263

Zelecimect Rostudirsen Targets the Underlying Cause of Duchenne Muscular Dystrophy (DMD) to Enable Sustained Functional Improvement in Males with *DMD* Mutations Amenable to Exon 51 Skipping Enrolled in the Phase 1/2 DELIVER Trial

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DELIVER

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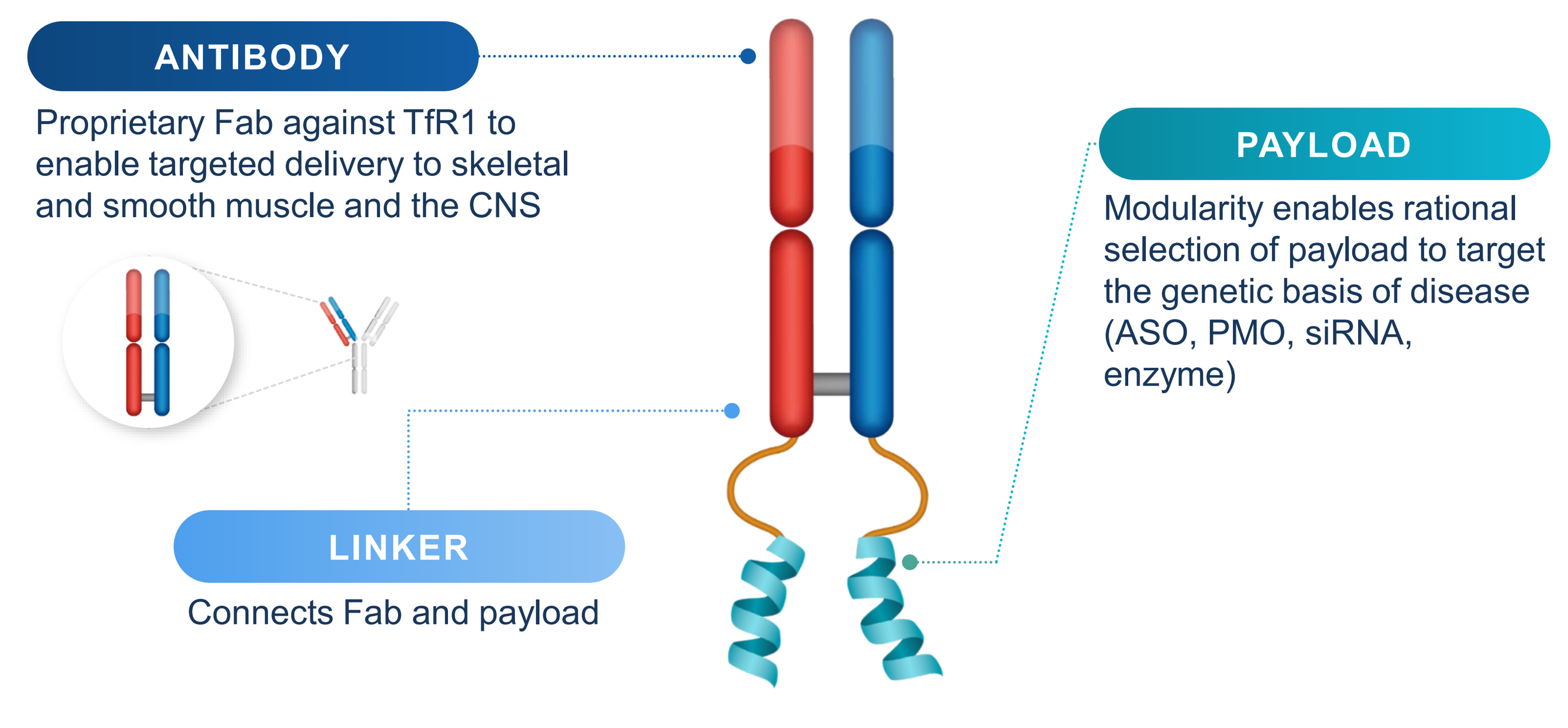
BACKGROUND

