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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BACKGROUND

- Duchenne muscular dystrophy (DMD) is a rare, X-linked neuromuscular disorder caused by mutations in the *DMD* gene resulting 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, modest production of dystrophin, and frequent dosing.[3]
- Adeno-associated virus (AAV)-mediated micro-dystrophin-producing gene therapies can result in a substantial amount of micro-dystrophin; however, these constructs are ~one-third the size of full-length dystrophin and exclude key domains that support overall muscle health.[3,4] Micro-dystrophin-producing gene therapies lack long-term durability data and are currently limited by the inability for redosing in the event of waning efficacy.[3,5] Additionally, cases of serious immune-mediated complications and death have been reported in clinical trials of AAV-mediated micro-dystrophin-producing DMD gene therapies.[5,6]
- 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 in affected tissues and enabling functional improvement.[2,7]
- The safety and efficacy of DYNE-251 are being investigated in the Phase 1/2 DELIVER trial (NCT05524883; EudraCT number 2021-005478-24).[8]

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 participants 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), an open-label extension (OLE) period (24 weeks), and a long-term extension (LTE) period (96 weeks).[9]
  - 54 participants have received DYNE-251 or placebo in 7 different dose/dose regimen cohorts (Table 2) in the placebo-controlled MAD portion.[9] Participants were transitioned to DYNE-251 20 mg/kg every 4 weeks (Q4W) in the OLE/LTE at non-uniform times; transition to 20 mg/kg started either in the placebo-controlled period or the OLE for participants initiated at the 40 mg/kg dose.
  - In the MAD portion of the study, muscle biopsies were collected at baseline and 24 weeks (except for cohorts 0.7 mg/kg and 1.4 mg/kg).[9]
  - The primary endpoints are safety and tolerability and change from baseline in dystrophin protein levels by western blot.[9]
  - Select additional endpoints include pharmacokinetics, change from baseline in exon 51-skipping levels, as well as multiple assessments of muscle function (including North Star Ambulatory Assessment [NSAA] score, stride velocity 95th centile [SV95C], and certain timed functional tests).[9] SV95C is a digital objective endpoint of continuous ambulatory performance in participants' normal daily environments that has been validated by the European Medicines Agency as a primary endpoint in studies in boys with DMD ≥ 4 years old.[10–12] Participants in DELIVER wore the device on each ankle for 3 weeks before the clinical visit.
  - 20 mg/kg Q4W has been selected as the dose/dose regimen for the DELIVER registrational expansion cohort, which is fully enrolled (N=32, 3:1 randomization for DYNE-251 vs placebo).
  - Here, we present long-term motor function assessments data (up to 18 months of follow-up) for participants initiated at 10 mg/kg Q4W and escalated to the 20 mg/kg Q4W dose in the OLE/LTE, as well as for participants initiated at 20 mg/kg Q4W in the placebo-controlled period who remained on the 20 mg/kg Q4W dose in the OLE/LTE. Safety data are as of February 7, 2025 and include all 54 participants enrolled in DELIVER.

RESULTS

Table 1. Baseline characteristics

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, %)[a]		
Daily	8 (100)	8 (100)
Other	0 (0.0)	0 (0.0)
Duration of corticosteroid treatment (years)[b]	1.6 (1.8)	2.0 (2.1)
Prior DMD therapy		
Eteplirsen	1 (12.5)	0 (0.0)
Other	1 (12.5)	2 (25.0)
NSAA total score[c]	25.3 (6.40)	15.6 (5.09)
Time to rise from floor (sec)[c]	6.3 (5.60)	5.1 (2.28)
Timed 10-meter walk/run (sec)[c]	4.6 (1.86)	7.7 (3.84)
SV95C (m/sec)[c]	1.9 (0.45)	1.4 (0.47)

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

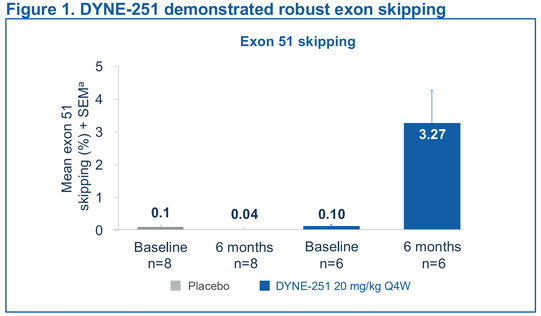
Table 2. DYNE-251 safety profile is favorable to date (summary of TEAEs)[a]

