PP01.71

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

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Additional data from DELIVER primary analysis

Comparison with propensity score-weighted untreated control

Baseline characteristics 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)

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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.

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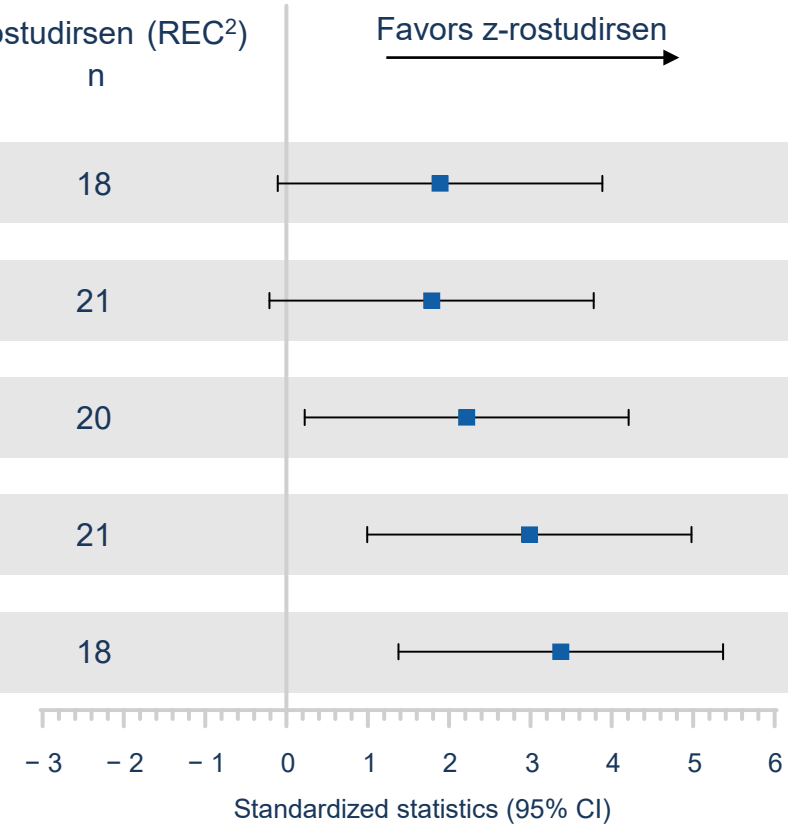
Z-rostudirsen showed functional improvement at 6 months compared to a large untreated cohort across multiple clinical measures

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



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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.

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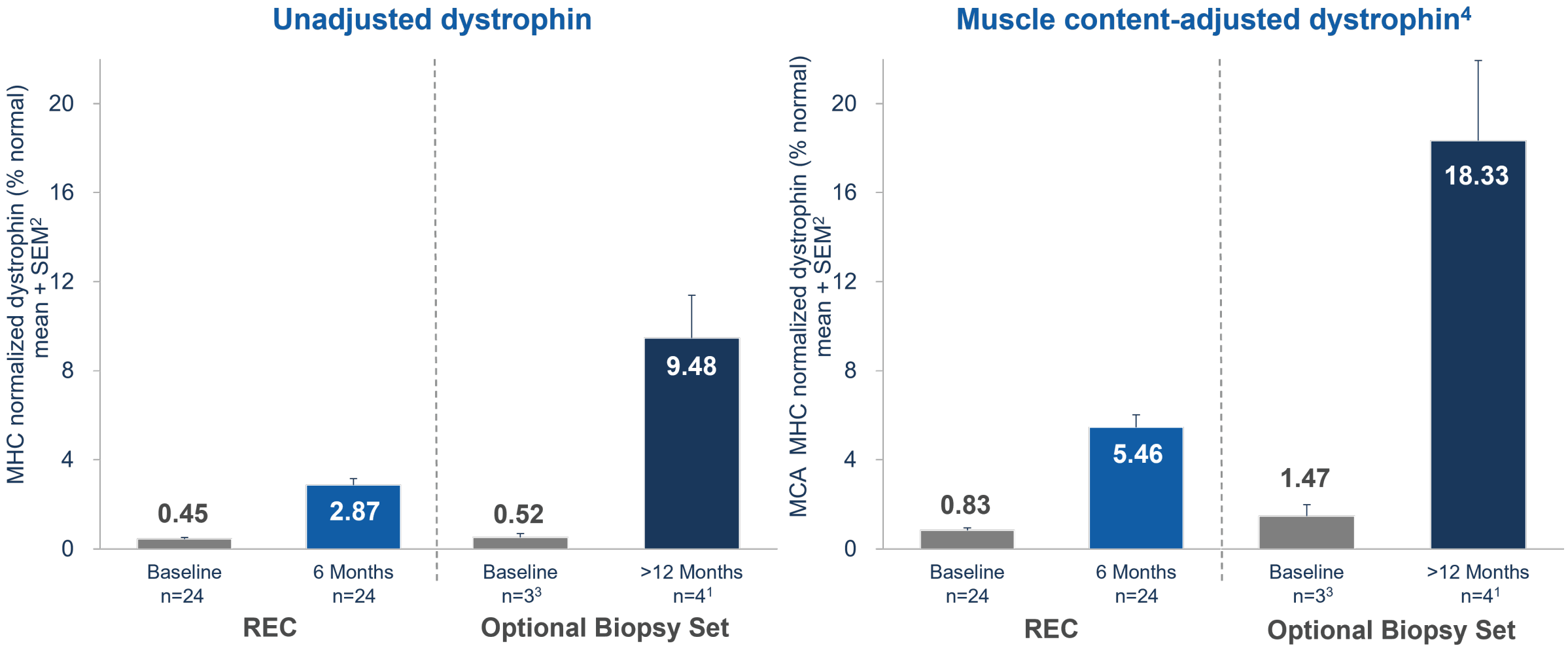
Additional data from DELIVER primary analysis

