth De Waele
UZ Leuven

AUSTRALIA
Michelle Lorentzos
Children's Hospital at Westmead

SPAIN
Andres Nascimento
Hospital Sant Joan de Déu Universidad de Barcelona
Francina Munell Casadesus
Hospital Universitario Vall d'Hebron - PPDS

ITALY
Marika Pane
Fondazione Policlinico Universitario A Gemelli
Claudio Bruno
Istituto G Gaslini Ospedale Pediatrico IRCCS - INCIPIT - PIN
Valeria Sansone
NeMO Clinical Research Center
Stefano Previtali
Ospedale San Raffaele S.r.l. - PPDS

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