- DMD is a progressive, X-linked neuromuscular disorder caused by deficiency of functional dystrophin protein, leading to loss of ambulation, cardiopulmonary complications, and premature mortality.[1–6]
- This severe clinical burden is accompanied by substantial increases in healthcare resource utilization (HCRU). Patients with DMD show a ~10-fold increase in hospitalizations and direct medical costs versus age-matched peers, with expenditures rising sharply as function declines.[7]
- Functional improvement in DMD requires therapeutic approaches that improve the quantity, quality, and distribution of dystrophin to key muscles (skeletal, including respiratory, cardiac, and smooth) and the central nervous system (CNS)[3,5,8]
- Currently available therapies have several limitations, including limited delivery to muscle and the CNS.[9,10] In addition, the currently approved exon 51-skipping therapy has low dystrophin production (<1%) and a high patient and caregiver burden due to weekly dosing.[11] Gene therapy-produced micro-dystrophin lacks key domains for optimal functionality, the durability of effect is unknown, and is limited by safety considerations and the inability to redose[10,12–14]
- Dyne's proprietary FORCE platform was developed to overcome the limitations of therapeutic delivery to muscle and the CNS. The platform consists of a transferrin receptor 1 (TfR1)-targeting antigen-binding fragment (Fab) conjugated to a payload which has been rationally selected to target the underlying cause of the disease. By leveraging the natural expression of TfR1, FORCE enables broad delivery of therapeutics to tissues such as muscle (skeletal, cardiac, and smooth) and the CNS which are relevant to neuromuscular diseases (Figure 1)
- Zelecimect rostudirsen (z-rostudirsen, also known as DYNE-251) leverages TfR1 to deliver an exon 51-skipping phosphorodiamidate morpholino oligomer (PMO) to key tissues relevant to DMD, with the goal of acting on RNA splicing signals in a manner that leads to production of near-full-length, functional dystrophin[15,16]

Figure 1. FORCE™ Platform-based Therapeutics for Neuromuscular Diseases



ANTIBODY
Proprietary Fab against TfR1 to enable targeted delivery to skeletal and smooth muscle and the CNS
PAYLOAD
Modularity enables rational selection of payload to target the genetic basis of disease (ASO, PMO, siRNA, enzyme)
LINKER
Connects Fab and payload

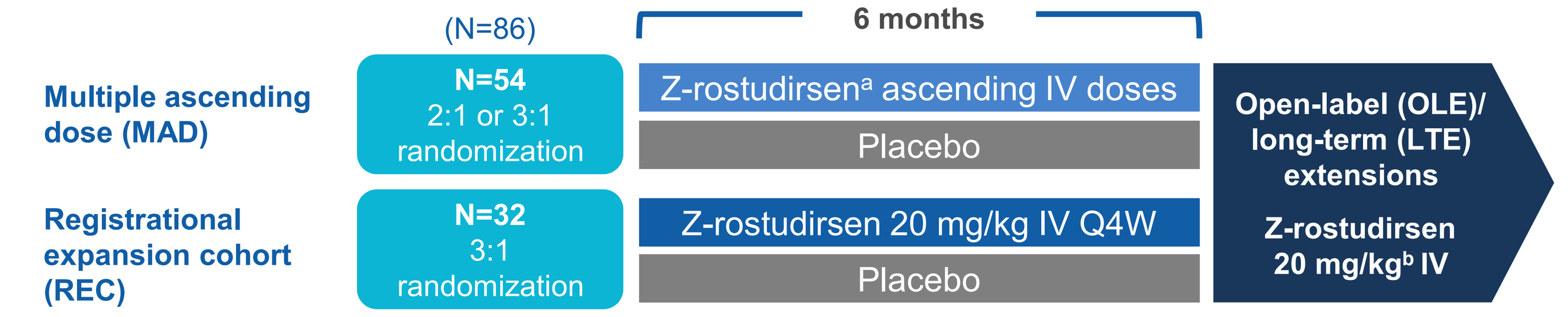
The FORCE platform and z-rostudirsen (also known as DYNE-251) are investigational or otherwise in development and have not been approved as safe or effective by the FDA or any other regulatory authority.
ASO, antisense oligonucleotide; CNS, central nervous system; Fab, antigen-binding fragment; PMO, phosphorodiamidate morpholino oligomer; siRNA, small interfering RNA; TfR1, transferrin receptor 1. Adapted from Ohrt T, et al. *Nucleic Acids Res*. 2006;34(5):1369.

