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Initial Data From the DELIVER Trial of DYNE-251 in Males With *DMD* Mutations Amenable to Exon 51 Skipping

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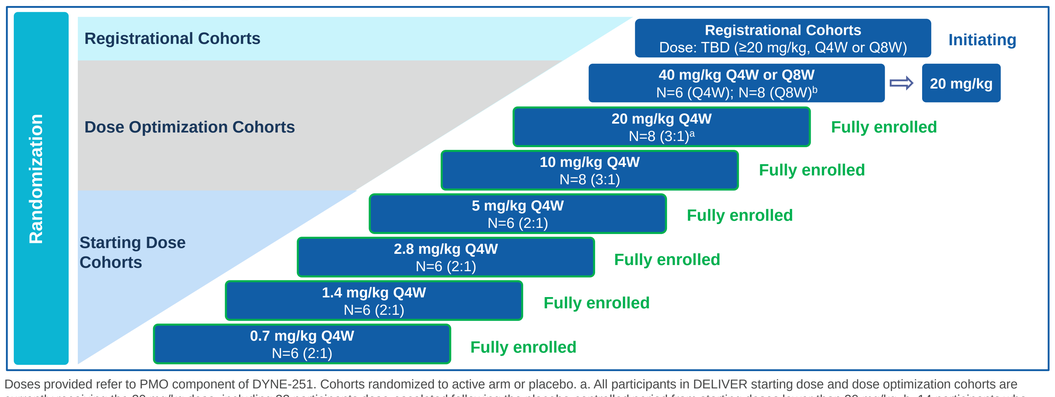
BACKGROUND

- Duchenne muscular dystrophy (DMD) is a rare, X-linked neuromuscular disorder caused by mutations in the *DMD* gene that result in the absence of functional dystrophin protein. DMD is characterized by progressive loss of muscle function leading to premature death.[1,2]
- The therapeutic potential of approved, unconjugated phosphorodiamidate morpholino oligomer (PMO) therapies for DMD is limited by poor delivery to muscle, especially cardiac muscle, modest production of dystrophin, and frequent dosing.[3]
- DYNE-251 is an investigational therapeutic that consists of an exon 51-skipping PMO conjugated to an antigen-binding fragment (Fab) targeting transferrin receptor 1 (TfR1), with the goal of restoring dystrophin expression in DMD muscle.[2,4]
- The safety and efficacy of DYNE-251 are being investigated in the Phase 1/2 DELIVER trial (NCT05524883; EudraCT number 2021-005478-24).[5]

METHODS

- DELIVER is a global, randomized, placebo-controlled study evaluating once monthly or less frequent intravenous administrations of DYNE-251 in ambulant and non-ambulant male patients with DMD (4–16 years old) with mutations amenable to exon 51 skipping therapy. It consists of a multiple ascending dose (MAD) period (24 weeks; **Figure 1**), an open-label extension period (24 weeks), and a long-term extension period (96 weeks).[5,6]
- All participants in DELIVER starting dose and dose optimization cohorts are currently receiving the 20 mg/kg dose, including 32 participants who dose-escalated following the placebo-controlled period from starting doses lower than 20 mg/kg, and 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.
  - Muscle biopsies were collected at baseline and 24 weeks in the 2.8 mg/kg every 4 weeks (Q4W) to 20 mg/kg Q4W cohorts.[6]
  - The primary endpoints are safety and tolerability, and change from baseline in dystrophin protein levels by Western blot.[5,6]
  - Additional endpoints include pharmacokinetics, change from baseline in exon 51 skipping levels and muscle tissue percent dystrophin-positive fibers, and multiple assessments of muscle function (including North Star Ambulatory Assessment [NSAA] score, stride velocity 95th centile [SV95C], and certain timed functional tests).[5,6] SV95C is a digital measure that has been validated as a primary endpoint for DMD trials in Europe.[7]

Figure 1. Design of the MAD Portion of the DELIVER Trial



Doses provided refer to PMO component of DYNE-251. Cohorts randomized to active arm or placebo. a. All participants in DELIVER starting dose and dose optimization cohorts are currently receiving the 20 mg/kg dose, including 32 participants dose-escalated following the placebo-controlled period from starting doses lower than 20 mg/kg. b. 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. 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.
MAD, multiple ascending dose; PMO, phosphorodiamidate morpholino oligomer; Q4W, every 4 weeks; Q8W, every 8 weeks; TBD, to be determined.

- Here we present exon skipping and dystrophin data from the 5, 10, and 20 mg/kg cohorts and functional data from the 10 and 20 mg/kg cohorts.
- Safety data are as of August 21, 2024, and include all 54 participants dosed in DELIVER.