Long-term dystrophin and functional outcomes data

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



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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

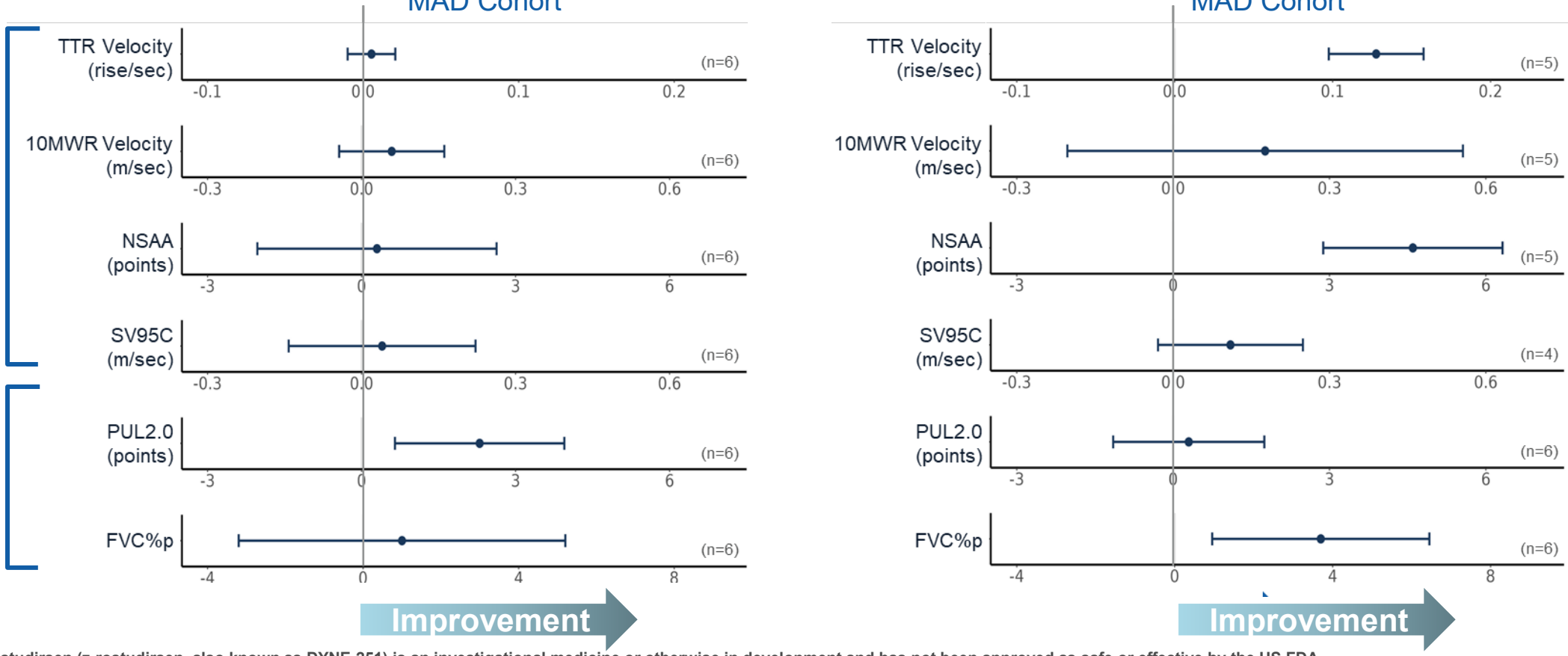
Functional improvement compared with baseline across all 6 measures up to 24 months in the OLE/LTE