METHODS

- The safety and efficacy of z-rostudirsen are being investigated in the Phase 1/2 DELIVER trial (NCT05524883; EU Trial [CTIS] number 2023-510351-31-00)
- DELIVER is a global, randomized, double-blind, placebo-controlled study evaluating intravenous administrations of z-rostudirsen in ambulant and non-ambulant male participants with DMD (4–16 years old) with mutations amenable to exon 51-skipping therapy
- DELIVER consists of a multiple ascending dose (MAD) cohort and a registrational expansion cohort (REC); both have a 24-week placebo-controlled period followed by an open-label extension (OLE) period (24 weeks), and a long-term extension (LTE) period (192 weeks) (Figure 2)
- Here, we present the 6-month results of the registrational expansion cohort, as well as safety data based on all 86 participants[a] enrolled in the DELIVER trial

a. As of August 19, 2025.

Figure 2. DELIVER Study Design



(N=86)
6 months
Multiple ascending dose (MAD)
N=54
2:1 or 3:1 randomization
Z-rostudirsen[a] ascending IV doses
Placebo
Registrational expansion cohort (REC)
N=32
3:1 randomization
Z-rostudirsen 20 mg/kg IV Q4W
Placebo
Open-label (OLE)/ long-term (LTE) extensions
Z-rostudirsen 20 mg/kg[b] IV

Select inclusion/exclusion criteria

- Inclusion: Ambulatory or non-ambulatory; age 4 to 16 years inclusive; stable dosage of glucocorticoids for at least 12 weeks
- Exclusion: Exon-skipping/dystrophin-modifying therapy or givinostat within 12 weeks of randomization; gene therapy at any time

Primary endpoints: Change from baseline in dystrophin protein levels by Western blot; safety and tolerability

Key functional endpoints: TTR velocity, 10MWR velocity, NSAA, SV95C, PUL2.0, FVC%p

a. Z-rostudirsen doses in the MAD cohorts ranged from 0.7 mg/kg to 40 mg/kg every 4 or 8 weeks; b. Transition to 20 mg/kg dose occurred at non-uniform times during OLE or LTE; for participants initiated at 40 mg/kg, transition started either in the placebo-controlled period or OLE.
10MWR, 10-meter walk/run; FVC%p, forced vital capacity percent predicted; IV, intravenous; NSAA, North Star Ambulatory Assessment; PUL2.0, performance upper limb v2.0; Q4W, every 4 weeks; SV95C, stride velocity 95th centile; TTR, time to rise.