RESULTS

Table 1. Baseline Characteristics

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 at 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)
CS dosing regimen[a] Daily Other	 4 (66.7%) 2 (33.3%)	 4 (66.7%) 3 (50.0%)	 5 (83.3%) 2 (33.3%)	 6 (100%) 0	 8 (100%) 0	 8 (100%) 2 (25.0%)
Prior DMD therapy Eteplirsen Other	 4 (66.7%) 2 (33.3%)	 2 (33.3%) 1 (16.7%)	 5 (83.3%) 0	 1 (16.7%) 0	 1 (12.5%) 1 (12.5%)	 0 2 (25.0%)
NSAA total Score[b]	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)[b]	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)[b]	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)[b]	N/A	N/A	N/A	N/A	1.9 (0.5)	1.4 (0.5)

Q4W and placebo arms are reported together for baseline characteristics. N/A: not applicable as data not collected. a. Historical corticosteroid regimen based on medical history; a participant can be counted in multiple categories. b. Data exclude patients who were not able to complete the assessment. BMI, body mass index; CS, corticosteroid; DMD, Duchenne muscular dystrophy; NSAA, North Star Ambulatory Assessment; Q4W, every 4 weeks; sec, seconds; SD, standard deviation; SV95C, stride velocity 95th centile.

Table 2. DYNE-251 Safety Profile Is Favorable to Date[a] (Summary of TEAEs)

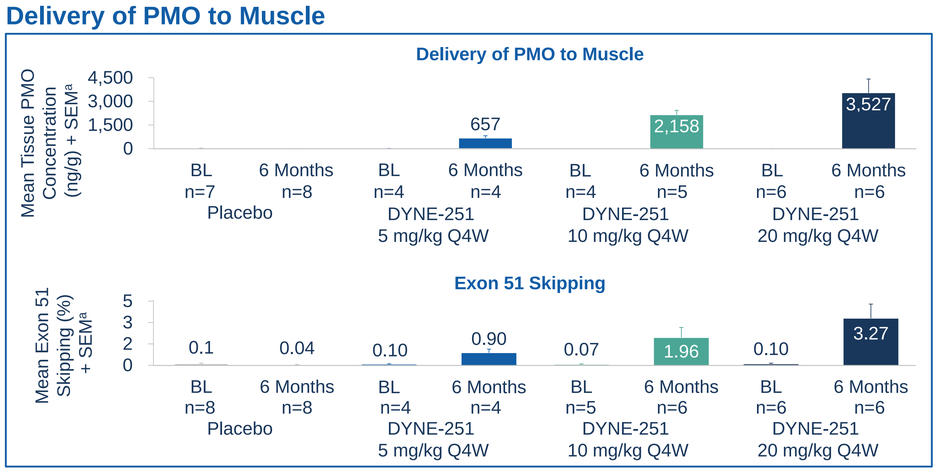
TEAE Category	Participants With ≥1 TEAE – n (%)								
	0.7 mg/kg Q4W N=6	1.4 mg/kg Q4W N=6	2.8 mg/kg Q4W N=6	5 mg/kg Q4W N=6	10 mg/kg Q4W N=8	20 mg/kg Q4W N=8	40 mg/kg Q8W[b] N=8	40 mg/kg Q4W[b] N=6	Overall N=54
Any TEAE	6 (100%)	6 (100%)	4 (67%)	6 (100%)	7 (88%)	8 (100%)	6 (75%)	4 (67%)	47 (87%)
Any 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

a. Data as of August 21, 2024.
b. 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.
Q4W, every 4 weeks; Q8W, every 8 weeks; TEAE, treatment-emergent adverse events.

- 3 serious treatment-emergent adverse events (TEAEs) potentially related to study drug in 2 participants
  - Acute kidney injury (1); thrombocytopenia (1)[a]
  - Pancytopenia (1)[b]
  - 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)[c]
  - Tibia fracture (1)
  - Febrile convulsion (1); pyrexia (1)[c]
- Most common TEAEs (>20% participant incidence)[d]
  - Pyrexia (32%)
  - Nasopharyngitis, headache, vomiting (each 26%)
  - Fall (26%)
  - Infusion-related reaction (20%)
- No participants have demonstrated clinically meaningful changes in electrolytes, including magnesium