18-month CFB[1]
20 mg/kg Q4W
MAD Cohort

24-month CFB[1]
10 → 20 mg/kg Q4W[2]
MAD Cohort

Ambulatory participants

Ambulatory & non-ambulatory participants



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1. Mean change from baseline +/- SEM; TTR velocity, 10MWR velocity, NSAA, and SV95C analyzed from ambulant participants; PUL2.0 and FVC%p analyzed from ambulant and non-ambulant participants; Out-of-threshold and/or missing values imputed except for FVC%p. 2. Participants transitioned from 10 mg/kg Q4W to 20 mg/kg Q4W after 6M; all participants treated with 20 mg/kg Q4W for at least 12M in the 24M assessment.

10MWR, 10-meter walk/run; CFB, change from baseline; FVC%p, forced vital capacity percent predicted; LTE, long-term extension; m, meters; MAD, multiple ascending dose; NSAA, North Star Ambulatory Assessment; OLE, open-label extension; PUL2.0, performance upper limb v2.0; Q4W, every 4 weeks; sec, second; SEM, standard error of the mean; SV95C, stride velocity 95th centile; TTR, time to rise.

DELIVER

Interpreting effects of dose escalation over time in a MAD study

Each time point represents a group of participants at varied dose levels and duration	
Dose levels	Since doses were escalated sequentially, later timepoints are enriched with participants starting at low doses and who may have dose escalated through multiple doses
Dose duration	Each timepoint reflects a group of participants with varying amounts of time on any specific dose

Implications
Because most participants accrued substantial time on doses lower than 20 mg/kg Q4W prior to escalation, the observed long-term efficacy does not reflect the effect of continuously maintaining 20 mg/kg Q4W and may be an underestimate of the true effect

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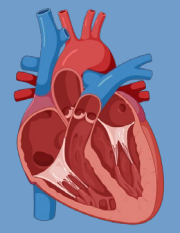
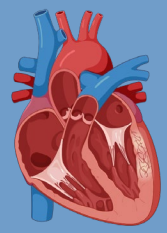
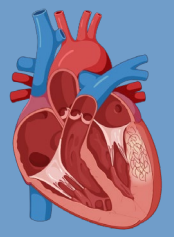
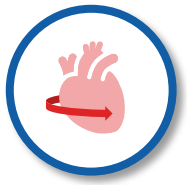
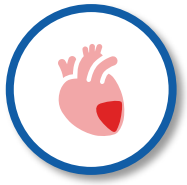
MAD, multiple ascending dose; Q4W, every 4 weeks.

DELIVER

CMR can detect early cardiac dysfunction and is the gold standard for assessing systolic function in DMD[1–3]

