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FORZETTO, a Phase 3 Study of Zeleciment Rostudirsen in Ambulatory Males with *DMD* Mutations Amenable to Exon 51 Skipping

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FORZETTO

BACKGROUND

- Duchenne muscular dystrophy (DMD) is a rare, X-linked, recessive, progressive, neuromuscular disorder in which mutations in the *DMD* gene lead to a greatly reduced or absent dystrophin protein, which is essential for muscle structure, function, and preservation[1–4]
- DMD is a multisystem disease that affects skeletal (including pulmonary), smooth, and cardiac muscle, as well as the central nervous system (CNS), and individuals with DMD typically exhibit progressive muscle weakness followed by loss of ambulation and cardiopulmonary failure, the leading cause of mortality[2,5,6]
- Functional improvement in DMD may be achieved with dystrophin-producing therapies that improve the quantity, quality, and distribution of dystrophin to skeletal (including pulmonary), cardiac and smooth muscle and the CNS[3,5,7]
- DELIVER (NCT05524883) is an ongoing global, randomized, placebo-controlled, Phase 1/2 clinical trial evaluating the safety and efficacy of zeleciment rostudirsen (z-rostudirsen, also known as DYNE-251) in ambulatory and non-ambulatory male participants (aged 4–16 years) with *DMD* mutations amenable to exon 51 skipping[8–10]
  - DELIVER enrolled multiple ascending dose and registrational expansion cohorts into a placebo-controlled period (24 weeks), open-label period (24 weeks), and long-term extension period (192 weeks)
  - At the registrational dose (20 mg/kg PMO every 4 weeks [Q4W]), z-rostudirsen drove a significant increase ($p<0.0001$) in dystrophin at Week 25 compared with baseline and early and sustained trends in functional improvement across multiple clinical measures of muscle function, with a favorable safety and tolerability profile (as of August 19, 2025, in participants followed for up to 36 months)[9,10]
- FORZETTO (NCT07608432) is a Phase 3 trial designed to further demonstrate the potential of z-rostudirsen to enable functional improvement for individuals with DMD amenable to exon 51 skipping[11]

Z-ROSTUDIRSEN MECHANISM OF ACTION

- Z-rostudirsen leverages the FORCE™ platform to deliver an exon 51-skipping phosphorodiamidate morpholino oligomer (PMO) via a transferrin receptor 1 (TfR1) fragment antibody (Fab) to skeletal (including pulmonary), cardiac, and smooth muscle, with the aim of producing near-full length, functional dystrophin in the tissues impacted by DMD (Figure 1)[12–14]

Figure 1. Z-rostudirsen addresses the central pathobiology of DMD amenable to exon 51 skipping