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	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 (100.0)	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.[b]
  - Pancytopenia.[c]
- **Most frequent TEAEs.**[d]
  - Pyrexia (48%).
  - Headache and vomiting (each 37%).
  - Fall (35%).
  - Nasopharyngitis (33%).
  - Cough (26%).
  - Infusion-related reaction (24%).[e]
- **Additional safety data.**
  - Except 2 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[a], with 546 doses of study drug at 20 mg/kg dose level administered to date.[f]

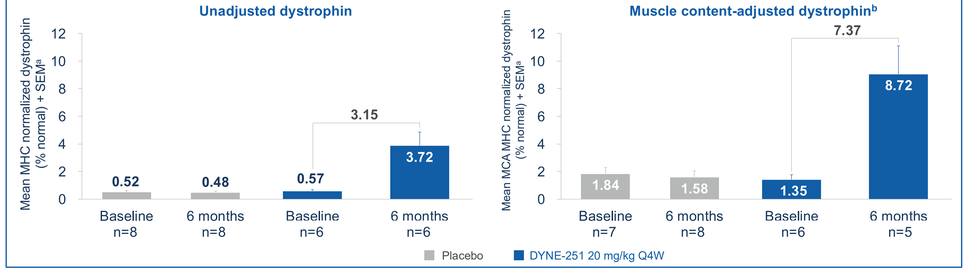
a. Data as of February 7, 2025, all participants, placebo-controlled period, open-label period, long-term extension period; b. Events have same day of onset in a single participant with a non-serious related TEAE of anemia in the context of fever, hemolysis, diarrhea and positive blood in stool; together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

Figure 1. DYNE-251 demonstrated robust exon skipping



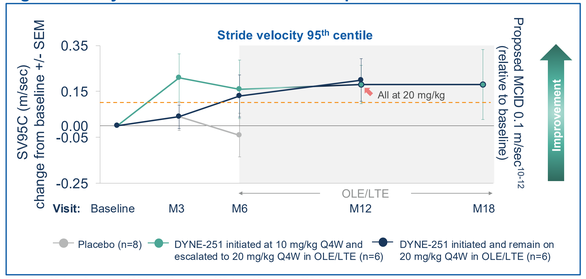
a. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER. PMO, phosphorodiamidate morpholino oligomer; Q4W, every 4 weeks; SEM, standard error of mean.

Figure 2. DYNE-251 achieved robust dystrophin expression at 6 months



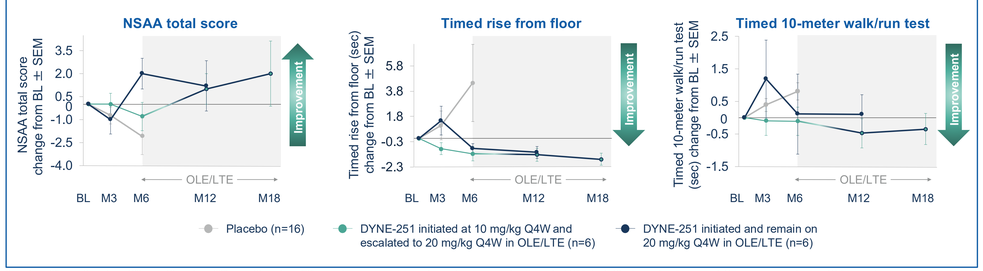
a. DELIVER biopsy taken approximately 28 days after most recent dose; 6 months = Week 25 for DELIVER; b. MCA dystrophin = dystrophin (MHC normalized) / % muscle content.
MCA, muscle content adjusted; MHC, major histocompatibility complex; Q4W, every 4 weeks; SEM, standard error of mean.

Figure 3. Early and sustained functional improvement in SV95C



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.

Figure 4. Long-term functional improvement versus baseline observed across multiple endpoints through 18 months



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.

CONCLUSIONS

- The safety profile of DYNE-251 is favorable to date, with some participants on therapy for ~2.5 years.[a]
- 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, through18 months.
  - Functional improvement versus baseline in SV95C, a reliable measure of continuous real-world function, demonstrated at the registrational dose level of 20 mg/kg Q4W.
  - Proposed minimal clinically important difference 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.[13]

a. Data as of February 7, 2025.

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DISCLOSURE INFORMATION

Chris Mix, Soma Ray, Dazhe Wang, Ashish Dugar, Douglas Kerr, and Maria L. Naylor are (or were) 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.

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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.

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