Zeleciment Rostudirsen Significantly Increased Dystrophin Protein Levels and Led to Functional Improvement in Clinical Measures in the DELIVER Trial

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Disclosures

- Dr Flanigan has received clinical trial support from Sarepta, Dyne, Avidity, Ultragenyx, and Solid. He has served on advisory boards for Armatus, Encoded, Insmed, Dyne, Solid, Precision Biosciences, and received consultation fees from Satellos
- 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

DELIVER

Individuals with exon 51 skip amenable *DMD* mutations: A population with severe disease and significant unmet need, despite approved therapies

Progressive clinical presentation

- Greatly reduced or absent dystrophin protein expression[1]
  - Low baseline dystrophin levels in patients with genetic mutations that are amenable to exon 51 skipping compared with most other *DMD* mutations[2–8]
- Muscle weakness and gait abnormalities[9]
- Progressive loss of upper and lower limb strength and function[9]
- Cognitive function impairment and neuropsychiatric disorders[10]
- Respiratory/cardiac failure (leading cause of death)[11]

Limitations with current therapies

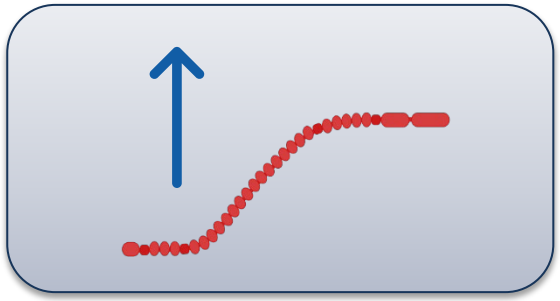
- Limited delivery to skeletal muscle, heart, and CNS[12,13]
- High patient and caregiver burden due to frequent IV dosing (e.g., Q1W)[2]
- <1% dystrophin production with currently approved exon 51 skipping therapy[2]
- Micro-dystrophin lacks domains key for optimal functionality[14–16]
- Unknown durability and inability to redose with gene therapy[13]
- Safety considerations[12,17–19]

CNS, central nervous system; DMD, Duchenne muscular dystrophy; Q1W, every 1 week.

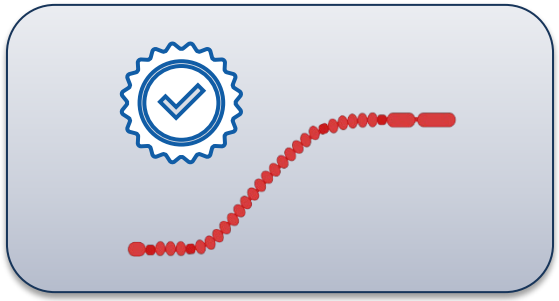
1. de Feraudy Y, et al. *Ann Neurol*. 2021;89:280–292; 2. Exondys 51 Prescribing Information; 3. McMillan H, et al. 2025 WMS Annual Meeting, 19O; 4. Vyondys 53 Prescribing Information; 5. Amondys 45 Prescribing Information; 6. Viltepso Prescribing Information; 7. Veerapandiyan A, et al. 2025 MDA Clinical and Scientific Conference, O72; 8. Aoki Y, et al. 2025 ASGCT Annual Meeting, Abstract 1351; 9. Bushby K, et al. *Lancet Neurol*. 2010;9:77–93; 10. Ohlendieck K, Swandulla D. *Pflügers Arch*. 2022;473(12):1813–1839; 11. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:251–267; 12. Chwalenia K, et al. *J Muscle Res Cell Motil*. 2025;46(4):293–300; 13. Gonzalez Castillo Z, et al. *J Transl Genet Genom*. 2025;9:338–351; 14. Chamberlain JS, et al. *Hum Gene Ther*. 2023;34(9-10):404–415; 15. Harper S, et al. *Hum Mol Genet*. 2002;11(16):1807–1815; 16. Davies KE, Guiraud S. *Mol Ther*. 2019;27(3):486–488; 17. Montagna C, et al. *Int J Mol Sci*. 2025;26(14):6742; 18. D'Ambrosio ES, Mendell JR. *Neurotherapeutics*. 2023;20(6):1669–1681; 19. Komaki H. *Brain Dev*. 2025;47(5):104397.

DELIVER

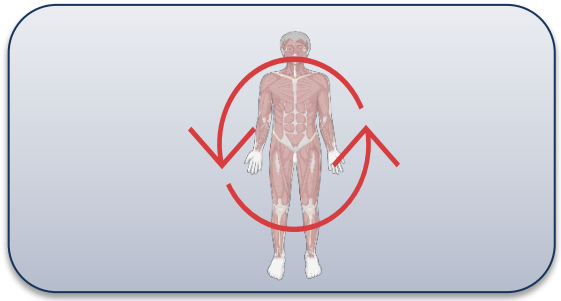
Functional improvement in DMD requires therapeutic approaches that improve the quantity, quality, and distribution of dystrophin



Increased dystrophin production



Production of high-quality dystrophin



Broad and effective distribution of dystrophin restorative treatments to key muscles (skeletal, smooth, and cardiac) and the CNS

Functional improvement

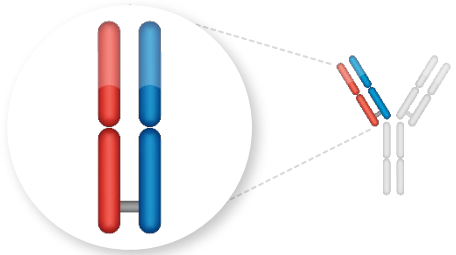
CNS, central nervous system; DMD, Duchenne muscular dystrophy.

DELIVER

Z-rostudirsen leverages the FORCE™ platform for broad delivery of an exon 51-skipping PMO to tissues impacted by DMD

