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

#4

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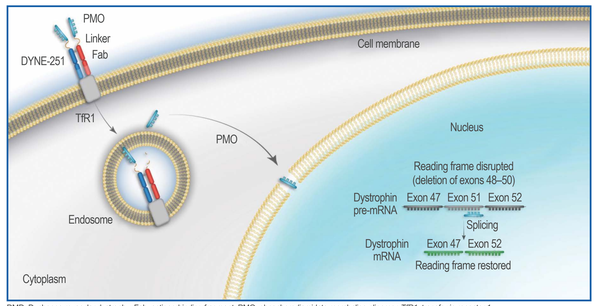
DELIVER

BACKGROUND

- Duchenne muscular dystrophy (DMD) is a rare, X-linked, progressive neuromuscular disorder caused by mutations in the *DMD* gene that lead to an absence of functional dystrophin protein[1–6]
- DMD affects 1 in 3,500 to 6,000 newborn boys worldwide[2,7,8]
- DMD presents with multisystem involvement and progressive muscle weakness, which leads to loss of ambulation and early death due to cardiorespiratory failure[4,9–11]
- Approved phosphorodiamidate morpholino oligomer (PMO) therapies induce exon skipping to restore the *DMD* mRNA reading frame, which leads to the production of truncated, functional dystrophin, but their potential is limited by poor delivery to muscle[12–16]
  - Weekly dosing with eteplirsen, the standard of care for the population amenable to exon 51 skipping, results in 0.3% dystrophin in muscle at 6 months[12,a]
- DYNE-251 is an investigational therapeutic for DMD. It consists of an exon 51 skipping PMO conjugated to a transferrin receptor 1 (TfR1)-targeting antibody fragment (Fab) to deliver increased levels of PMO to muscles (**Figure 1**)
- The objective of the Phase 1/2 DELIVER trial (NCT05524883) is to determine the safety, tolerability, and efficacy of DYNE-251 in ambulant and non-ambulant males aged 4 to 16 years with *DMD* mutations amenable to exon 51 skipping

[a]No head-to-head trials have been conducted comparing DYNE-251 with eteplirsen. Eteplirsen data may not be directly comparable due to differences in trial protocols, dosing regimens, and patient populations. Accordingly, cross-trial comparisons may not be reliable.

Figure 1. DYNE-251 leverages TfR1 to deliver an exon 51 skipping PMO to affected muscle in DMD

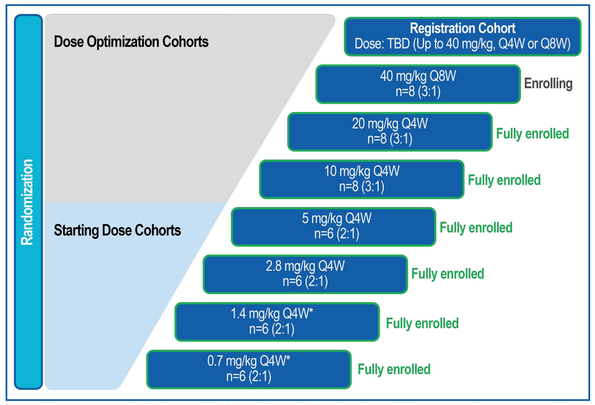


DMD, Duchenne muscular dystrophy; Fab, antigen-binding fragment; PMO, phosphorodiamidate morpholino oligomer; TfR1, transferrin receptor 1.
Note: This figure shows the intended mechanism of action of DYNE-251.

