DELIVER, a Randomized, Double-blind, Placebo-Controlled, Multiple Ascending Dose Study of DYNE-251 in Boys With DMD Amenable to Exon 51 Skipping

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is characterized by progressive loss of muscle function leading to premature death.[1]
- Dyne developed the FORCE™ platform, which harnesses the natural expression of transferrin receptor 1 (TfR1) on muscle cells for targeted delivery of oligonucleotides (**Figure 1**).[2,3]
- 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.[4]
- DYNE-251 is an exon 51–skipping PMO conjugated to an antigen-binding fragment (Fab) targeting TfR1 (**Figure 2**).
- In non-human primates (NHP), DYNE-251 led to pronounced exon 51 skipping in cardiac and skeletal muscle and demonstrated a favorable safety profile.[5]
- Additionally, FORCE-M23D, a mouse-specific FORCE conjugate, achieved robust and durable exon skipping and dystrophin expression in skeletal and cardiac muscle and functional improvement in the *mdx* mouse model of DMD.[6]
- DELIVER, a Phase 1/2 randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) trial of DYNE-251 is underway to evaluate the safety, tolerability, and dystrophin protein levels in participants with *DMD* mutations amenable to exon 51 skipping (NCT05524883). Trial design methodology together with key endpoints are detailed in this presentation.

Figure 1. Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

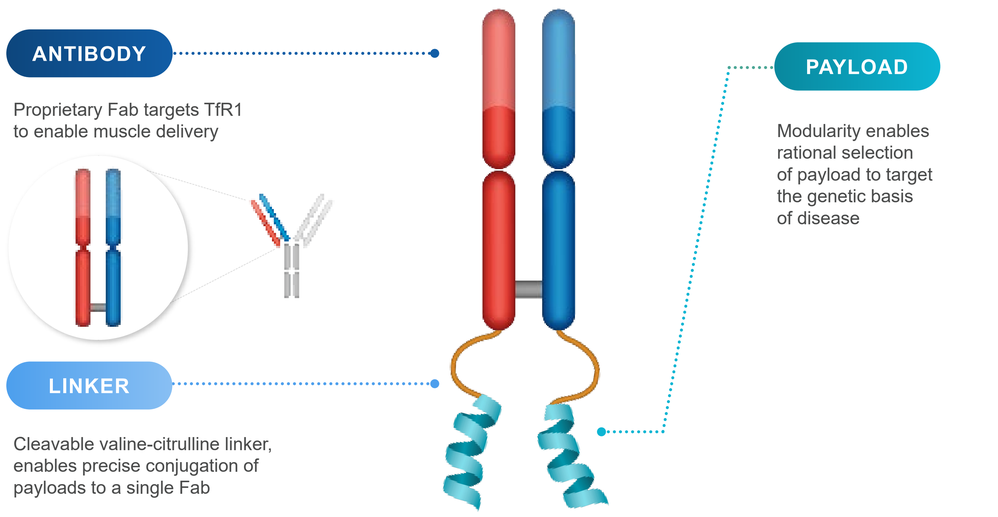
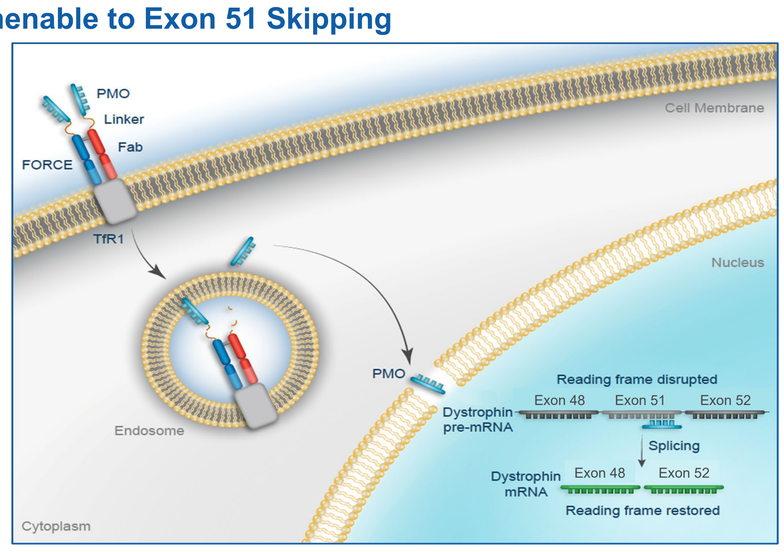


Figure 2. DYNE-251is Designed to Target the Genetic Basis of DMD in Patients Amenable to Exon 51 Skipping



Note: Image depicts intended mechanism of action of DYNE-251.