ANTIBODY

Proprietary Fab against TfR1 to enable targeted delivery to muscle and CNS

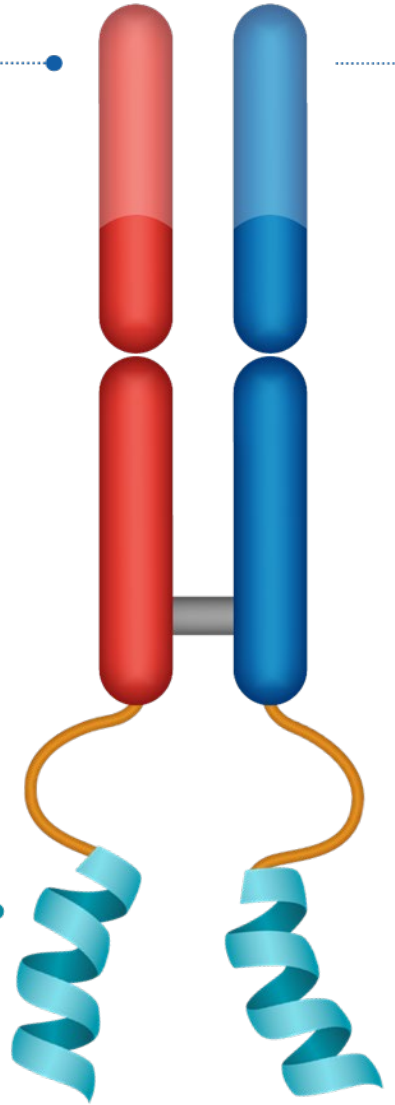


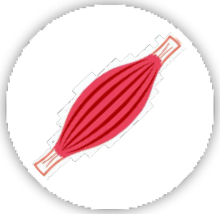
LINKER

Connects Fab and payload

PAYLOAD

Targets the genetic basis of disease





Skeletal (including diaphragm) and smooth muscle

Cardiac muscle

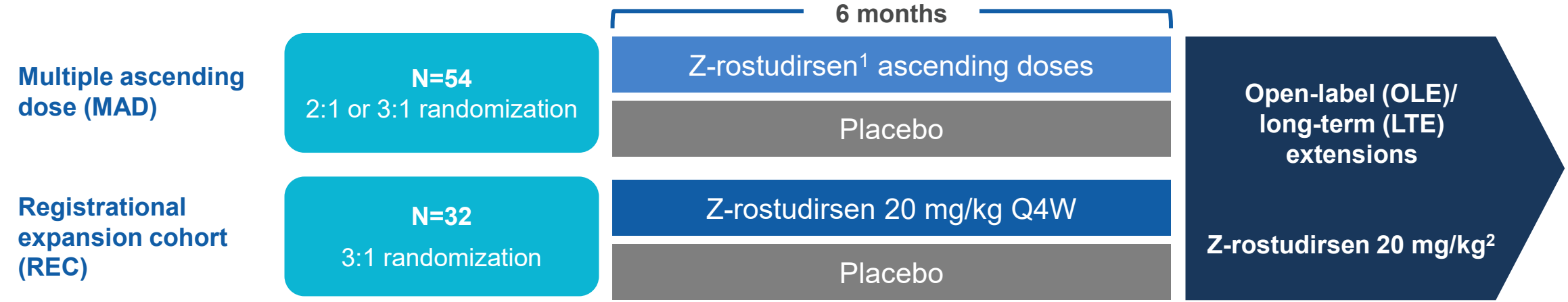
CNS

CNS, central nervous system; DMD, Duchenne muscular dystrophy; Fab, fragment antibody-binding; PMO, phosphorodiamidate morpholino oligomer; TfR1, transferrin receptor 1.

DELIVER

DELIVER study design

DELIVER (N=86)



Select inclusion/exclusion criteria

Inclusion criteria

- Ambulatory or non-ambulatory
- Age 4 to 16 years inclusive
- Stable dosage of glucocorticoids for at least 12 weeks

Exclusion criteria

- Exon-skipping/dystrophin-modifying therapy or givinostat within 12 weeks of randomization
- Gene therapy at any time

Endpoints

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

1. Z-rostudirsen doses in the MAD cohorts ranged from 0.7 mg/kg to 40 mg/kg every 4 or 8 weeks. 2. 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.

DELIVER

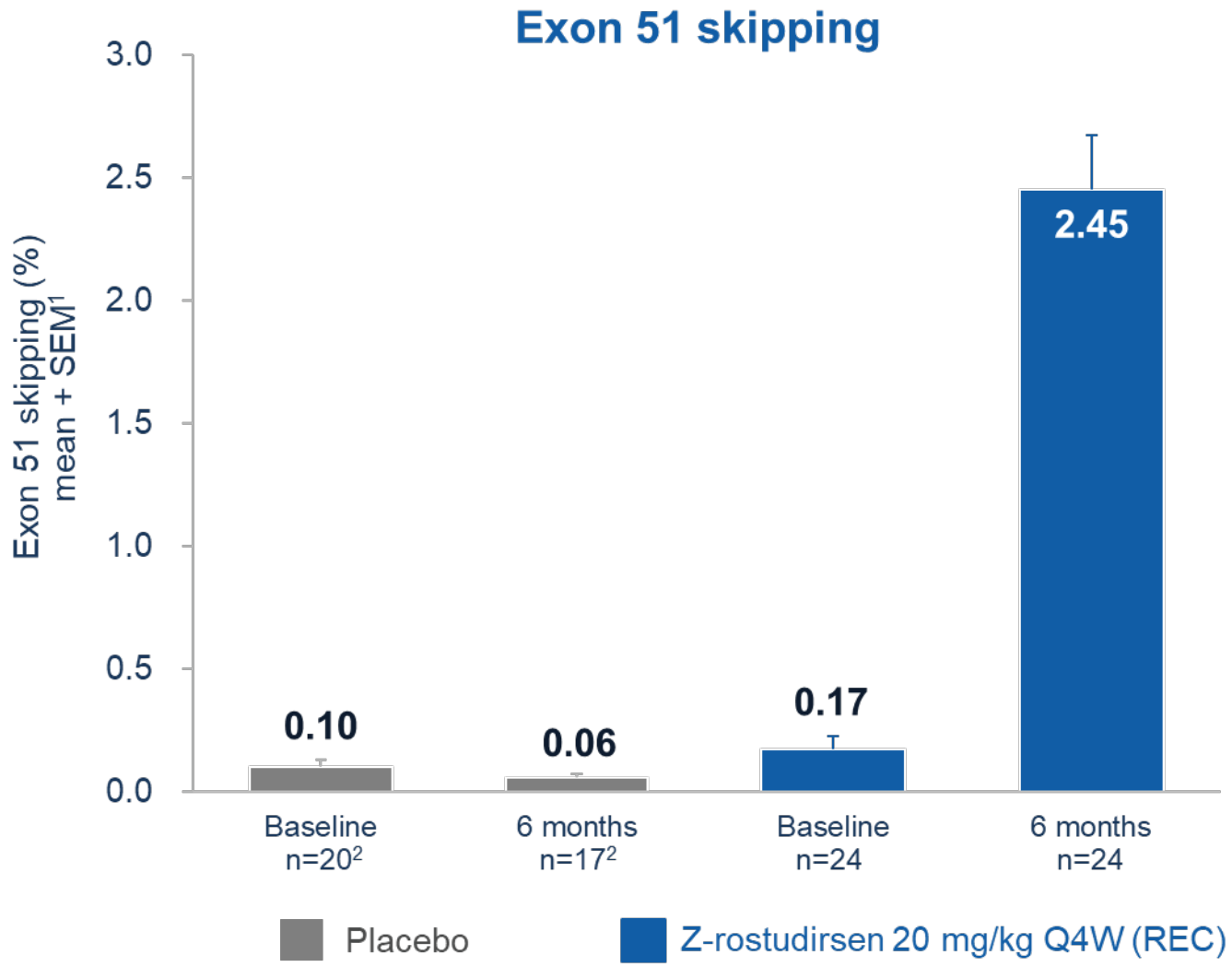
Baseline characteristics: DELIVER pooled placebo vs REC