METHODS

- The DELIVER trial is a Phase 1/2, global, randomized, placebo-controlled study of DYNE-251
- The trial includes three stages, multiple ascending dose (MAD, 24 weeks), open-label extension (OLE, 24 weeks), and long-term extension (LTE, 96 weeks)
  - In the MAD portion of DELIVER, patients are randomized to receive intravenous administrations of DYNE-251 or placebo once every 4 weeks (Q4W) or once every 8 weeks (Q8W) for 6 months across seven PMO dose levels up to 40 mg/kg
  - Muscle biopsies are conducted at baseline and 6 months in the 2.8- to 20-mg/kg cohorts. In the 40-mg/kg cohort, muscle biopsies are conducted at baseline and 12 months
  - Patients in MAD escalate to highest tolerable dose in the OLE and LTE portions of the study
  - The primary endpoints are the change from baseline in dystrophin protein levels by Western Blot at 6 months and the number of patients reporting treatment-emergent adverse events (TEAEs) through study completion
  - Key secondary endpoints include the pharmacokinetics of DYNE-251 and changes from baseline in exon 51 skipping levels, muscle tissue percent dystrophin-positive fibers (PDPF), and muscle function assessments including North Star Ambulatory Assessment (NSAA) score and timed functional tests
- Presented here are analyses of exon skipping and dystrophin data from the 5-mg/kg cohort, in which four patients received DYNE-251 and two received placebo
  - Safety and tolerability were based on 37 patients enrolled through the 20-mg/kg cohort as of the December 6, 2023, data cutoff date

Figure 2. Design of the MAD portion of the DELIVER trial



*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.
Q4W, once every 4 weeks; Q8W, once every 8 weeks.

RESULTS

Table 1. Baseline characteristics

	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 (%)*				
Daily	4 (66.7)	4 (66.7)	5 (83.3)	6 (100.0)
Other	2 (33.3)	3 (50.0)	1 (16.7)	0
Prior DMD therapy, n (%)				
Eteplirsen	4 (66.7)	2 (33.3)	5 (83.3)	1 (16.7)
Other	2 (33.3)	1 (16.7)	0	0

*Historical corticosteroid regimen based on medical history; a patient can be counted in multiple categories.
BMI, body mass index; DMD, Duchenne muscular dystrophy; SD, standard deviation.

Table 2. Summary of TEAEs during the placebo-controlled period of DELIVER

	Patients with ≥1 TEAE, n (%)						
TEAE Category	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=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 of study drug	0	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0	0

*All cohorts combined.
Note: Data as of December 6, 2023.
Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event.

ACKNOWLEDGEMENTS

This study was funded by Dyne Therapeutics.

Medical writing and editorial support was provided by Jennifer Gibson, PharmD, of Kay Square Scientific, Newtown Square, PA. This support was funded by Dyne Therapeutics.

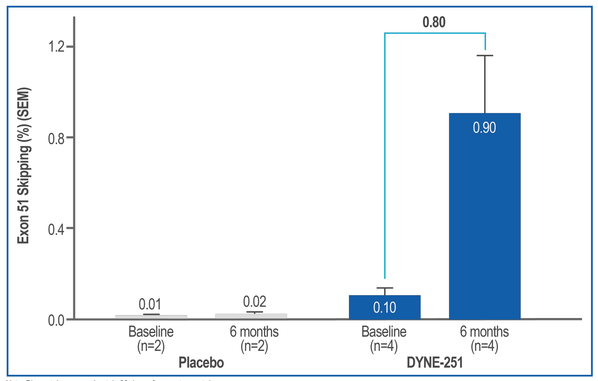
The authors wish to thank the clinical trial investigators and site coordinators and, most importantly, all the patients, families, and caregivers for their willingness to participate in this clinical trial, which was sponsored by Dyne Therapeutics.

The safety profile of DYNE-251 is favorable to date,[a] with the majority of TEAEs reported as mild or moderate.