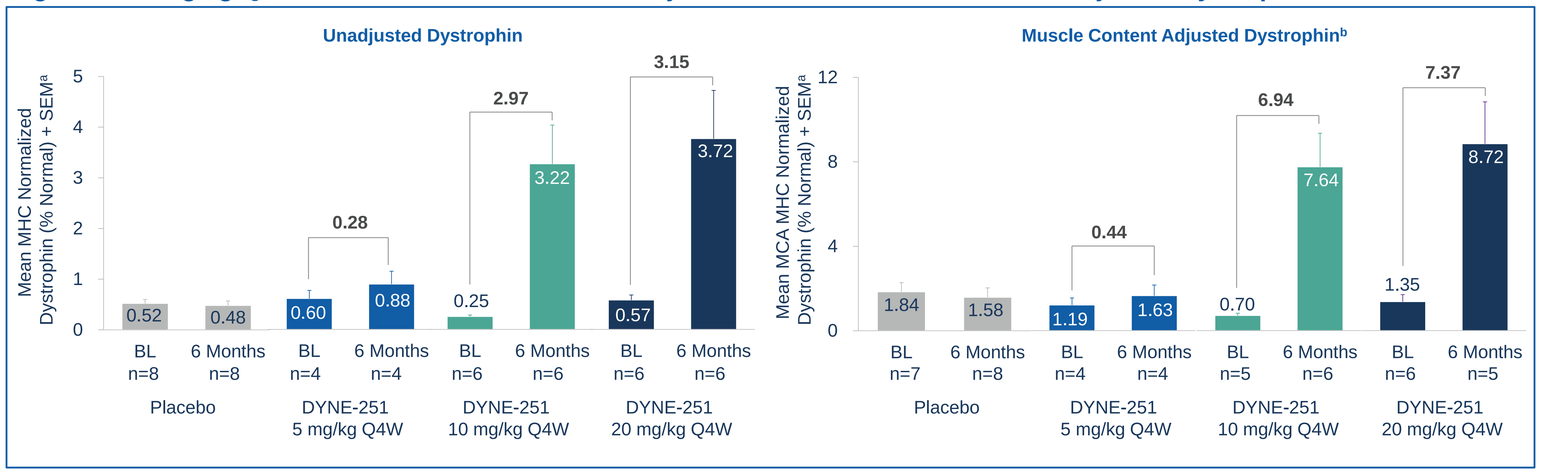
a. Events have same day of onset in a single participant in the context of fever, hemolysis, diarrhea, and positive blood in stool; together, these events are potentially consistent with hemolytic uremic syndrome with a potential infectious etiology. b. Participant had a history of hemolytic anemia of unidentified etiology prior to enrolling in DELIVER. Presented with fever and tonsilitis; all symptoms resolved without therapeutic intervention. c. Events occurred in same participant at different times. d. All cohorts combined; preferred terms are reported.

Figure 2. DYNE-251 Demonstrated Dose-Dependent Exon Skipping and Delivery of PMO to Muscle



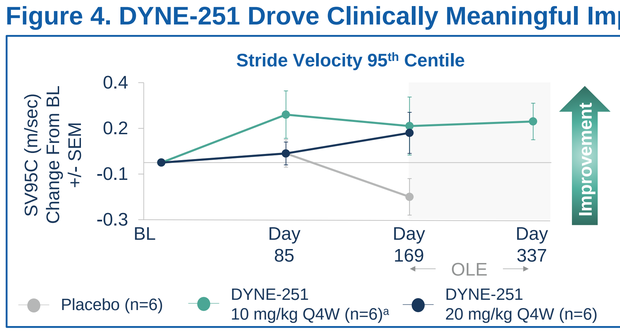
a. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER.
BL, baseline; Q4W, every 4 weeks; PMO, phosphorodiamidate morpholino oligomer; SEM, standard error of mean.

Figure 3. 20 mg/kg Q4W DYNE-251 Showed 3.7% Unadjusted and 8.7% Muscle Content Adjusted Dystrophin at 6 Months



a. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER. b. MCA dystrophin = dystrophin (MHC normalized) / % muscle content.
BL, baseline; MCA, muscle content adjusted; MHC, major histocompatibility complex; Q4W, every 4 weeks; SEM, standard error of mean.

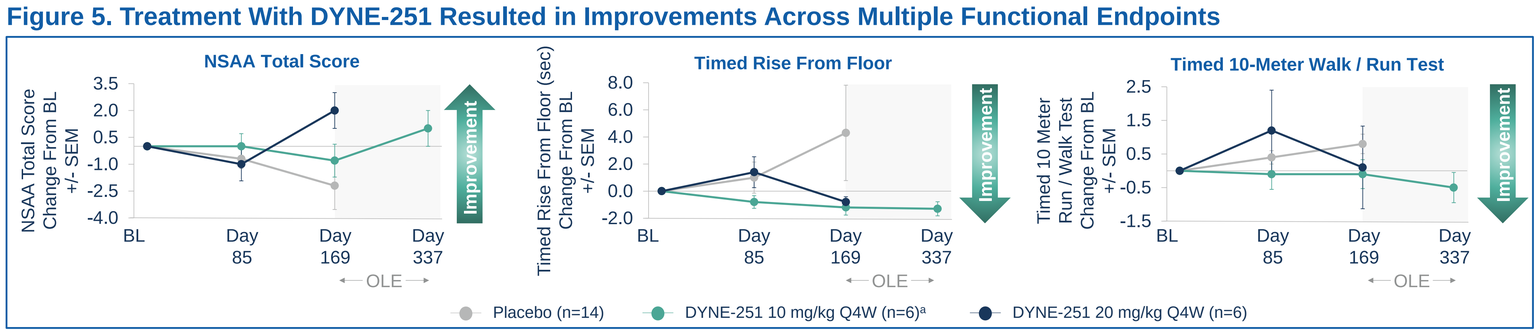
Figure 4. DYNE-251 Drove Clinically Meaningful Improvements in SV95C