	Placebo (MAD+REC) N=24[5] 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/m^2)	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 (%)[1] Daily Other	 20 (83.3) 4 (16.7)	 20 (83.3) 4 (16.7)
Duration of corticosteroid treatment (years)[2]	2.1 (2.4)	2.4 (2.5)
Prior DMD therapy, n (%) Eteplirsen Other	 4 (16.7) 2 (8.3)	 2 (8.3) 5 (20.8)
PUL2.0 total score[3]	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)[4]	0.20 (0.10)	0.22 (0.12)
10MWR velocity (m/sec)[4]	2.0 (0.5)	1.8 (0.5)
NSAA total score[4]	21.6 (6.3)	20.6 (5.0)
SV95C (m/sec)[4]	1.7 (0.5)	1.5 (0.4)

1. Most recent corticosteroid regimen refers to corticosteroid at time of randomization. 2. Cumulative duration of previous and most recent corticosteroid treatment at the time of randomization.
3. Missing values imputed. 4. Ambulant participants; out-of-threshold and/or missing values imputed. 5. 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; kg, kilogram; 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.

DELIVER

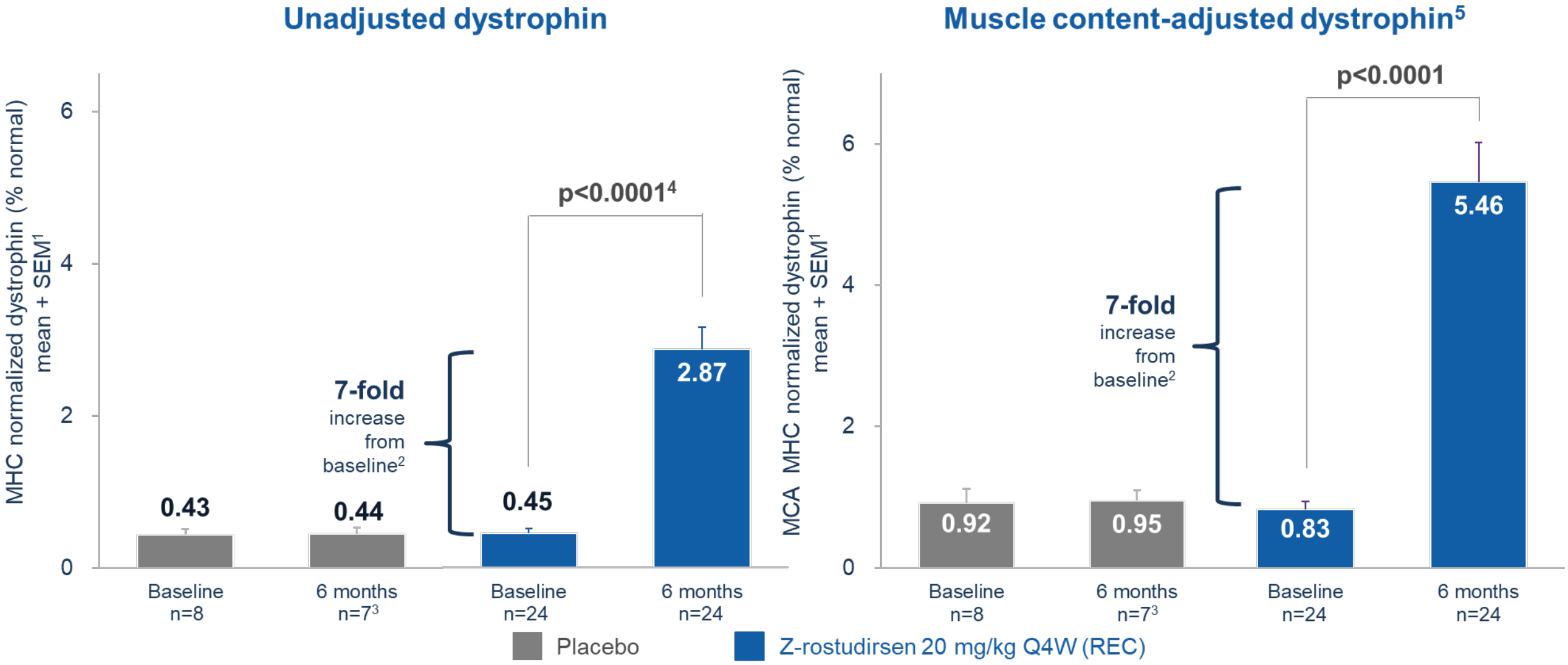
Z-rostudirsen had robust target engagement at 6 months relative to baseline



1. Biopsies taken approximately 28 days after most recent dose. 2. 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.

DELIVER

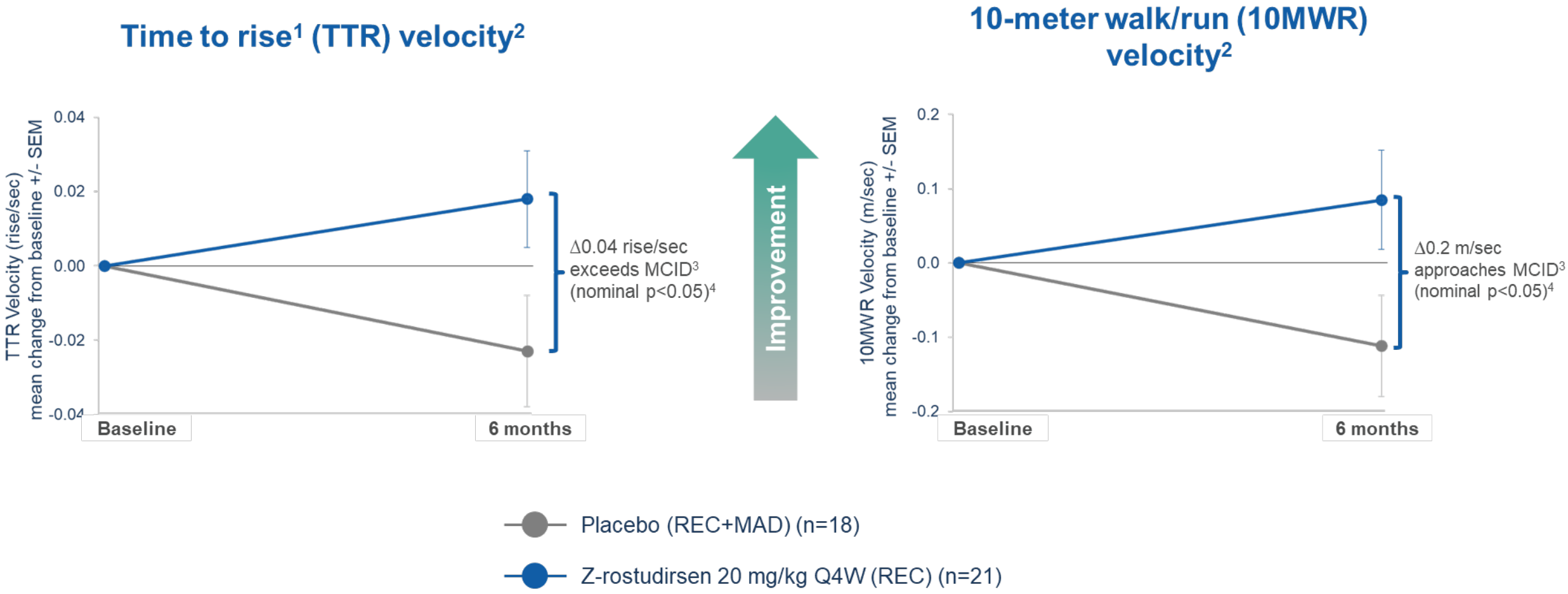
Z-rostudirsen achieved a statistically significant increase in dystrophin expression relative to baseline at 6 months