RESULTS

Table 1. Baseline Characteristics: DELIVER Pooled Placebo vs REC

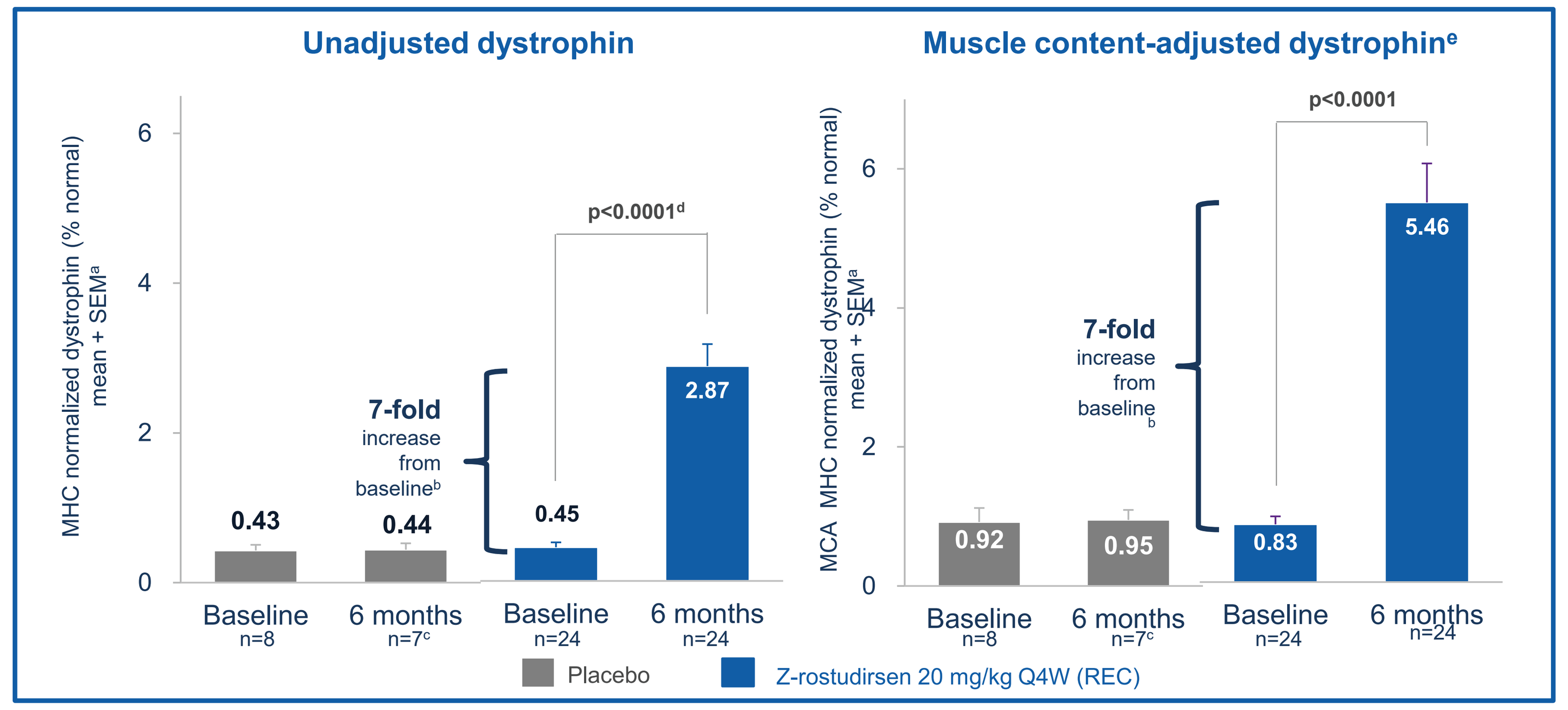
	Placebo (MAD+REC) N=24[e] Mean (SD) or n (%)	20 mg/kg Q4W z-rostudirsen (REC) N=24 Mean (SD) or n (%)
Age (years)	8.2 (2.5)	7.8 (3.6)
BMI (kg/m²)	19.8 (4.7)	17.6 (4.5)
Age of symptom onset (years)	3.4 (1.8)	2.5 (1.7)
Most recent corticosteroid dosing regimen, n (%)[a]		
Daily	20 (83.3)	20 (83.3)
Other	4 (16.7)	4 (16.7)
Duration of corticosteroid treatment (years)[b]	2.1 (2.4)	2.4 (2.5)
Prior DMD therapy, n (%)		
Eteplirsen	4 (16.7)	2 (8.3)
Other	2 (8.3)	5 (20.8)
PUL2.0 total score[c]	36.3 (4.0)	36.3 (5.0)
FVC%p	92.7 (17.6)	90.0 (22.2)
Ambulant (%)	19 (79.2)	21 (87.5)
TTR velocity (rise/sec)[d]	0.20 (0.10)	0.22 (0.12)
10MWR velocity (m/sec)[d]	2.0 (0.5)	1.8 (0.5)
NSAA total score[d]	21.6 (6.3)	20.6 (5.0)
SV95C (m/sec)[d]	1.7 (0.5)	1.5 (0.4)