- SV95C is a digital objective endpoint of ambulatory performance in patients' normal daily environment[7]
- Patients in DELIVER wore the device on each ankle for 4 weeks prior to the clinic visits
- The change from baseline met the published MCID by the EMA[8]

a. During the OLE, all participants in the 10 mg/kg cohort were dose escalated to the 20 mg/kg Q4W regimen. BL, baseline; EMA, European Medicines Agency; OLE, open-label extension; MCID, minimal clinically important difference; Q4W, every 4 weeks; sec, seconds; SEM, standard error of mean; SV95C, stride velocity 95th centile.

Figure 5. Treatment With DYNE-251 Resulted in Improvements Across Multiple Functional Endpoints



a. During the OLE, all participants in the 10 mg/kg cohort were dose escalated to the 20 mg/kg Q4W regimen.
BL, baseline; NSAA, North Star Ambulatory Assessment; OLE, open-label extension; Q4W, every 4 weeks; sec, seconds; SEM, standard error of mean.

CONCLUSIONS

- DYNE-251 has demonstrated a favorable safety profile to date.[a]
- DYNE-251 drove dose-dependent PMO delivery and exon skipping in muscle, resulting in robust dystrophin expression at 6 months.
- Broad distribution of DYNE-251 led to improvements in multiple functional endpoints, including SV95C, a real-world outcome measure.
- The data support the continued development of DYNE-251 for the treatment of DMD.

a. Data as of August 21, 2024.

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DISCLOSURE INFORMATION

Chris Mix, Soma Ray, Dazhe Wang, Wildon Farwell, Ashish Dugar, and Maria L. Naylor are employees of Dyne Therapeutics and may hold stock in the company; Liesbeth De Waele is PI on studies sponsored by Sarepta Therapeutics, Italfarmaco, Pfizer and Dyne Therapeutics and has participated in ad hoc advisory board activities for Santhera, Pfizer and Italfarmaco; Craig Campbell is Site Investigator for AMO, Biogen, Dyne Therapeutics, Italfarmaco, Pfizer, Roche, PTC, Sarepta Therapeutics and Wave Pharma and is DSMB member for PepGen, Edgewise and Solid Biosciences; Nicolas Deconinck is PI on studies sponsored by Sarepta Therapeutics, Dyne Therapeutics, Roche, Novartis, Scholar Rock and Santhera and a member of advisory boards for Roche and Novartis; Kevin Flanigan has received clinical trial support from Dyne Therapeutics, Avidity and Ultragenyx and has received advisor compensation from Apic Bio, Encoded, BioMarin, LocanaBio and Sanofi, and has served on a scientific advisory board for Armatus Bio; Michelle Lorentzos is PI on studies sponsored by Dyne Therapeutics, Pfizer, Sarepta Therapeutics, Antisense Therapeutics, PTC and NS Pharma; Han Phan is PI on studies sponsored by Sarepta Therapeutics, Avidity, Edgewise, NS Pharma, Harmony, Capricor, Dyne Therapeutics and Stealth; Perry Shieh is a consultant for Sarepta Therapeutics, Dyne Therapeutics, Biogen, Genentech, Novartis, Astellas, Solid, Sanofi, Alexion, Argenx, CSL Behring, Grifols and UCB and has received research grants from Sarepta Therapeutics, Solid Biosciences, PTC, Dyne Therapeutics, Biogen, Genentech, Novartis, Astellas, Avidity, AMO Pharma, Abcuro and Sanofi; Michela Guglieri chaired a study sponsored by ReveraGen (no financial benefits) and had research collaborations with ReveraGen and Sarepta Therapeutics. She acted as CI/PI for clinical trials sponsored by Dyne Therapeutics, Pfizer, Italfarmaco, Edgewise, Roche, Santhera, ReveraGen and Dynacure, and participated in advisory boards for Pfizer, NS Pharma, Dyne Therapeutics (consultancies through Newcastle University). She has received speaker honoraria from Sarepta Therapeutics, Italfarmaco and Novartis.