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Zeleciment Rostudirsen Increased Dystrophin and Led to Functional Improvement in Clinical Measures in DELIVER Trial

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DELIVER

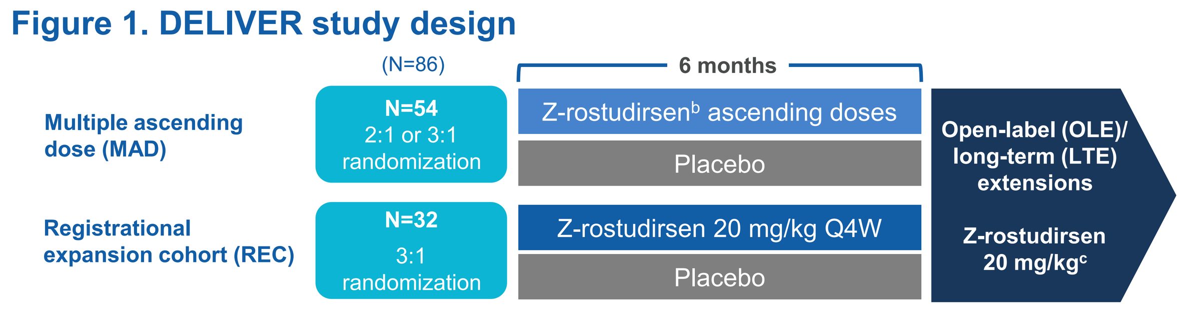
BACKGROUND

- 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 multi-system disease that affects skeletal, including pulmonary, smooth, and cardiac muscles 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 requires therapeutic approaches that improve the quantity, quality, and distribution of dystrophin to key muscles (skeletal, including respiratory, cardiac, and smooth) and the CNS[3,5,7]
- Currently available therapies have several limitations, including limited delivery to muscle and the CNS.[8,9] 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.[10] 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[9,11–13]
- Zeleciment rostudirsen (z-rostudirsen, also known as DYNE-251) leverages transferrin receptor 1 (TfR1) to deliver an exon 51-skipping phosphorodiamidate morpholino oligomer (PMO) to key tissues relevant to DMD, with the goal of producing near-full-length, functional dystrophin[14,15]

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, placebo-controlled study evaluating intravenous administrations of z-rostudirsen in ambulatory and non-ambulatory male participants with DMD (4–16 years old) with mutations amenable to exon 51-skipping therapy
- DELIVER enrolled multiple ascending dose (MAD) cohorts and a registrational expansion cohort (REC); the study consisted of 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 1)
- Here, we present the 6-month results of the REC, as well as safety data based on all 86 participants[a] enrolled in the DELIVER trial

Figure 1. DELIVER study design



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. As of August 19, 2025. b. Z-rostudirsen doses in the MAD cohorts ranged from 0.7 mg/kg to 40 mg/kg every 4 or 8 weeks; c. 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; 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.