- The most common TEAEs (≥10% patient incidence)[b] were headache and nasopharyngitis (16% each), vomiting (14%), and infusion-related reaction,[c] fall, and cough (11% each)
- There was one serious TEAE unrelated to the study drug (dehydration due to gastroenteritis)
- No patients have demonstrated anemia or thrombocytopenia[d]
- No patients have demonstrated kidney injury[e]
- No patients have demonstrated clinically meaningful changes in electrolytes, including magnesium

[a]Data as of December 6, 2023.
[b]All cohorts combined.
[c]All infusion-related reactions have been mild or moderate in intensity; dosing has continued in all patients.
[d]Treatment-emergent hemoglobin or platelet count persistently below lower limit of normal or reported adverse event.
[e]Treatment-emergent and persistently abnormal renal parameters or reported adverse event.

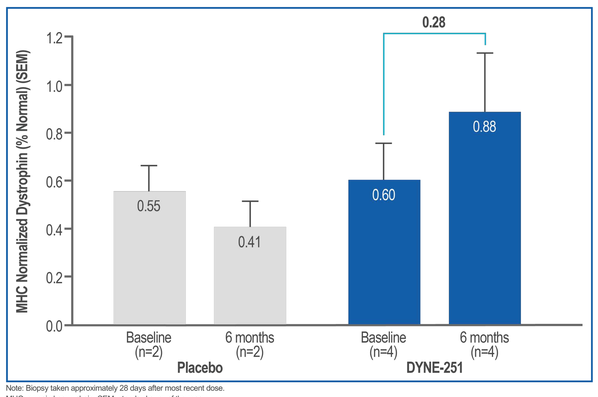
Figure 3. DYNE-251 administered monthly showed an increase in percent exon skipping at 6 months



Note: Biopsy taken approximately 28 days after most recent dose.
SEM, standard error of the mean.

- At 6 months, 5 mg/kg DYNE-251 showed a mean PMO concentration of 657 ng/g in muscle and a mean absolute exon skipping level of 0.90% (0.80% difference from baseline) (**Figure 3**)

Figure 4. DYNE-251 administered monthly showed an increase in percent dystrophin at 6 months



Note: Biopsy taken approximately 28 days after most recent dose.
MHC, myosin heavy chain; SEM, standard error of the mean.

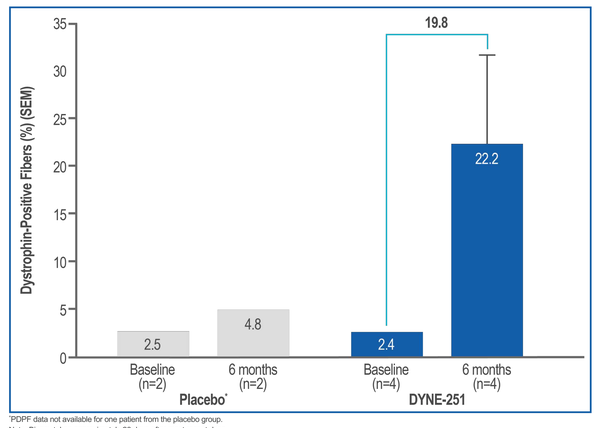
- Mean absolute dystrophin level, measured by Western blot, increased from 0.60% at baseline to 0.88% of normal at 6 months (**Figure 4**), and the mean level of PDPF increased from 2.4% at baseline to 22.2% at 6 months (**Figures 5**, **6**)

DISCLOSURE INFORMATION

DYNE-251 is an investigational medicine being evaluated in the ongoing DELIVER trial and has not received approval by the United States Food and Drug Administration, the European Medicines Agency, or any other regulatory authorities.

