

Zeleciment Basivarsen Targets the Underlying Cause of Myotonic Dystrophy Type 1 (DM1) to Enable Functional Improvement in the Phase 1/2 ACHIEVE Trial

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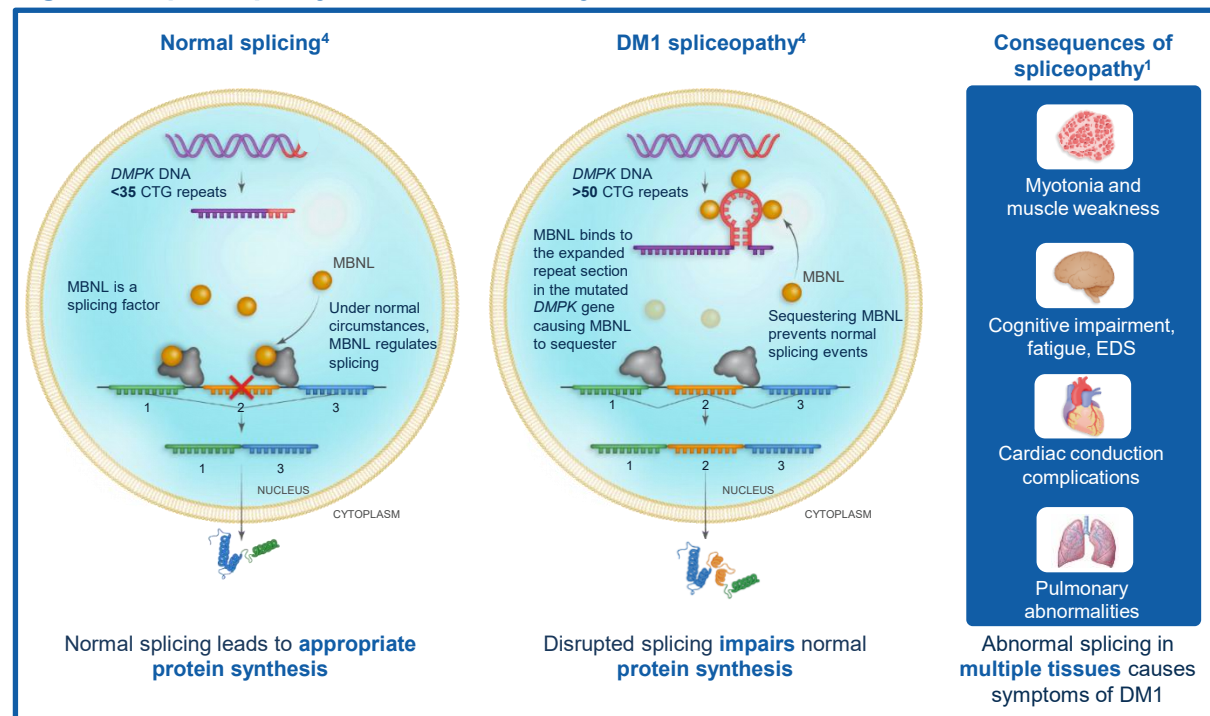
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BACKGROUND

- Myotonic dystrophy type 1 (DM1) is a rare neuromuscular disorder with multisystem presentation. It is caused by expansion of CTG repeats in the 3' untranslated region (3'UTR) of the dystrophin myotonia protein kinase (*DMPK*) gene. mRNA transcribed from the mutated gene forms hairpin-loop structures that sequester splicing regulators into toxic nuclear foci. This leads to widespread dysregulation of RNA splicing (spliceopathy) that drives the multisystemic clinical manifestations.¹⁻³