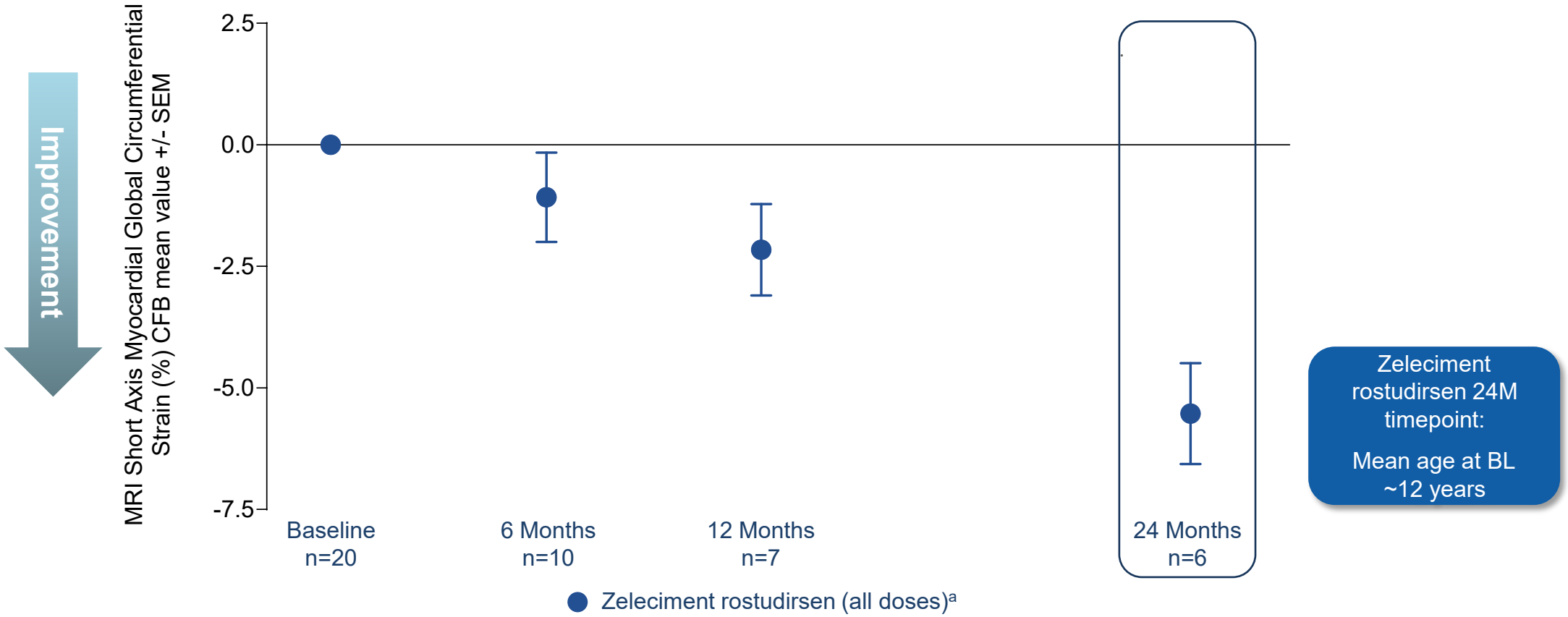
	Measure	Utility in DMD	Typical values		
			Healthy controls[4] 	DMD (Normal EF)[4] 	DMD (Reduced EF)[4] 
 **CMR-based global circumferential strain (GCS or εcc)**	Deformation of myocardial tissue in the circular plane as the heart wall contracts vs resting length[1,5]	An early marker that detects occult dysfunction before fibrosis (as detected by LGE) or EF decline is evident[1,6,7]	–17 to –21%[6]	–10 to –16%[6]	–5 to –12%[6]
			Magnitude of GCS reduces as disease progresses (negative value = relative shortening)[8]		
 **CMR-based left ventricular ejection fraction (LVEF)**	Stroke volume relative to the end-diastolic volume; reflecting LV systolic function[9]	Reflects LV systolic function; CMR allows for reproducible assessment[9,10]	~65 to ~70%[1,11]	>55%[1,6,7]	<55%[6]
			LVEF reduces as disease progresses		

εcc, circumferential strain; CMR, cardiac magnetic resonance; DMD, Duchenne muscular dystrophy; GCS, global circumferential strain; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction. DMD heart disease progression figures created in BioRender.

1. Batra A, et al. *BMC Cardiovasc Disord*. 2022;22(1):260; 2. Tseng WY, et al. *Acta Cardiol Sin*. 2016;32(2):129–144; 3. Ponikowski P, et al. *Eur Heart J*. 2016;37(27):2129–2200;
4. Kamdar F, Garry DJ. *J Am Coll Cardiol*. 2016;67(21):2533–2546; 5. Voigt JU, Cvijic M. *JACC Cardiovasc Imaging*. 2019;12(9):1849–1863; 6. Hor KN, et al. *J Am Coll Cardiol*. 2009;53(14):1204–1210;
7. Hor KN, et al. *J Cardiovasc Magn Reson*. 2011;13(1):60; 8. Duncan AE. *Anesth Analg*. 2015;121(6):1422–1424; 9. Vancheri F, et al. *Front Cardiovasc Med*. 2024;11:1340708;
10. Krittayaphong R, et al. *J Am Heart Assoc*. 2025;14(8):e039889; 11. van der Ven JPG, et al. *Eur Heart J Cardiovasc Imaging*. 2020;21(1):102–113.