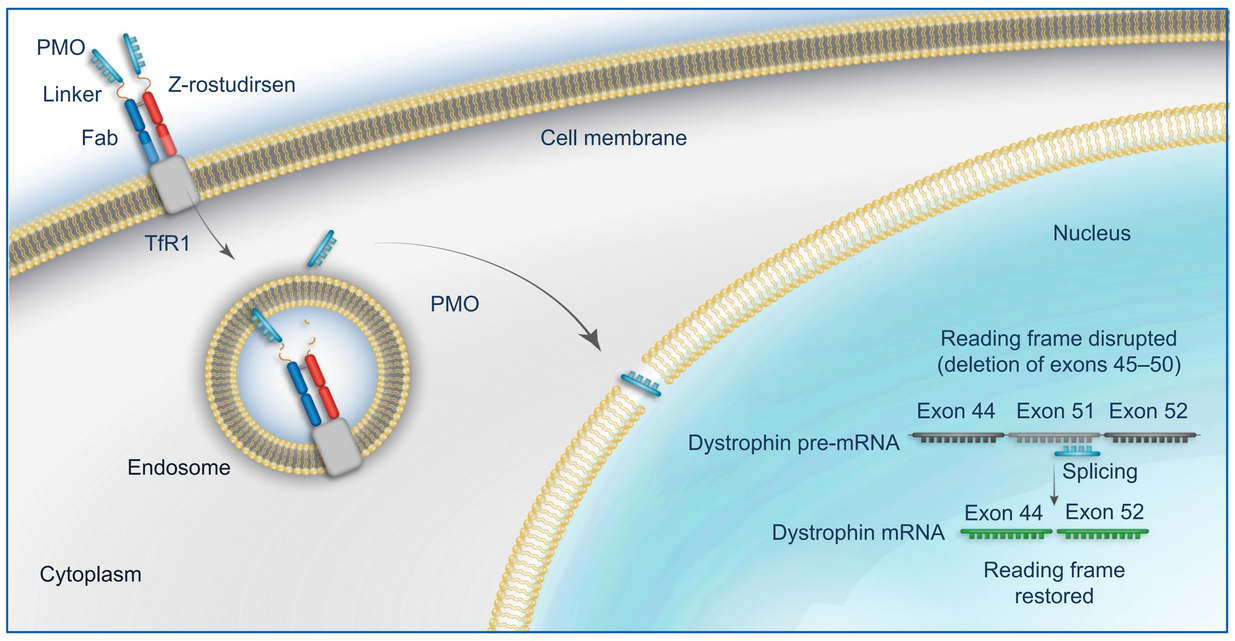


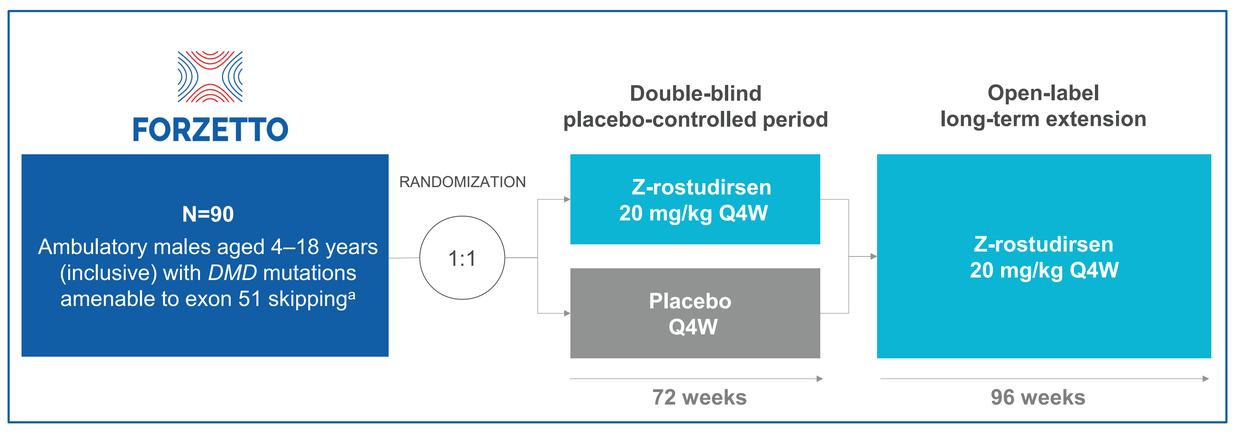
Image depicts intended mechanism of action of z-rostudirsen. Applicable to all DMD mutations amenable to skipping of exon 51.
DMD, Duchenne muscular dystrophy; Fab, antigen-binding fragment; mRNA, messenger RNA; PMO, phosphorodiamidate morpholino oligomer; TfR1, transferrin receptor 1.
Adapted from Desjardins CA, et al. *Nucleic Acids Res*. 2022;50(20):11401–11414.

OVERALL STUDY AIM

- FORZETTO is a global, randomized, placebo-controlled, double-blind, confirmatory Phase 3 trial designed to assess the efficacy, safety, and tolerability of z-rostudirsen administered intravenously to ambulatory male participants with *DMD* mutations amenable to exon 51 skipping[11,15]

TRIAL DESIGN

Figure 2. FORZETTO study design[11]



a. Additional eligibility criteria apply as per protocol. DMD, Duchenne muscular dystrophy; Q4W, every 4 weeks.