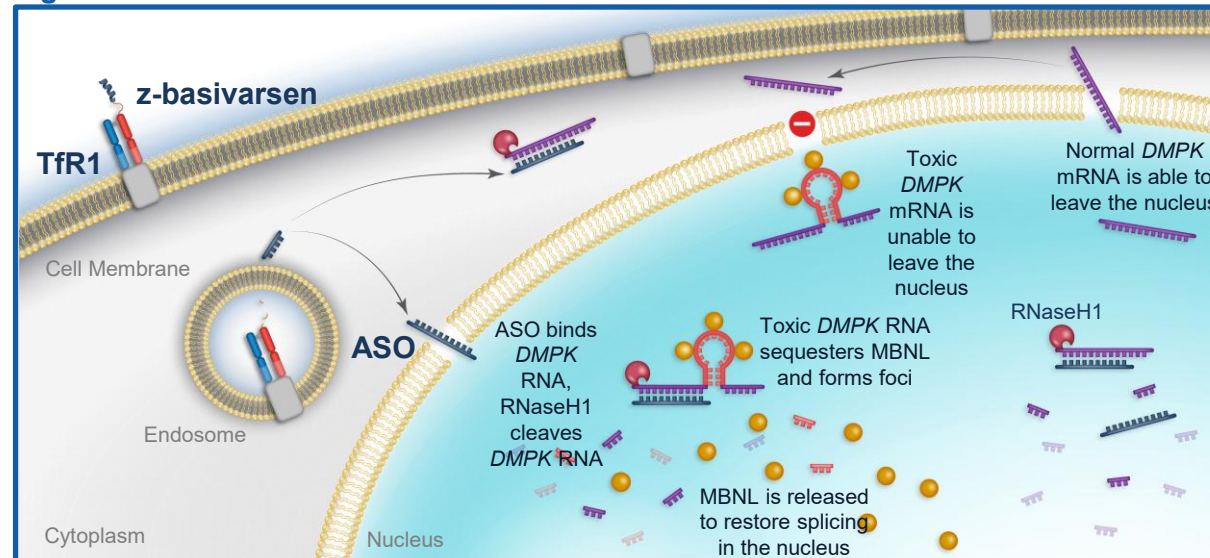
Figure 1. Spliceopathy Results in Multisystem Manifestations in DM1



CTG, cytosine, thymine, and guanine; DM1, myotonic dystrophy type 1; DMPK dystrophin myotonia protein kinase; EDS, excessive daytime sleepiness; MBNL, muscleblind-like.

- The clinical burden of DM1 is accompanied by an economic burden as individuals with DM1 have 137% higher annual healthcare costs and a 53% higher hospitalization rates compared with those without DM1,⁵ and 46% are unable to work.⁶
- No disease-modifying therapies are available, limiting treatment to symptom management.⁷
- Zeleciment basivarsen (z-basivarsen, also known as DYNE-101), an investigational therapeutic for treatment of DM1, consists of an antigen-binding fragment (Fab) that targets the transferrin receptor 1 (TFR1) conjugated to an antisense oligonucleotide (ASO) designed against mutant nuclear *DMPK* mRNA to correct splicing.⁸

Figure 2. Zeleciment Basivarsen Mechanism of Action



ASO, antisense oligonucleotide; DMPK, dystrophin myotonia protein kinase; MBNL, muscleblind-like; TFR1, transferrin receptor 1. Image depicts intended mechanism of action of z-basivarsen.

- The safety and efficacy of z-basivarsen are being investigated in the Phase 1/2 ACHIEVE trial (NCT05481879; EudraCT number 2022-000889-18).^{9,10}
- Data from this study have previously shown dose-dependent muscle delivery of z-basivarsen, consistent *DMPK* knockdown and splicing correction, and meaningful improvements in multiple functional endpoints, as well as improvements in patient-reported outcome (PRO) measures.¹⁰

METHODS

- ACHIEVE is a global, randomized, placebo-controlled study evaluating every 8 weeks (Q8W) or more frequent intravenous administrations of z-basivarsen in adults (18–49 years) with DM1. It consists of a multiple ascending dose (MAD) period (24 weeks), an open-label extension (OLE) period (24 weeks), and a long-term extension (LTE) period (96 weeks).^{9,10}
 - In the MAD portion of ACHIEVE:
 - 56 participants received z-basivarsen across five different ASO-equivalent doses/dose regimen cohorts (1.8 mg/kg every 4 weeks [Q4W], 3.4 mg/kg Q4W or Q8W, 5.4 mg/kg Q8W, and 6.8 mg/kg Q8W).^{9,10}
 - The primary endpoints were safety and tolerability.^{9,10} Additional endpoints included pharmacokinetics and pharmacodynamics, multiple assessments of muscle strength and function, myotonia, and PROs, including Myotonic Dystrophy Health Index (MDHI).^{9,10}
 - Based on safety and efficacy data collected in the MAD portion, 6.8 mg/kg Q8W was selected as the dose/dose regimen for the registrational expansion cohort of ACHIEVE.
 - Here we present 12-month data with the 6.8 mg/kg Q8W dose in participants who were enrolled in the MAD portion of ACHIEVE through 6.8 mg/kg Q8W.