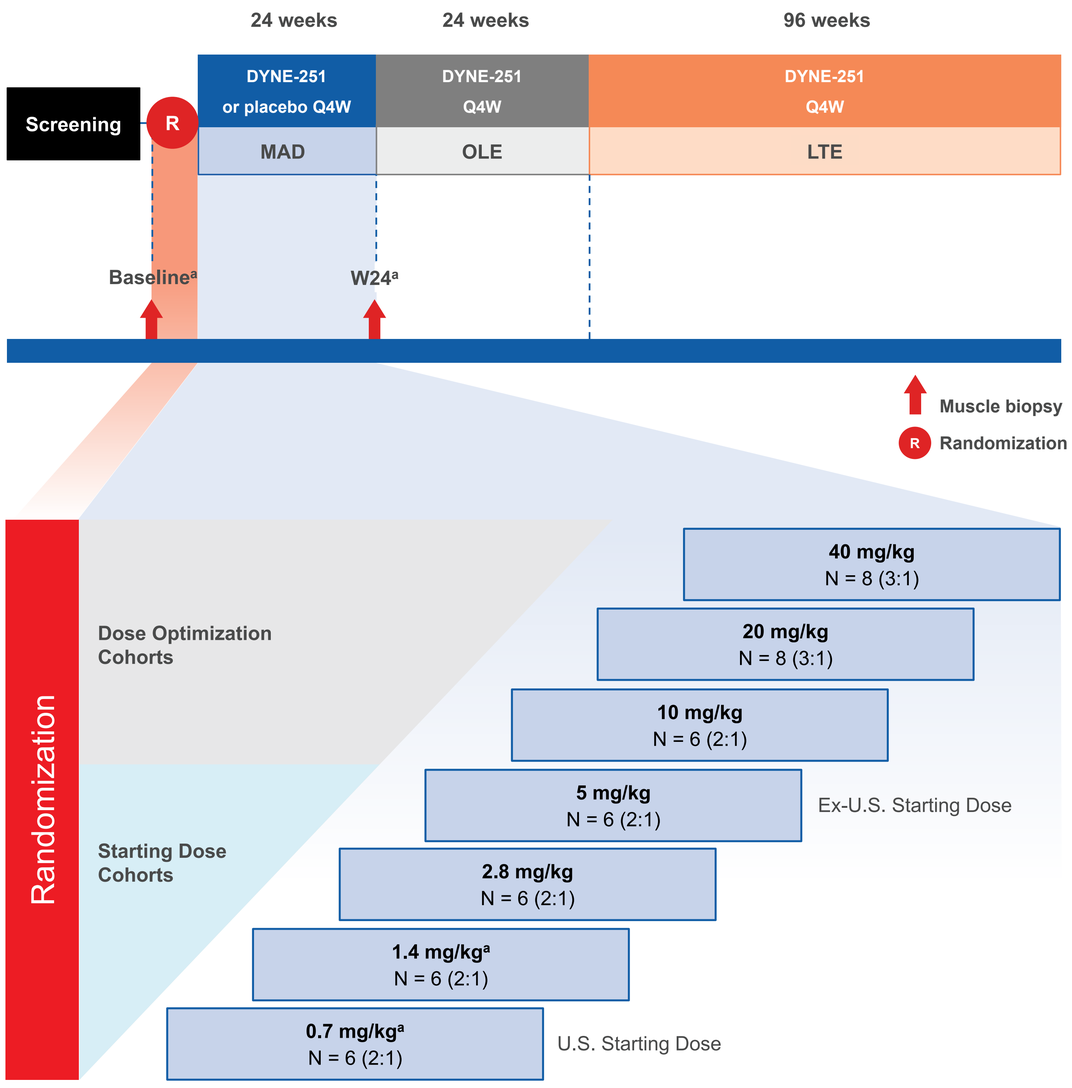
Figures adapted from Desjardins CA, et al. Enhanced exon skipping and prolonged dystrophin restoration achieved by TfR1-targeted delivery of antisense oligonucleotide using FORCE conjugation in mdx mice. *Nucleic Acids Res*. 2022;50(20):11401-11414. Oxford University Press.
Fab, antigen-binding fragment; TfR1, transferrin receptor 1.