DELIVER

CMR-based circumferential strain in zeleciment rostudirsen-treated participants



- The majority of participants at the 24M timepoint initiated treatment at the 0.7–2.8 mg/kg Q4W dose levels. One participant initiated treatment at 20 mg/kg Q4W
- All participants at the 24M timepoint received 20 mg/kg Q4W zeleciment rostudirsen for ≥6 months
- Natural history: ~1% annual increase in circumferential strain[1,2]

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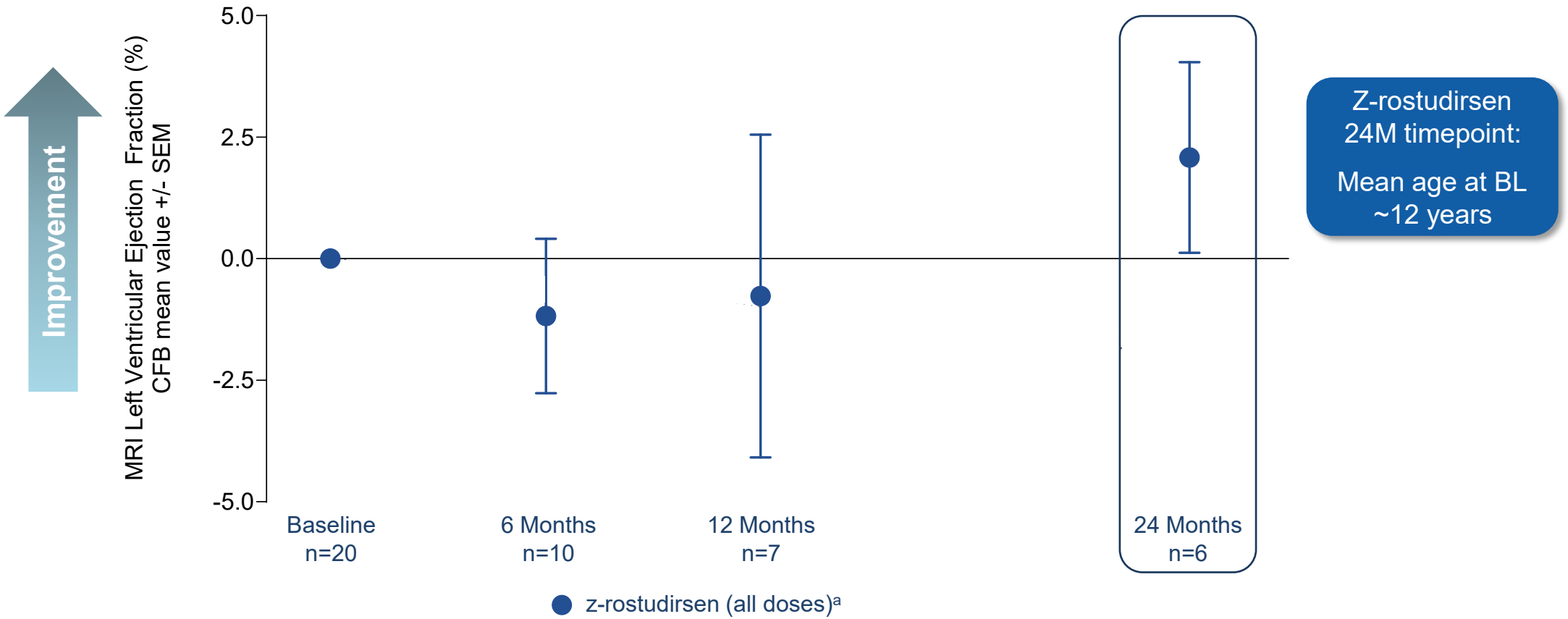
Results are reported as mean CFB through 24 months and presented with SEM. a. Shown are all DELIVER participants (REC + MAD) randomized to z-rostudirsen treatment at baseline (any dose, including dose escalation[s] or de-escalation) and for whom circumferential strain data were available. BL, baseline; CFB, change from baseline; CMR, cardiac magnetic resonance; MAD, multiple ascending dose; MRI, magnetic resonance imaging; NH, natural history; REC, registrational expansion cohort; SEM, standard error of the mean.