RESULTS

Table 1. Baseline Characteristics

	Mean (SD)	Placebo (N=14)	6.8 mg/kg Q8W (N=6)
Age (years)		32.6 (9.6)	37.2 (9.7)
BMI (kg/m ²)		24.4 (4.7)	23.4 (5.6)
CASI-22		0.68 (0.20)	0.74 (0.25)
CTG repeats		597 (246)	542 (191)
vHOT (middle finger) (sec)		7.5 (3.0)	7.8 (3.8)
QMT total (% predicted)		51.5 (14.3)	51.3 (10.4)
10-meter walk/run (sec)		3.34 (0.48)	3.94 (1.56)
5 times sit-to-stand (sec)		9.24 (2.03)	9.98 (3.33)
MDHI total ^a		18.7 (13.8)	26.5 (13.7)
9-hole peg test (sec)		19.5 (2.54)	19.1 (2.41)

^aScored from 0–100, with 0 representing no disease burden, 100 maximal disease burden.

BMI, body mass index; CASI, composite alternative splicing index; CTG, cytosine, thymine, and guanine; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks; QMT, quantitative muscle testing; SD, standard deviation; sec, seconds; vHOT, video hand opening time.

Table 2. Summary of TEAEs

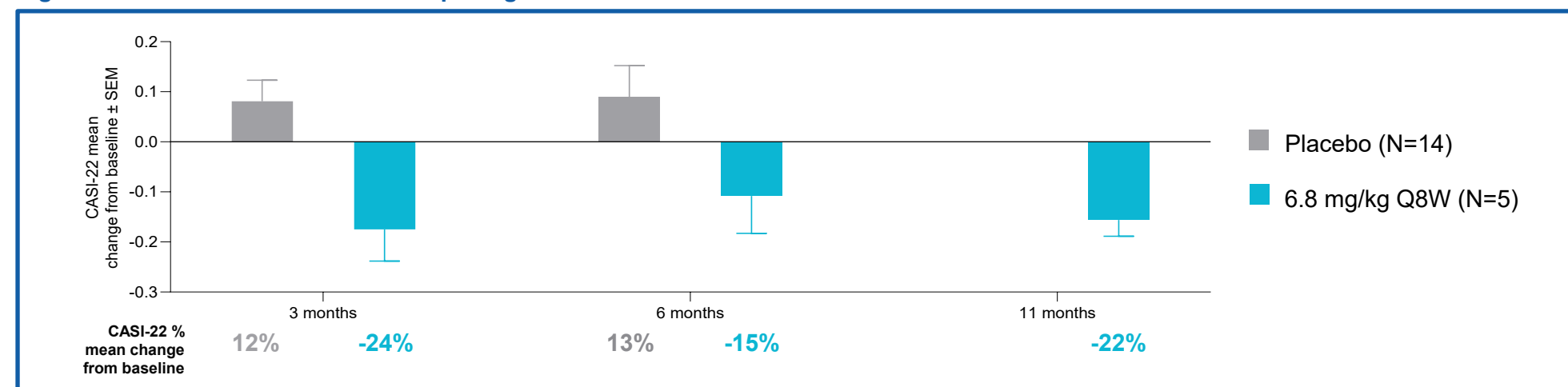
TEAE category	Participants with ≥1 TEAE – n (%)				
	1.8 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q8W N=8	5.4 mg/kg Q8W N=8	6.8 mg/kg Q8W N=8
Any TEAE	16 (100)	16 (100)	8 (100)	8 (100)	8 (100)
Any related TEAE	9 (56)	10 (63)	3 (38)	6 (75)	6 (75)
Any serious TEAE	4 (25)	0	1 (13)	0	0
Any serious related TEAE	0	0	0	0	0
Any TEAE leading to withdrawal from study	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0

Data as of April 23, 2025. Q4W, every 4 weeks; Q8W, every 8 weeks; Rec, recovery; TEAE, treatment-emergent adverse event.