1. Biopsies taken approximately 28 days after most recent dose. 2. Based on geometric mean. 3. One REC placebo participant sample could not be analyzed at Week 25.
4. Prespecified nominal p-value with no adjustment for multiplicity. 5. 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.

DELIVER

Improvement in TTR velocity and 10MWR velocity approached or exceeded MCID relative to placebo

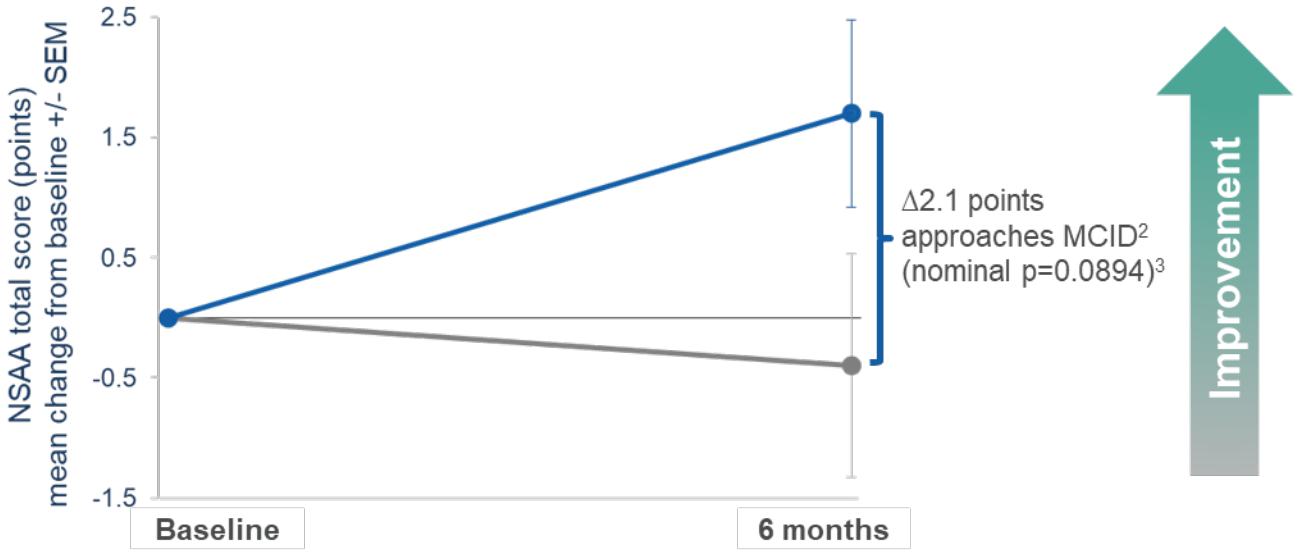


1. Also referred to as rise from floor (RFF). 2. Ambulant participants; out-of-threshold or missing values imputed. 3. Duong T, et al. *J Neuromusc Dis.* 2021;8(6):939–948;
RFF velocity MCID = 0.023 rise/sec; 10MWR velocity MCID = 0.212 m/sec. 4. Post-hoc analysis; prespecified statistical analysis plan did not include formal hypothesis testing for any functional endpoint.
6 months = 169 days. MAD, multiple ascending dose; MCID, minimal clinically important difference; Q4W, every 4 weeks; REC, registrational expansion cohort; sec, second; SEM, standard error of mean.

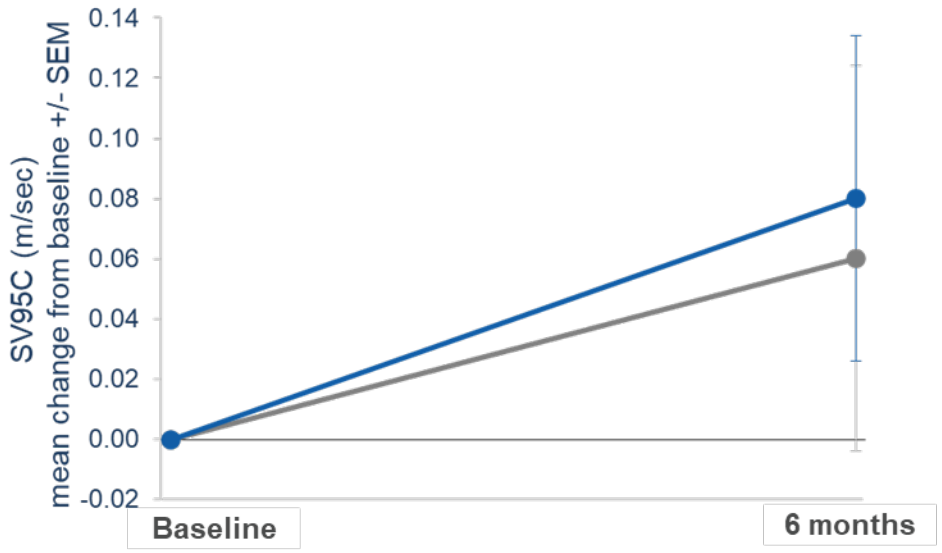
DELIVER

Treatment with z-rostudirsen led to improvement in NSAA and SV95C

North Star Ambulatory Assessment (NSAA)[1]



Stride velocity 95th centile (SV95C)[1]



Placebo (REC+MAD) (n=18)

Z-rostudirsen 20 mg/kg Q4W (REC) (n=21)

Placebo (REC+MAD)[4] (n=12)