METHODS

TRIAL DESIGN AND PATIENT POPULATION

- DELIVER is a Phase 1/2, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) trial which includes a MAD/placebo-controlled period (24 weeks), an open-label extension period (OLE, 24 weeks), and a long-term extension (LTE) period (96 weeks; **Figure 3**).
  - Approximately 46 patients globally will be enrolled into 7 cohorts: 0.7, 1.4, 2.8, 5, 10, 20, and 40 mg/kg of DYNE-251 (doses refer to PMO component of DYNE-251).
  - Participants will be randomized in a 2:1 or in a 3:1 DYNE-251–to–placebo ratio, administered intravenously every 4 weeks during the MAD/placebo-controlled period.
  - All participants will be escalated to the highest safe and tolerable dose of DYNE-251 during the OLE and LTE periods.

Figure 3. DELIVER Trial Design



Patient cohorts will be dosed from 0.7 mg/kg to 40 mg/kg in the United States. Outside the United States, patient cohorts will be dosed from 5 mg/kg to 40 mg/kg. Doses provided refer to PMO component of DYNE 251.
[a]Muscle biopsies taken at baseline and 24 weeks in 2.8 mg/kg and higher cohorts; biopsies not taken in 0.7 mg/kg and 1.4 mg/kg cohorts.
LTE, long-term extension; MAD, multiple ascending dose; OLE, open-label extension; PMO, phosphorodiamidate morpholino oligomer; Q4W, dosing every 4 weeks; R, randomization; W24, 24 weeks.

1 PRIMARY OUTCOME MEASURES

- Number of participants with treatment-emergent adverse events (TEAEs; through trial completion, up to week 145)
- Change from baseline in dystrophin protein levels in muscle tissue as determined by Western Blot analysis at week 25

2 SELECT SECONDARY OUTCOME MEASURES

- Change from baseline in muscle tissue exon 51 skipping levels at week 25
- Change from baseline in muscle tissue percent dystrophin-positive fiber (PDPF) at week 25
- Change from baseline in blood creatine kinase (CK) levels up to week 145
- Change from baseline in North Star Ambulatory Assessment (NSAA) total score in ambulatory participants up to week 145
- Change from baseline in time to rise from floor in ambulatory participants up to week 145
- Change from baseline in 10-meter run/walk (10-MRW) time in ambulatory participants up to week 145
- Change from baseline in Performance Upper Limb (PUL) scale v2.0 score up to week 145
- Change from baseline in percent predicted forced vital capacity (FVC) up to week 145
- Pharmacokinetics endpoints

Inclusion Criteria	Exclusion Criteria
❑ Age 4 to 16 years inclusive, at the time of informed consent/assent	❑ Uncontrolled clinical symptoms and signs of congestive heart failure (CHF)
❑ Male with a confirmed DMD mutation in the dystrophin gene, characterized by exon deletion amenable to exon 51 skipping	❑ Any change in prophylaxis/treatment for CHF within 3 months prior to the start of trial treatment
❑ Ambulatory or non-ambulatory. A non-ambulatory participant must have been non-ambulatory for <2 years before enrollment	❑ History of major surgical procedure within 12 weeks prior to the start of trial drug administration or an expectation of a major surgical procedure during the trial
❑ Brooke Upper Extremity Scale score of 1 or 2	❑ Requirement of daytime ventilator assistance
❑ Upper extremity muscle group that is amenable to muscle biopsy	❑ Percent predicted FVC <40% (applies only for participants who are ≥7 years of age)
❑ Receiving a stable dosage of glucocorticoids for ≥12 weeks prior to the start of trial drug administration	❑ Receipt of eteplirsen, or alternative exon-skipping/ dystrophin-modifying therapy, within 12 weeks of randomization
❑ Left ventricular ejection fraction of ≥50% by echocardiogram or ≥55% by cardiac magnetic resonance imaging (MRI)	❑ Receipt of non-exon skipping investigational drug within 4 months before the start of trial drug administration
	❑ Receipt of gene therapy at any time

Note: Other inclusion and exclusion criteria may apply.

CONCLUSIONS

- In preclinical studies in *mdx* mice, FORCE-M23D demonstrated exon skipping and dystrophin expression in skeletal and cardiac muscle and functional improvement.[6] In NHPs, DYNE-251 led to pronounced exon 51 skipping in cardiac and skeletal muscle and demonstrated a favorable safety profile.[5]
- The preclinical data on the use of the FORCE platform supported initiation of clinical development of DYNE-251. The Phase 1/2 DELIVER trial will inform further development of DYNE-251 for the treatment of DMD.

REFERENCES

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