- Six serious treatment-emergent adverse events (TEAEs) unrelated to study drug:
 - Atrioventricular (AV) block first degree (1)^a
 - Pneumonia (two events in same participant)
 - Pulmonary embolism (1)^b
 - Hyponatremia (1)
 - Influenza (1)
- Most common TEAEs (≥20% participant incidence):^c
 - Nasopharyngitis (41%)
 - Procedural pain (34%)
 - Influenza (30%)
 - Infusion-related reaction (29%)
 - Headache (27%)
 - Diarrhea (23%)
- Liver enzyme elevations have been observed in a minority of participants:
 - No impact on liver function (bilirubin or coagulation)
 - Interpretation is complicated by underlying disease and elevated baseline values up to ~2.5× greater than the upper limit of normal
- No participants have demonstrated persistent related anemia or thrombocytopenia

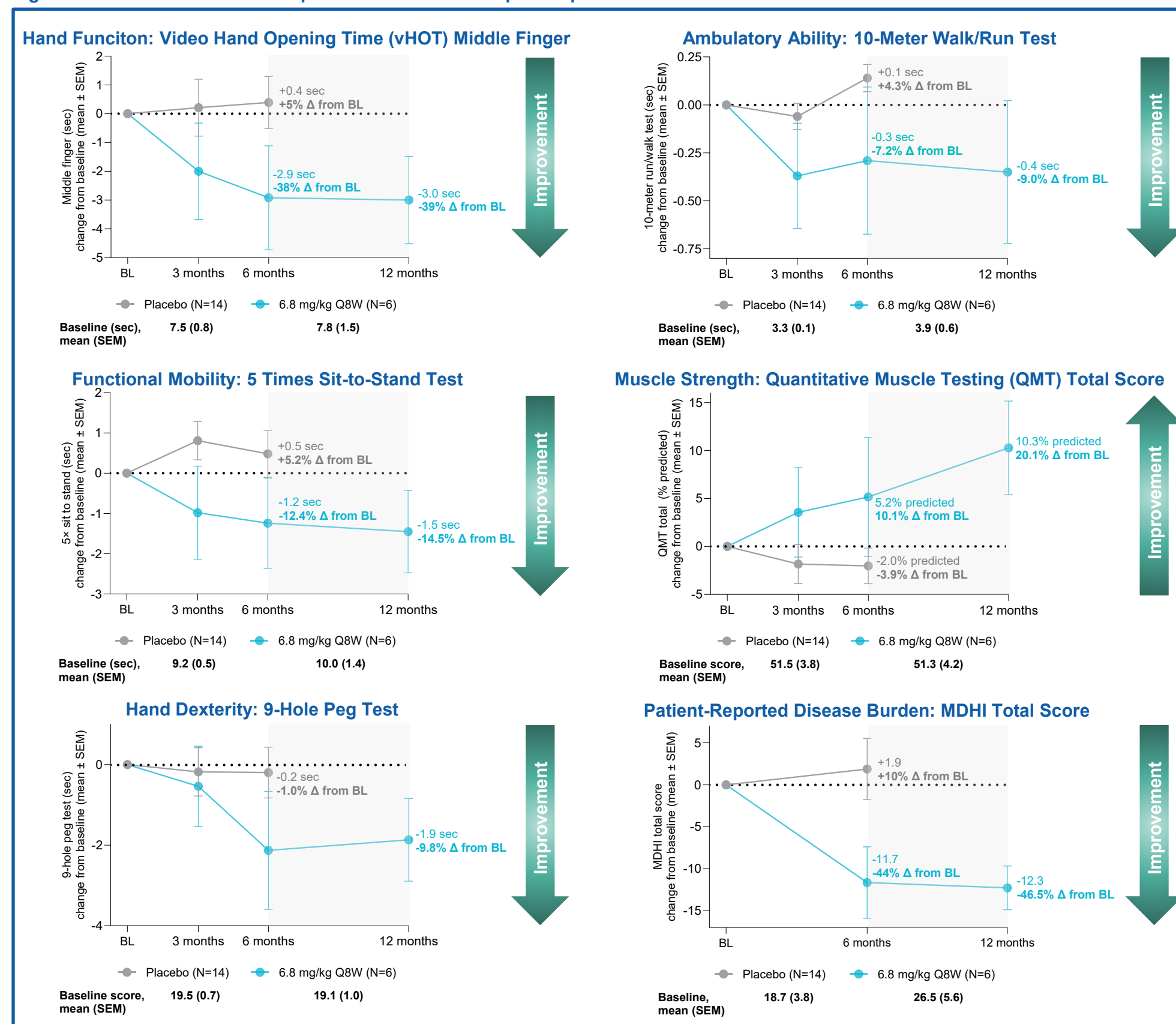
^aTransient worsening of AV block in a participant with ongoing medical history of first-degree AV block; ^bAttributed to risk factors for pulmonary embolism; ^cAll cohorts combined; preferred terms are reported.