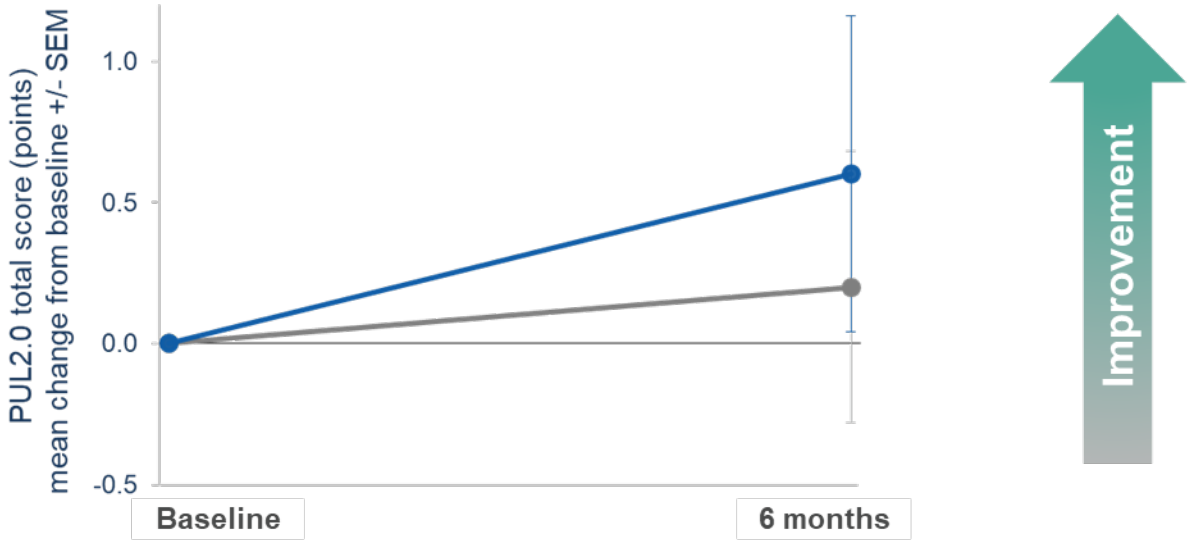
Z-rostudirsen 20 mg/kg Q4W (REC) (n=20)

1. Ambulant participants; missing values imputed. 2. Ayyar Gupta, et al. *PLoS One*. 2023;18(4):e0283669; NSAA MCID ≥2.3 points. 3. Post-hoc analysis; prespecified statistical analysis plan did not include formal hypothesis testing for any functional endpoint. 4. Placebo impacted by single participant with change from baseline of 0.46 m/sec at 6 months; if this participant were excluded, mean change from baseline at 6 months for placebo would be approximately 0.02 m/sec. 6 months = 169 days.
m, meters; MAD, multiple ascending dose; MCID, minimal clinically important difference; Q4W, every 4 weeks; REC, registrational expansion cohort; sec, second; SEM, standard error of mean.

DELIVER

Z-rostudirsen improved upper limb function and preserved lung function at 6 months

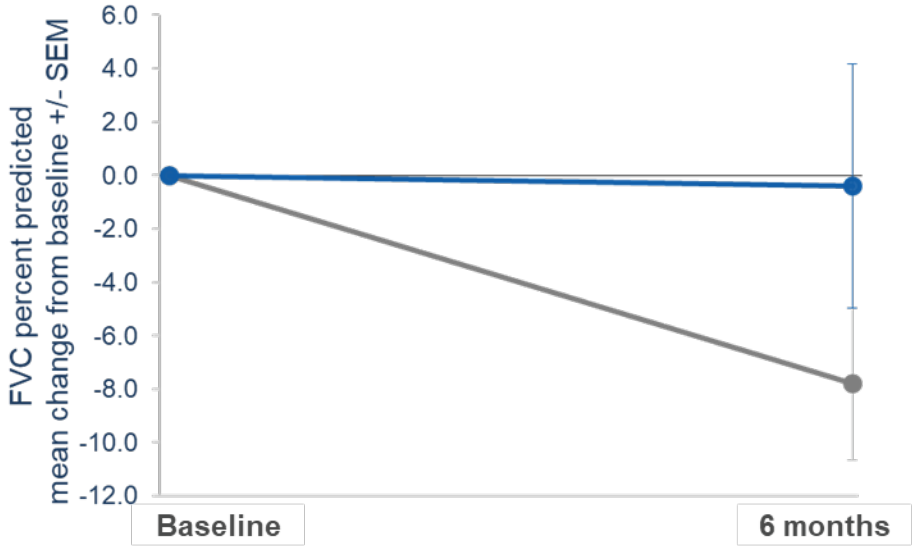
Performance upper limb v2.0 (PUL2.0)[1]



Placebo (REC+MAD) (n=23)

Z-rostudirsen 20 mg/kg Q4W (REC) (n=22)

Forced vital capacity percent predicted (FVC%p)[1]



Placebo (REC+MAD) (n=20)

Z-rostudirsen 20 mg/kg Q4W (REC) (n=15)

1. Ambulant and non-ambulant participants; missing values imputed for PUL2.0. 6 months = 169 days.
MAD, multiple ascending dose; Q4W, every 4 weeks; REC, registrational expansion cohort; SEM, standard error of mean.

DELIVER

Untreated cohorts provide a larger comparator population and may validate placebo cohort findings

- ✓ Functional improvement with z-rostudirsen vs baseline
- ✓ Functional improvement with z-rostudirsen vs placebo
- Functional improvement with z-rostudirsen vs expected disease trajectory

DELIVER

Baseline characteristics were well balanced after propensity score weighting: Ambulant z-rostudirsen vs untreated control

ActiLiège Next study:[1] Contemporaneous, ongoing natural history study collecting digital and clinic-based outcome measures

Inclusion criteria:

- Age 4–16 years
- Ambulant
- Corticosteroid treatment for ≥12 weeks
- DMD excluding mutations amenable to exon 44 skipping (ActiLiège)

BL covariates included in propensity score:[2]

- Age, height, NSAA total score, 10MWR velocity, TTR velocity, and SV95C

	Untreated control[5,6] N=60 Mean (SD) or n (%)	z-rostudirsen[6] (REC) N=21[7] Mean (SD) or n (%)
Age (years)	7.4 (2.8)	6.7 (5.4)
Height (cm)	117.5 (11.9)	117.4 (26.0)
Time since first symptom (years)	4.9 (2.8)	4.9 (5.2)
Receiving ongoing corticosteroid treatment	60 (100)	21 (100)
Duration of corticosteroid treatment (years)[3]	2.7 (2.3)	1.7 (3.4)
TTR velocity (rise/sec)[4]	0.22 (0.14)	0.23 (0.17)
10MWR velocity (m/sec)[4]	1.9 (0.6)	1.9 (0.7)
NSAA total score (points)[4]	23.1 (7.3)	21.8 (7.6)
SV95C (m/sec)[4]	1.6 (0.5)	1.6 (0.6)

1. ActiLiège Next study (ClinicalTrials.gov: NCT05982119). 2. 1/PS for z-rostudirsen and 1/(1-PS) for control were used as weight in analysis. 3. Cumulative duration of previous and most recent corticosteroid treatment at the time of randomization. 4. Ambulant participants; out-of-threshold values imputed. 5. Untreated control cohort includes a prespecified analysis of 55 ambulant participants from ActiLiège and five ambulant participants from DELIVER REC placebo. 6. Data shown are after propensity score weighting. 7. Three non-ambulant participants from the z-rostudirsen REC treatment cohort removed from analyses.