a. Most recent corticosteroid regimen refers to corticosteroid at time of randomization; b. Cumulative duration of previous and most recent corticosteroid treatment at the time of randomization; c. Missing values imputed; d. Ambulant participants; out-of-threshold and/or missing values imputed; e. All placebo participants pooled from MAD and REC.
10MWR, 10-meter walk/run; BMI, body mass index; DMD, Duchenne muscular dystrophy; FVC%p, forced vital capacity percent predicted; m, meters; MAD, multiple ascending dose; NSAA, North Star Ambulatory Assessment; PUL2.0, performance upper limb v2.0; Q4W, every 4 weeks; REC, registrational expansion cohort; SD, standard deviation; sec, second; SV95C, stride velocity 95th centile; TTR, time to rise.

- Z-rostudirsen 20 mg/kg Q4W showed an increase in muscle PMO concentration in the REC, reaching 4153 ng/g at 6 months
- Z-rostudirsen 20 mg/kg Q4W showed robust target engagement at 6 months relative to baseline, as demonstrated by increases in mean exon 51 skipping (2.45% vs 0.17%, respectively, compared with 0.10% vs 0.06% for placebo)

RESULTS

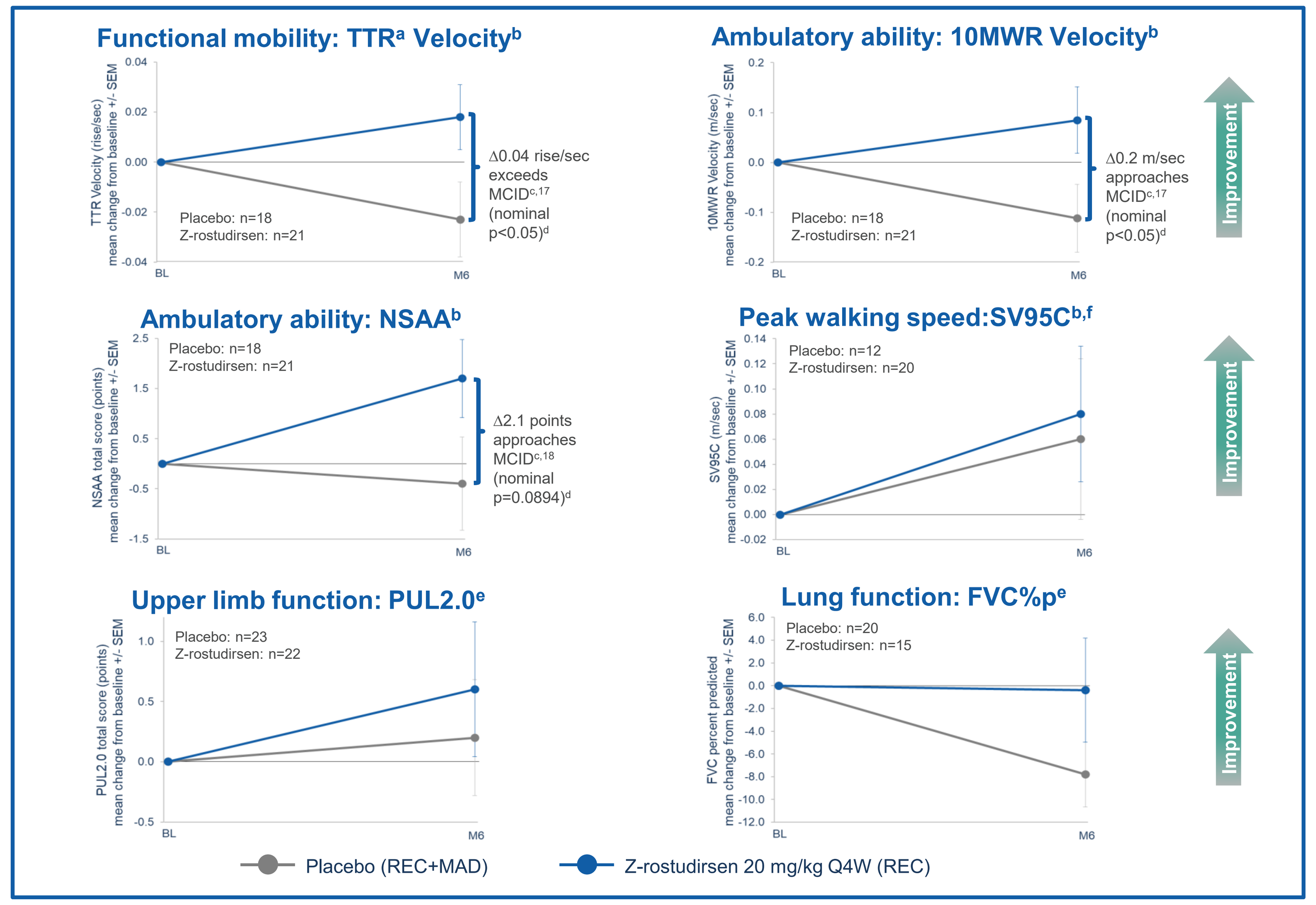
Figure 3. Z-Rostudirsen Achieved a Statistically Significant Increase in Dystrophin Expression Relative to Baseline at 6 Months