Figure 3. Consistent and Sustained Splicing Correction with Z-Basivarsen



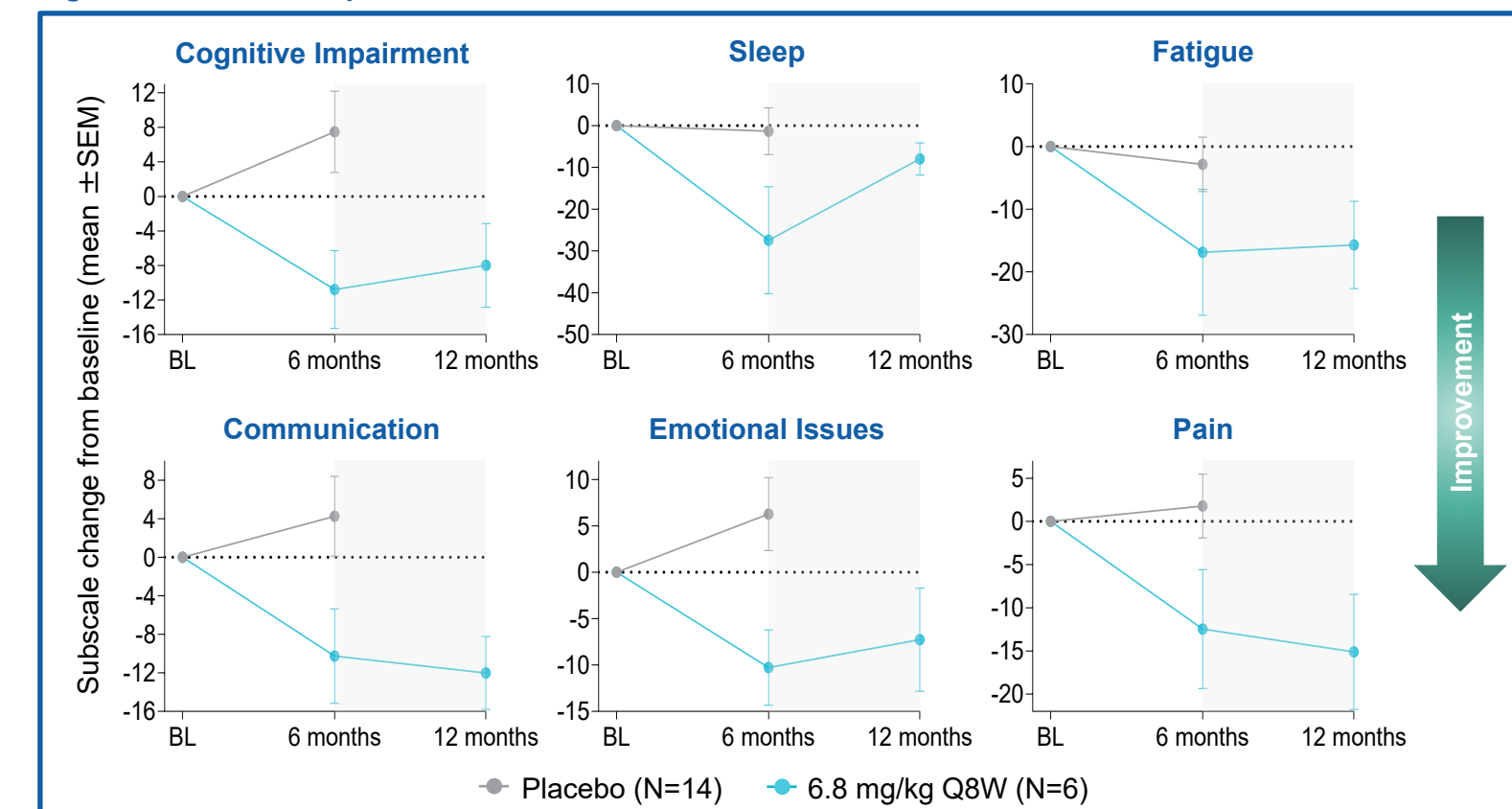
All patients transitioned to treatment at Month 6. Multiple aliquot approach, all aliquots are tested and median taken across those with valid results, up to 4. One baseline sample in 6.8 mg/kg treatment groups not included within splicing assay as the sample did not meet QC criteria. Percent mean change, calculated as mean change from baseline divided by baseline mean. 3 months = 85 days; 6 months = 169 days; 11 months = 337 days. CASI, composite alternative splicing index; QC, quality control; Q8W, every 8 weeks dosing; SEM, standard error of the mean.