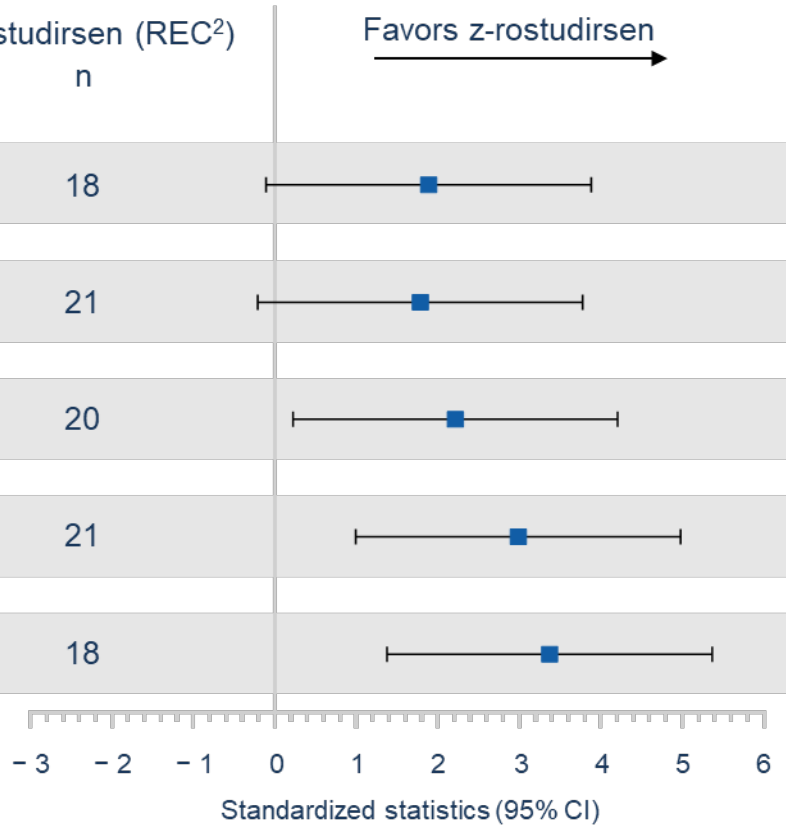
10MWR, 10-meter walk/run; BL, baseline; cm, centimeter; DMD, Duchenne muscular dystrophy; m, meters; MAD, multiple ascending dose; NH, natural history; NSAA, North Star Ambulatory Assessment; REC, registrational expansion cohort; SD, standard deviation; sec, second; SV95C, stride velocity 95th centile; TTR, time to rise.

DELIVER

Z-rostudirsen showed functional improvement at 6 months compared to a large untreated cohort across multiple clinical measures

Change from baseline at Month 6

	Untreated control[1] n	Z-rostudirsen (REC[2]) n	LSM change difference (95% CI)	p-value
TTR velocity	56	18	**0.03 rise/sec** (−0.00 to 0.05)	0.0632
10MWR velocity	59	21	**0.11 m/sec** (−0.01 to 0.23)	0.0784
SV95C	60	20	**0.09 m/sec** (0.01 to 0.18)	0.0298
NSAA	59	21	**2.0 points** (0.7 to 3.4)	0.0038
Composite score[3]	56	18	**0.32** (0.13 to 0.50)	0.0012



1. Untreated control cohort includes 55 ambulant participants from ActiLiège who met analysis inclusion criteria and five ambulant participants from DELIVER REC placebo,
2. Ambulant participants treated with z-rostudirsen in the REC. 3. Composite score: a global statistics test derived as the average of SV95C, NSAA, TTR velocity, and 10MWR velocity after standardization for each participant at each visit.
10MWR, 10-meter walk/run; CI, confidence interval; LSM, least-squares mean; m, meters; NSAA, North Star Ambulatory Assessment; REC, registrational expansion cohort; sec, second; SV95C, stride velocity 95th centile; TTR, time to rise.