Unadjusted dystrophin
MHC normalized dystrophin (% normal) mean + SEM[a]
0.43
0.44
7-fold increase from baseline[b]
0.45
2.87
p<0.0001[d]
Baseline n=8
6 months n=7[c]
Baseline n=24
6 months n=24
Muscle content-adjusted dystrophin[e]
MCA MHC normalized dystrophin (% normal) mean + SEM[a]
0.92
0.95
7-fold increase from baseline[b]
0.83
5.46
p<0.0001
Baseline n=8
6 months n=7[c]
Baseline n=24
6 months n=24
Placebo
Z-rostudirsen 20 mg/kg Q4W (REC)

a. Biopsies taken approximately 28 days after most recent dose; b. Based on geometric mean; c. One REC placebo participant sample could not be analyzed at Week 25; d. Prespecified nominal p-value with no adjustment for multiplicity; e. Muscle content-adjusted dystrophin = MHC normalized dystrophin / % muscle content. 6 months = Week 25.
MCA, muscle content-adjusted; MHC, myosin heavy chain; Q4W, every 4 weeks; REC, registrational expansion cohort; SEM, standard error of the mean.

Figure 4. Treatment With Z-Rostudirsen Led to Improvement in Multiple Measures of Muscle Function



Functional mobility: TTR[a] Velocity[b]
TTR Velocity (rise/sec) mean change from baseline +/- SEM
Placebo: n=18
Z-rostudirsen: n=21
Δ0.04 rise/sec exceeds MCID[c,17] (nominal p<0.05)[d]
Ambulatory ability: 10MWR Velocity[b]
10MWR Velocity (m/sec) mean change from baseline +/- SEM
Placebo: n=18
Z-rostudirsen: n=21
Δ0.2 m/sec approaches MCID[c,17] (nominal p<0.05)[d]
Ambulatory ability: NSAA[b]
NSAA total score (points) mean change from baseline +/- SEM
Placebo: n=18
Z-rostudirsen: n=21
Δ2.1 points approaches MCID[c,18] (nominal p=0.0894)[d]
Peak walking speed:SV95C[b,f]
SV95C (m/sec) mean change from baseline +/- SEM
Placebo: n=12
Z-rostudirsen: n=20
Upper limb function: PUL2.0[e]
PUL2.0 total score (points) mean change from baseline +/- SEM
Placebo: n=23
Z-rostudirsen: n=22
Lung function: FVC%p[e]
FVC percent predicted mean change from baseline +/- SEM
Placebo: n=20
Z-rostudirsen: n=15
BL
M6
Improvement
Placebo (REC+MAD)
Z-rostudirsen 20 mg/kg Q4W (REC)