Figure 4. Sustained Functional Improvement Across Multiple Endpoints with Z-Basivarsen



vHOT Middle Finger (sec) is the average of all myotonia trials for an individual participant in ACHIEVE. 3 months = 85 days; 6 months = 169 days; 12 months = 337 days. BL, baseline; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks dosing; sec, seconds; SEM, standard error of the mean.

Figure 5. Sustained Improvement in CNS-related MDHI Subscales with Z-Basivarsen



PROs including MDHI collected at baseline, 6 months (169 days), and 12 months (337 days). BL, baseline; CNS, central nervous system; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks dosing; PRO, patient-reported outcome; SEM, standard error of the mean.

CONCLUSIONS

- Z-basivarsen shows a continued favorable safety profile,^a with no serious related TEAEs.
- Z-basivarsen targets the underlying cause of DM1 (dysregulated RNA splicing) to enable functional improvement in multiple systems, including improvement in measures of myotonia, muscle strength and function, and PROs.
- Key clinical outcomes were supported by patient-reported improvement in MDHI total score and subscales.
- These functional improvements, if confirmed, may lessen the clinical impact and economic burden of DM1.

^aData as of April 23, 2025.

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DISCLOSURE INFORMATION

Valeria Sansone has acted as a consultant and participated in advisory boards for ARTHEx Biotech, Avidity Biosciences, Biogen, Dyne Therapeutics, Italfarmaco, Novartis, Roche, Sanofi, Scholar Rock, Solid Biosciences, and Vertex Pharmaceuticals; Guillaume Bassez, Marika Pane, and Richard H Roxburgh have nothing to disclose; Jordi Diaz-Manera has received funding for participating on advisory boards or presenting at conferences on behalf of Sanofi, Sarepta, Lupin, Amicus, and Astellas. He has received funding for research from Sanofi, Sarepta, Spark, and Boehringer-Ingelheim; James B Lilleker has participated in advisory boards and/or conference support/presentations for Roche, Sanofi, and Dyne Therapeutics; Karlien Mul has acted as a consultant for Dyne Therapeutics and Avidity Biosciences (payments to institution), and receives research funding from PepGen; Benedikt Schoser has received unrestricted research grants from Amicus, Astellas, Roche, Marigold Foundation, AMDA Foundation, and speaker's honoraria from Amicus Therapeutics Inc., Alexion, Kedron, and Sanofi. He has participated as a scientific advisor for Amicus Therapeutics Inc., Argene, Astellas, Bayer, Pepgen, Sanofi, Spark, and Taysa. He declares no stocks or shares; Christopher Turner has acted as a consultant for PepGen and Vertex Pharmaceuticals; David Danese, Soma Ray, Huaihou Chen, Shauna Andersson, and Douglas Kerr are employees of Dyne Therapeutics and may hold stock in the company.

Zeleciment basivarsen (z-basivarsen, also known as DYNE-101) is investigational or otherwise in development and has not been approved as safe or effective by the US FDA, EMA, or any other regulatory authority.