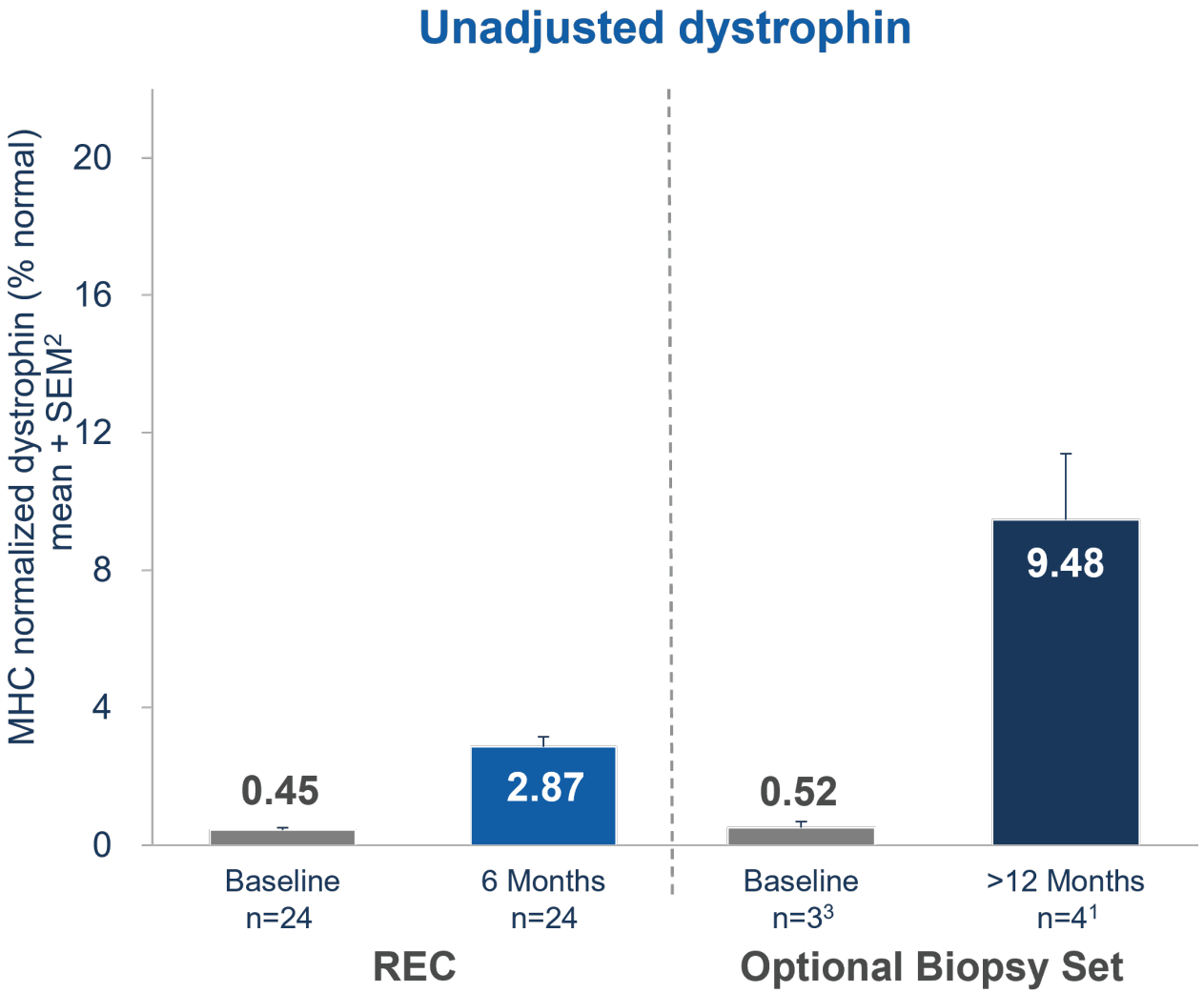
DELIVER

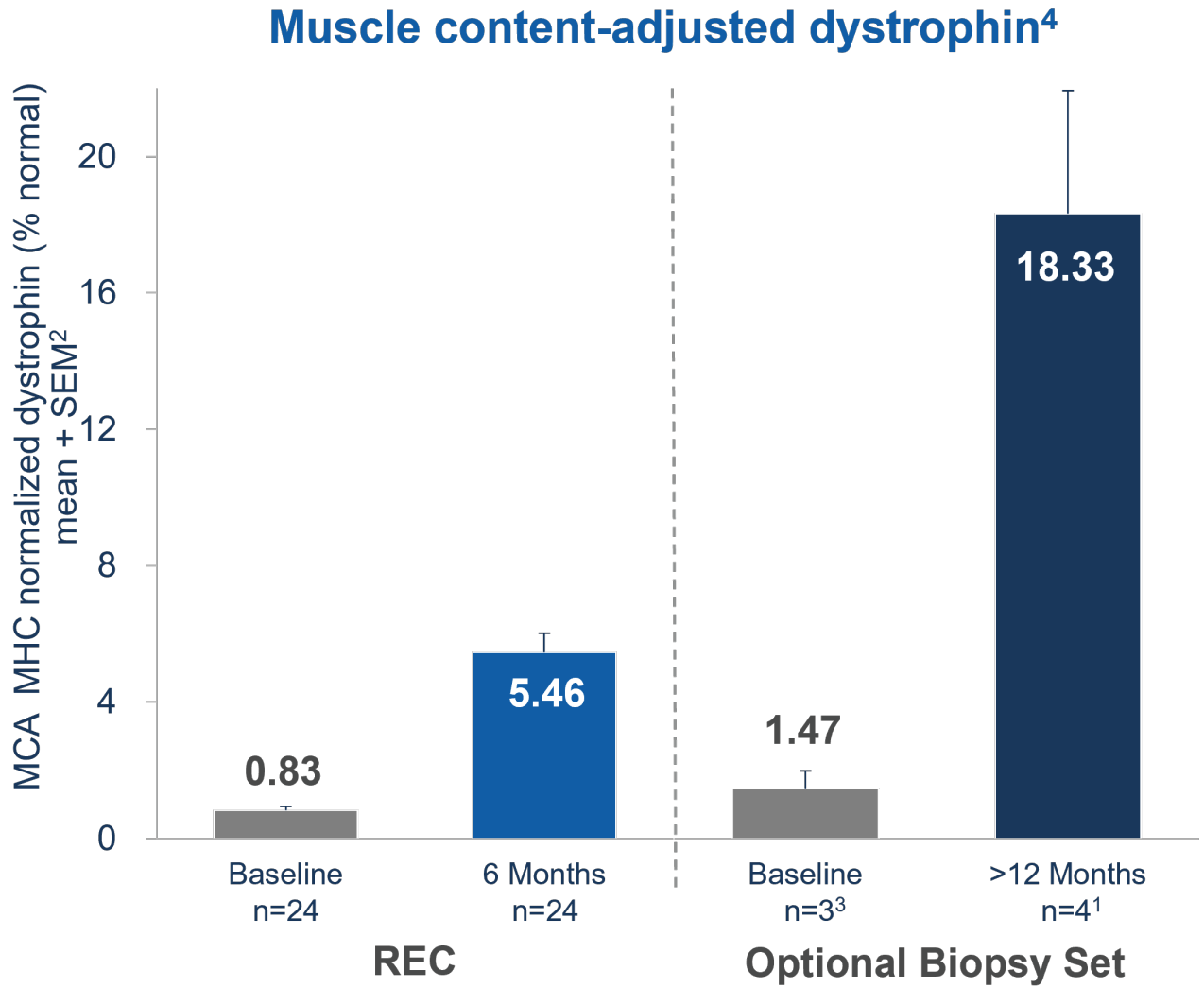
Untreated cohort validates DELIVER placebo findings

- ✓ Functional improvement with z-rostudirsen vs baseline
- ✓ Functional improvement with z-rostudirsen vs placebo
- ✓ Functional improvement with z-rostudirsen vs expected disease trajectory

DELIVER

Dystrophin levels observed in optional biopsies from participants treated with 20 mg/kg Q4W z-rostudirsen for >12M[1]





1. >12 month data reflect 4 participants who were dosed with 20 mg/kg Q4W for 67-104 weeks at the time of biopsy. This biopsy was optional per trial protocol in participants who received at least 48 weeks of 20 mg/kg Q4W z-rostudirsen treatment. The sample reported here reflects all optional biopsies collected. 2. Biopsies in REC taken approximately 28 days after most recent dose; optional biopsies taken after at least 48 weeks of 20 mg/kg Q4W z-rostudirsen treatment. 3. Baseline biopsies are pre-treatment biopsies for 3 participants with >12M optional biopsies. One participant with a >12M optional biopsy did not have a baseline biopsy. 4. Muscle content-adjusted dystrophin = MHC normalized dystrophin / % muscle content. 6 months = Week 25 for DELIVER; > 12M = Greater than 48 weeks. REC, registrational expansion cohort; MCA, muscle content-adjusted; MHC, myosin heavy chain; Q4W, every 4 weeks; SEM, standard error of the mean.