a. Also referred to as rise from floor (RFF); b. Ambulant participants; out-of-threshold or missing values imputed; c. RFF velocity MCID = 0.023 rise/sec; 10MWR velocity MCID = 0.212 m/sec; NSAA MCID = ≥2.3 points; d. Post-hoc analysis; prespecified statistical analysis plan did not include formal hypothesis testing for any functional endpoint; e. Ambulant and non-ambulant participants; missing values imputed for PUL2.0; f. Placebo impacted by single participant with change from baseline of 0.46 m/sec at M6; if this participant were excluded, mean change from baseline at M6 for placebo would be approximately 0.02 m/sec.
10MWR, 10-meter walk/run; BL, baseline; FVC%p, forced vital capacity percent predicted; m, meters; M, month; MAD, multiple ascending dose; MCID, minimal clinically important difference; NSAA, North Star Ambulatory Assessment; PUL2.0, performance upper limb v2.0; Q4W, every 4 weeks; REC, registrational expansion cohort; sec, second; SEM, standard error of mean; SV95C, stride velocity 95th centile; TTR, time to rise. M6 = 169 days.

Table 2. Safety Profile of Z-Rostudirsen 20 mg/kg Q4W Remains Favorable[a]

Study period	Placebo-controlled period (0 to 6M)		All study periods (0 to ≤36M)
Participants with ≥1 TEAE – n (%)	Placebo (MAD+REC) N=24[b]	Z-rostudirsen 20 mg/kg Q4W (MAD+REC) N=30[c]	Z-rostudirsen pooled doses[d] (MAD+REC) N=85[e]
Any TEAE	22 (91.7)	29 (96.7)	80 (94.1)
Any related TEAE	3 (12.5)	10 (33.3)	41 (48.2)
Any serious TEAE	1 (4.2)	2 (6.7)	10 (11.8)
Any serious related TEAE	0	0	4 (4.7)
Any TEAE leading to withdrawal from study	0	0	0
Any TEAE leading to death	0	0	0

- Most related TEAEs were mild or moderate
- Potentially related serious TEAEs
  - 2 participants at 20 mg/kg Q4W (registrational dose)
    - Pyrexia (fever) and malaise[f]
  - 2 participants at 40 mg/kg Q4W
    - Acute kidney injury; thrombocytopenia[g]
    - Pancytopenia[h]
- Most frequent related TEAEs ≥10%[i]
  - Pyrexia (fever) (18%)
  - Headache (13%)
- Additional safety data at 20 mg/kg Q4W
  - No treatment-related discontinuations or deaths in the DELIVER study
  - No participants have reported persistent related anemia[j] or thrombocytopenia