1. Batra A, et al. *BMC Cardiovasc Disord.* 2022;22:260, *2.* Hagenbuch SC, et al. *Am J Cardiol.* 2010;105:1451–1455.

DELIVER

CMR-based left ventricular ejection fraction in z-rostudirsen-treated participants



- The majority of participants at the 24M timepoint initiated treatment at the 0.7–2.8 mg/kg Q4W dose levels. One participant initiated treatment at 20 mg/kg Q4W
- All participants at the 24M timepoint received 20 mg/kg Q4W z-rostudirsen for ≥6 months
- Natural history: ~1% annual decline in LVEF[1,2]

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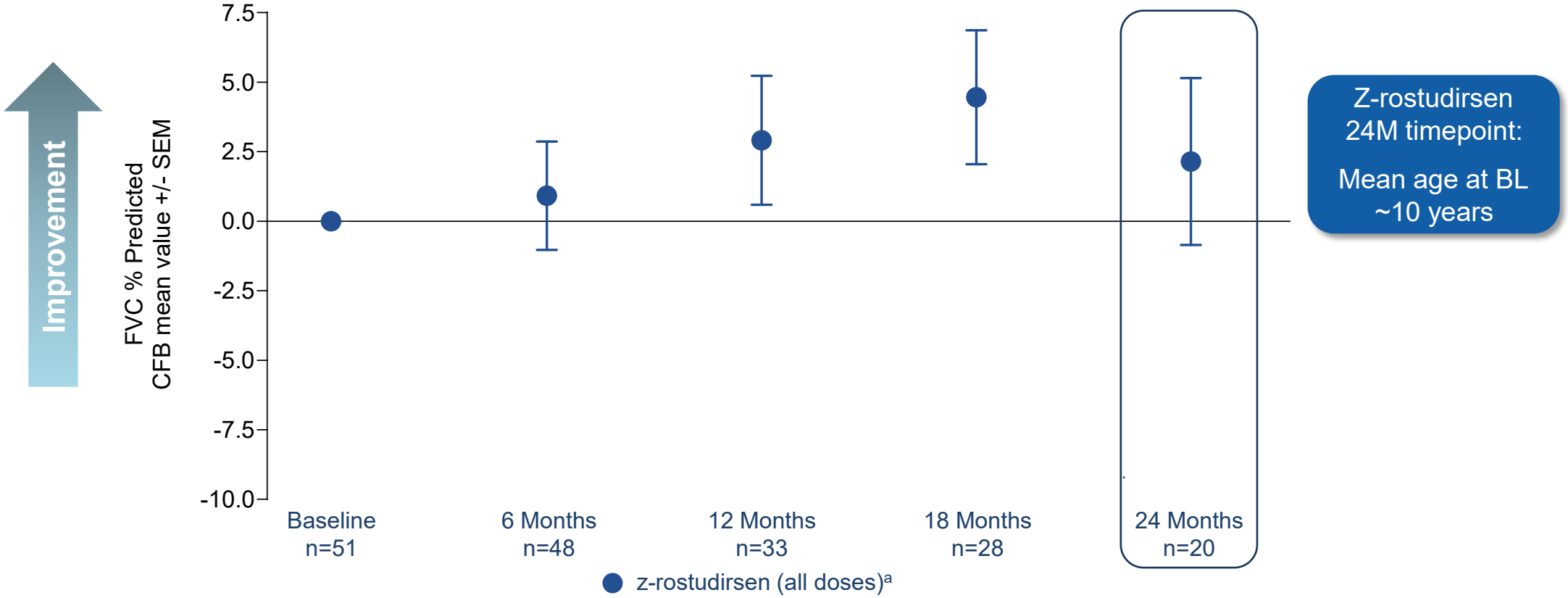
1. Batra A, et al. *BMC Cardiovasc Disord.* 2022;22:260, 2. Hagenbuch SC, et al. *Am J Cardiol.* 2010;105:1451–1455.

DELIVER

Long-term lung function with z-rostudirsen



- The majority of participants at the 24M timepoint initiated treatment at the 0.7–2.8 mg/kg Q4W dose levels. One participant initiated treatment at 20 mg/kg Q4W
- All participants at the 24M timepoint received 20 mg/kg Q4W z-rostudirsen for ≥9 months
- Natural history: ~5% annual FVC%p decline

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1. Mayer OH, et al. *Pediatr Pulmonol.* 2015;50:487–494; 2. McDonald CM, et al. *Neuromuscul Disord.* 2018;28:897–909; 3. Meier T, et al. *Neuromuscul Disord.* 2017;27:307–314.

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