DELIVER

Safety profile of z-rostudirsen 20 mg/kg Q4W remains favorable

Summary of treatment-emergent adverse events (TEAEs)[1]

Study period	Placebo-controlled (PC) period (0 to 6M)		All study periods (0 to ≤36M)
Participants with ≥1 TEAE – n (%)	Placebo (MAD+REC) N=24[2]	Z-rostudirsen 20 mg/kg Q4W (MAD+REC) N=30[3]	Z-rostudirsen Pooled doses[4] (MAD+REC) N=85[5]
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[6]
- 2 participants at 40 mg/kg Q4W
  - Acute kidney injury; thrombocytopenia[7]
  - Pancytopenia[8]

Most frequent related TEAEs ≥10%[9]

- Pyrexia (fever) (18%)
- Headache (13%)

Additional safety data at 20 mg/kg Q4W

- No participants have persistent related anemia[10] or thrombocytopenia

1441 doses of z-rostudirsen administered to date representing 113 patient-years of follow-up (up to 36 months)[1]
1062 doses of z-rostudirsen at 20 mg/kg dose level administered to date[1]

1. Data as of August 19, 2025; all participants, placebo-controlled period, OLE, and LTE. 2. All placebo participants pooled from MAD and REC. 3. All participants randomized to z-rostudirsen 20 mg/kg Q4W in MAD and REC cohorts. 4. 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. 5. One participant randomized to placebo in REC not yet dosed with z-rostudirsen as of August 19, 2025. 6. 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. 7. 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. 8. Participant has a history of hemolytic anemia of unidentified etiology; presented with fever and tonsilitis; symptoms resolved without therapeutic intervention. 9. All cohorts combined; preferred terms reported. 10. No participants have persistent related anemia with Hgb levels <11.2 g/dL (threshold for anemia in children (ref: Powers JM. Approach to the child with anemia. UpToDate, Connor RF (Ed), Wolters Kluwer. Accessed December 2, 2025).
Hgb, hemoglobin; LTE, long-term extension; M, months; MAD, multiple ascending dose; OLE, open-label extension; Q4W, every 4 weeks; REC, registrational expansion cohort.

DELIVER

Conclusions

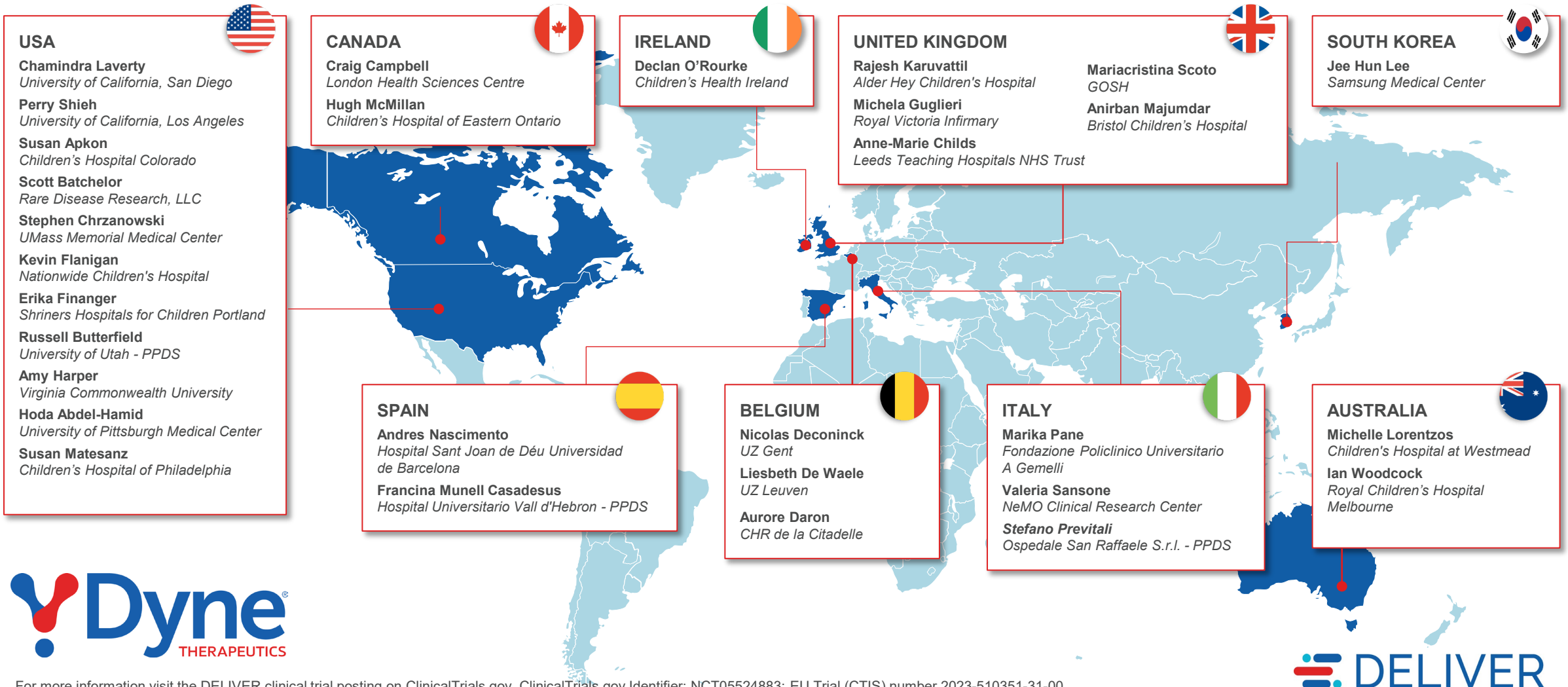
- At the registrational dose (20 mg/kg Q4W), z-rostudirsen demonstrated a statistically significant increase in mean muscle content-adjusted dystrophin at 6 months compared to baseline
- At 6 months, functional improvement was observed across multiple clinical measures of muscle function, suggesting 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
  - Comparison with propensity score-weighted untreated control is consistent with functional improvement observed with z-rostudirsen treatment relative to placebo
- Optional biopsies collected from 4 participants showed a further increase in dystrophin levels after at least 12 months of treatment at 20 mg/kg Q4W
- Z-rostudirsen demonstrated a favorable safety and tolerability profile in participants enrolled in DELIVER and followed for up to 36 months[1]
- 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

1. As of August 19, 2025.

DELIVER

Acknowledgments

DELIVER participants and their families



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For more information visit the DELIVER clinical trial posting on ClinicalTrials.gov. ClinicalTrials.gov Identifier: NCT05524883; EU Trial (CTIS) number 2023-510351-31-00.