1441 doses of z-rostudirsen administered to date representing 113 patient-years of follow-up (up to 36 months).[a] 1062 doses of z-rostudirsen at 20 mg/kg dose level administered to date[a]

a. Data as of August 19, 2025; all participants, placebo-controlled period, OLE, and LTE; b. All placebo participants pooled from MAD and REC; c. All participants randomized to z-rostudirsen 20 mg/kg Q4W in MAD and REC cohorts; d. All doses of z-rostudirsen from MAD and REC at doses ranging from 0.7 mg/kg to 40 mg/kg every 4 or 8 weeks; e. One participant randomized to placebo in REC not yet dosed with z-rostudirsen as of August 19, 2025; f. One participant with same day onset of pyrexia and malaise in OLE and separate single event of pyrexia in LTE; one participant with single event of pyrexia in LTE; both participants fully recovered and have continued to receive z-rostudirsen without interruption; g. Events had 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 were consistent with hemolytic uremic syndrome with a possible infectious etiology; h. Participant has a history of hemolytic anemia of unidentified etiology; presented with fever and tonsilitis; symptoms resolved without therapeutic intervention; i. All cohorts combined; preferred terms reported; j. No participants have persistent related anemia with Hgb levels <11.2 g/dL (threshold for anemia in children[19]).
Hgb, hemoglobin; LTE, long-term extension; M, months; MAD, multiple ascending dose; OLE, open-label extension; Q4W, every 4 weeks; REC, registrational expansion cohort; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Z-rostudirsen (20 mg/kg Q4W) demonstrated a significant increase in dystrophin at 6 months compared to baseline
- At 6 months, functional improvement was observed across multiple clinical measures of muscle function, suggesting broad therapeutic distribution
  - Improvements or stabilization were seen in lower and upper limbs as well as in lung function, suggesting effects in both ambulant and non-ambulant participants
- Z-rostudirsen demonstrated a favorable safety and tolerability profile in participants enrolled in DELIVER and followed for up to 36 months[a]
- Administration every 4 weeks may reduce treatment burden and offer a sustainable long-term option for people with DMD amenable to exon 51 skipping
- Data from the DELIVER trial support the potential of z-rostudirsen to address the unmet needs and potentially lower HCRU for individuals with *DMD* pathogenic variants amenable to exon 51 skipping

a. As of August 19, 2025.

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DISCLOSURE INFORMATION

Kevin Flanigan has received clinical trial support from Sarepta, Dyne Therapeutics, Avidity, Ultragenyx, and Solid. He has served on advisory boards for Armatus, Encoded, Insmed, Dyne Therapeutics, Solid, Precision Biosciences, and received consultation fees from Satellos; 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; 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; Chamindra G. Laverty has received consulting fees from Sarepta, Genentech, and Italfarmaco; Jeehun Lee has nothing to disclose; Hugh McMillan has received consulting fees from Roche, Novartis, Key Pharma, Regenxbio, Solid Biosciences, and Merck; Stefano C. Previtali has received honoraria for work performed including educational activities and attendance at advisory board meetings from EspeRare, Wave, Alexion, Argenx, Santhera, Takeda, Alia Therapeutics. He has been/is PI on clinical trials for Avidity, Alexion, Argenx, Wave, Fibrogen, Takeda, Dianthus, Immunovant, Dyne Therapeutics, Entrada, AstraZeneca, Mallinckrodt, Vertex, Kedrion, Sanofi; 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 Biosciences, 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; Ian R Woodcock has received honoraria for work performed including educational activities and attendance at advisory board meetings from pharmaceutical companies Avidity, Biogen, Juvena Therapeutics, Keros Therapeutics, Novartis, Pfizer, Roche, Solid Biosciences, and Soufflé Therapeutics. He has received grants for research work from Fulcrum Therapeutics, FSHD Global Research Foundation, FSHD Society, NIH, and has been PI on a number of industry-sponsored clinical trials, including those sponsored by Avidity, Biogen, Catabasis, Dyne Therapeutics, EryDel, Keros Therapeutics, Novartis, Pfizer, Percheron Therapeutics, PTC, Roche, Sarepta, Satellos, and Solid Biosciences. None of these disclosures affected the work he performed on this work; Crystal Henderson, David Danese, Soma Ray, Dazhe Wang, Douglas Kerr, and Maria L Naylor are employees of Dyne Therapeutics and may hold stock in the company.

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Dyne THERAPEUTICS