- The primary endpoint is the change from baseline in rise from floor (RFF) velocity, also referred to as time to rise (TTR) velocity, at Week 73.[11] RFF velocity is a clinically meaningful measure of muscle strength and motor coordination commonly used in DMD clinical trials[16,17]
- Secondary endpoints include changes from baseline in stride velocity 95th centile (SV95C), North Star Ambulatory Assessment (NSAA) total score, 10-meter walk/run (10MWR) velocity, 4-stair climb (4SC) velocity, and percent predicted forced vital capacity (FVC%p), as well as additional functional and patient-reported outcome measures, safety and tolerability, plasma pharmacokinetics, and immunogenicity[11]
- FORZETTO is intended to serve as a confirmatory trial to support the potential conversion of accelerated approval to traditional approval in the US and to support ex-US marketing applications[15]
- Informed by the Duchenne community, the FORZETTO Phase 3 study design reflects the company's commitment to patient-centered drug development[15]

TRIAL ENDPOINTS

Primary endpoint[11]

Change from baseline in RFF velocity at Week 73

Selected secondary endpoints[a,11]

Key functional endpoints

- SV95C[b]
- NSAA total score[b]
- 10MWR velocity[b]
- 4SC velocity[b]

Other functional outcomes

- Functional composite score[b]
- FVC%p[b]
- PGI-S[b]
- PGI-C[c]

Safety

- Safety and tolerability

a. All endpoints are measured at week 73, up to week 169 (TEAEs measured up to week 173); b. Change from baseline; c. Measured as an outcome.
4SC, 4-stair climb; 10MWR, 10-meter walk/run; FVC%p, forced vital capacity percent-predicted; NSAA, North Star Ambulatory Assessment; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; RFF, rise from floor; SV95C, stride velocity 95th centile; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Z-rostudirsen 20 mg/kg Q4W demonstrated a statistically significant increase in dystrophin and a trend towards functional improvement across clinical endpoints in the Phase 1/2 DELIVER study, supporting advancement to a Phase 3 study[9,10,15]
- The Phase 3 FORZETTO study will aim to confirm the clinical benefit of z-rostudirsen with endpoints that assess functional outcomes, and further evaluate safety in ambulatory participants with DMD amenable to exon 51 skipping[11]
- FORZETTO has been initiated and is open to enrollment[11]

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria[a,11]

- Ambulatory males with confirmed diagnosis of DMD and with a mutation in the dystrophin gene characterized by exon deletion amenable to exon 51 skipping
- RFF time must be <10 seconds for both screening assessments
- Receiving a stable daily or weekend dosage of glucocorticoids for at least 24 weeks prior to randomization with the expectation of maintaining a stable dose during the placebo-controlled period (unless dose adjustment is required by weight change)

Exclusion criteria[a,11]

- Receipt of ongoing immunosuppressive therapy (other than glucocorticoids) within 12 weeks prior to randomization
- Use of any pharmacologic treatment (other than glucocorticoids) that may have an effect on muscle strength or function within 12 weeks prior to randomization
- Any change in prophylaxis/treatment for CHF within 12 weeks prior to randomization
- Receipt of eteplirsen within 1 week prior to randomization
- Receipt of alternative exon-skipping or dystrophin-modifying therapy or z-rostudirsen within 24 weeks prior to randomization
- Receipt of givinostat within 12 weeks prior to randomization
- Receipt of gene therapy at any time

a. Additional eligibility apply.
CHF, congestive heart failure; RFF, rise from floor.

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DISCLOSURE INFORMATION

Douglas Kerr, Xiaoyan Yin, Katy Meilleur, Jordan Messer, Gabriel Helmlinger, Prashant Bansal, Soma Ray, Monica Fay, and Maria L. Naylor are employees of Dyne Therapeutics and may hold stock in the company.

ACKNOWLEDGMENTS

This study was funded by Dyne Therapeutics. Medical writing and editorial support was provided by Suriyea Ullah and Roberta Sottocornola of Obsidian Healthcare Group Ltd, UK. This support was funded by Dyne Therapeutics. The authors wish to thank the clinical trial investigators and site coordinators and, most importantly, all the participants, families, and caregivers for their willingness to participate in this clinical trial, which was sponsored by Dyne Therapeutics.

Zeleciment rostudirsen (z-rostudirsen, also known as DYNE-251) is an investigational medicine or otherwise in development and has not been approved as safe or effective by the US FDA, EMA, or any other regulatory authority

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