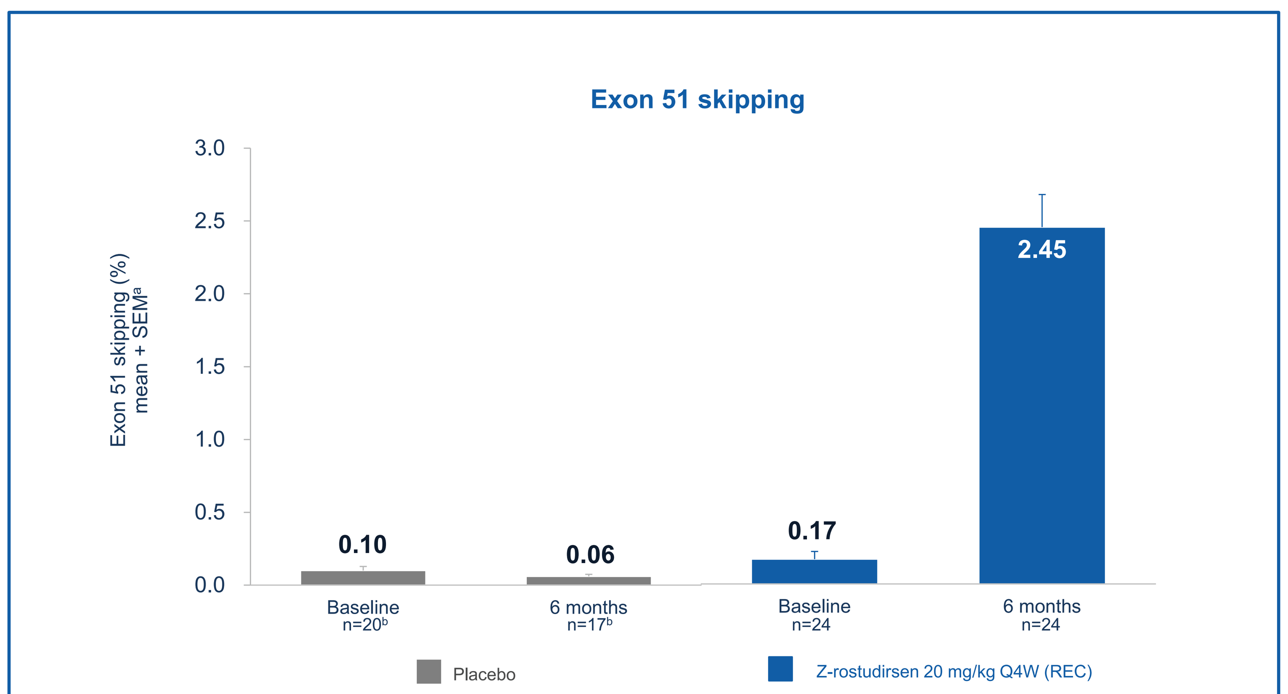
RESULTS

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)

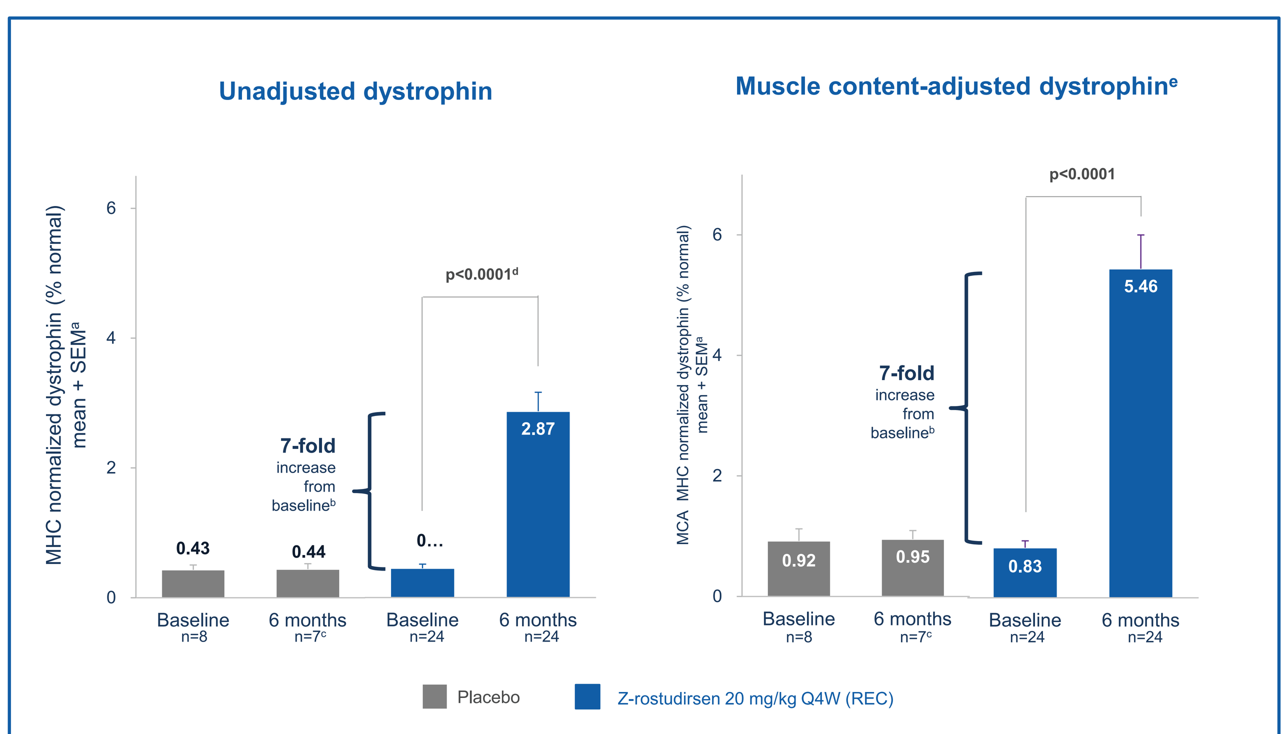
a. Most recent corticosteroid regimen refers to corticosteroid at time of randomization; b. Cumulative duration of previous and most recent corticosteroid treatment at the time of randomization; c. Missing values imputed; d. Ambulant participants; out-of-threshold and/or missing values imputed; e. All 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.