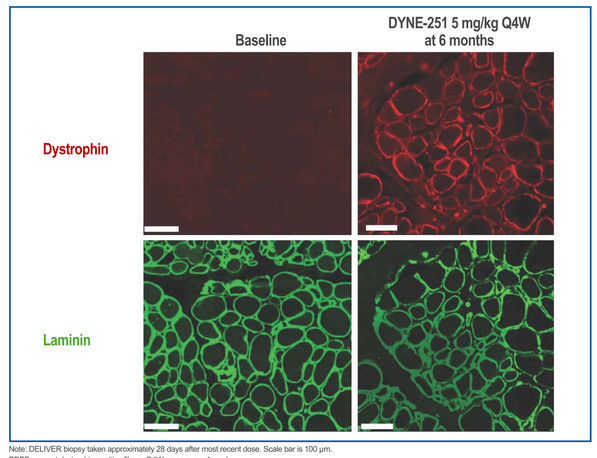
PS has received personal compensation for serving as a consultant for Sarepta, Genentech, Biogen, Alexion, argenx, UCB, CSL Behring, Grifols, Solid, Dyne, Novartis, Astellas, and Sanofi; and received research grants from Sarepta, Solid, PTC, Dyne, Biogen, Genentech, Novartis, Astellas, Avidity, AMO Pharma, Abcuro, and Sanofi. **CC** is a site investigator for AMO, Biogen, Dyne, Italfarmaco, Pfizer, Roche, PTC, Sarepta, and Wave, and a member of the DSMB for PepGen, Edgewise, and Solid. **ND** has served as a PI on studies sponsored by Sarepta, Dyne, Roche, Novartis, Scholar Rock, and Santhera, and as a member of advisory boards for Roche and Novartis. **LDW** served as a PI for clinical trial activities for Sarepta Therapeutics, Italfarmaco, Pfizer, and Dyne Therapeutics, and performed *ad-hoc* advisory board activities for Santhera Therapeutics, Pfizer, and Italfarmaco. **KF** has received clinical trial support from Dyne, Avidity, and Ultragenyx; advisor compensation from Apic Bio, Encoded, BioMarin, Locanabio, and Sanofi; and is on a scientific advisory board for Armatus Bio. **ML** served as a PI on clinical trials sponsored by Dyne, Pfizer, Sarepta, Antisense Therapeutics, PTC, and NS Pharma. **HP** served as a PI on studies sponsored by Sarepta, Avidity, Edgewise, NS Pharma, Harmony, Capricor, Dyne, and Stealth. **CM**, **SR**, **DW**, **WF**, **AD**, and **MLN** are employees of Dyne Therapeutics, Inc., and own stock and other equities. **MG** served as a study chair for a study sponsored by ReveraGen (no financial benefits); had research collaborations with ReveraGen and Sarepta; currently or previously acted as CI/PI for clinical trials sponsored by Dyne, Pfizer, Italfarmaco, Edgewise, Roche, Santhera, ReveraGen, and Dynacure; participated in advisory boards for Pfizer, NS Pharma, Dyne (consultancies through Newcastle University); and received speaker honoraria from Sarepta, Italfarmaco, and Novartis.

Figure 5. DYNE-251 administered monthly showed an increase in PDPF at 6 months



*PDPF data not available for one patient from the placebo group.
Note: Biopsy taken approximately 28 days after most recent dose.
PDPF, percent dystrophin-positive fibers; SEM, standard error of the mean.

Figure 6. PDPF: Clear improvement in dystrophin localization to sarcolemma



Note: DELIVER biopsy taken approximately 28 days after most recent dose. Scale bar is 100 µm.
PDPF, percent dystrophin-positive fibers; Q4W, once every 4 weeks.

CONCLUSIONS

- 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 a Phase 1/2, ongoing, randomized, placebo-controlled, global trial of DYNE-251 in ambulant and non-ambulant male patients with DMD mutations amenable to exon 51 skipping therapy. The trial is fully enrolled through the 20-mg/kg cohort and has a favorable safety profile that has supported dosing up to 40 mg/kg
- The safety profile of DYNE-251 is favorable to date,[a] with the majority of TEAEs reported as mild or moderate
- In patients treated with 5 mg/kg (PMO equivalent) DYNE-251, initial data show levels of exon skipping, dystrophin, and PDPF increased at 6 months compared with baseline
- These initial data support the continued clinical development of DYNE-251 for the treatment of DMD

[a]Data as of December 6, 2023.

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