Figure 2. Z-rostudirsen had robust target engagement at 6 months relative to baseline



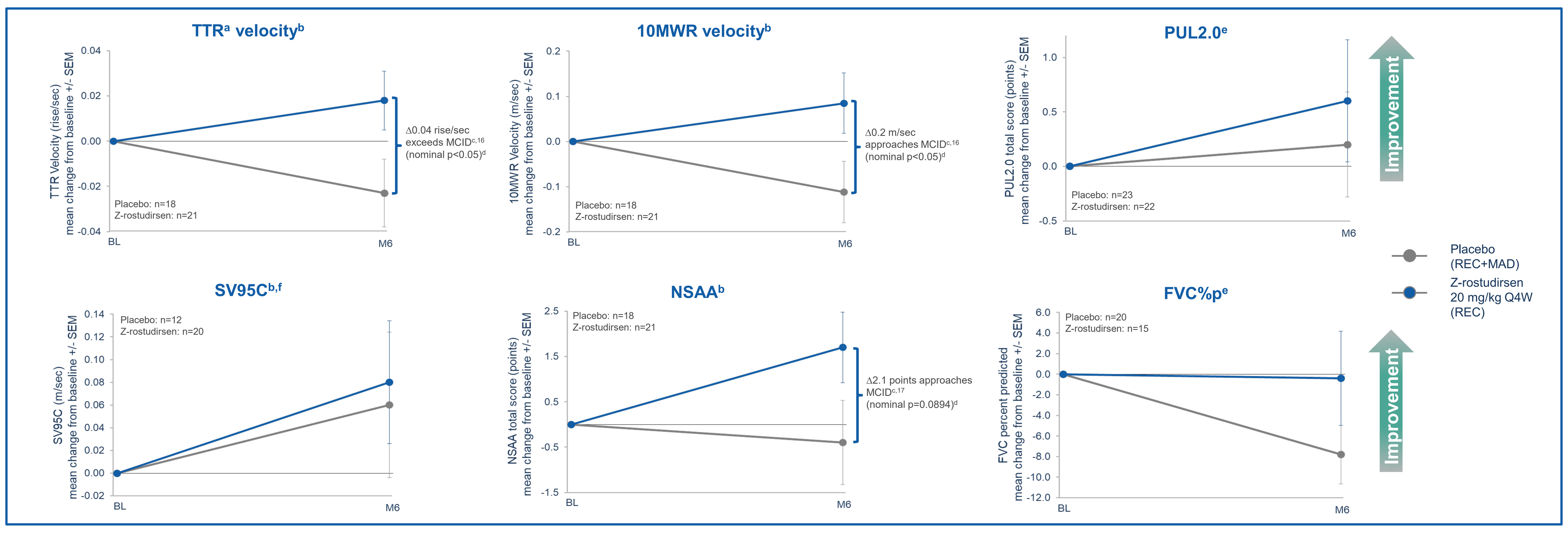
a. Biopsies taken approximately 28 days after most recent dose. b. Not all participant samples could be analyzed at baseline or Week 25. 6 months = Week 25.
Q4W, every 4 weeks; REC, registrational expansion cohort; SEM, standard error of the mean.

Figure 3. Z-rostudirsen achieved a statistically significant increase in dystrophin expression relative to baseline at 6 months



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



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 6M; if this participant were excluded, mean change from baseline at 6M 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 participants have 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] 1,062 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[18]). 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 statistically significant increase in mean muscle content-adjusted dystrophin at 6 months compared to baseline
- At 6 months, early trends in functional improvement or stabilization were 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 ambulatory and non-ambulatory participants
- Z-rostudirsen demonstrated a favorable safety and tolerability profile in participants enrolled in DELIVER and followed for up to 36 months[a]
- Data from the DELIVER trial support the potential of z-rostudirsen to address the unmet needs of individuals with DMD pathogenic variants amenable to exon 51 skipping

a. As of August 19, 2025.

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DISCLOSURE INFORMATION

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