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Zeleciment Basivarsen Targets the Underlying Cause of DM1 to Enable Functional Improvement in the Phase 1/2 ACHIEVE Trial

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ACHIEVE

Shauna Andersson[1], Guillaume Bassez[2], Jordi Diaz-Manera[3], James B. Lilleker[4], Karlien Mul[5], Marika Pane[6], Richard H Roxburgh[7], Benedikt Schoser[8], Christopher Turner[9], Soma Ray[1], Huaihou Chen[1], Douglas Kerr[1], Valeria Sansone[10]

[1]Dyne Therapeutics, Inc., Waltham, MA, USA; [2]Institut de Myologie, Paris, France; [3]John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle-Upon-Tyne, UK; [4]Muscle Disease Unit, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [5]Radboud University Medical Center, Nijmegen, Netherlands; [6]Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; [7]Neurogenetics Clinic Centre for Brain Research, University of Auckland, Auckland, NZ; [8]Friedrich-Baur-Institute, Dep. of Neurology LMU Clinics, Ludwig-Maximilians University, Munich, Germany; [9]University College London Hospitals, London, UK; [10]Centro Clinico NeMO, University of Milan, Milan, Italy

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 dystrophia myotonica 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]
- No disease-modifying therapies are available, limiting treatment to symptom management.[4]
- 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.[5]
- The safety and efficacy of z-basivarsen are being investigated in the Phase 1/2 ACHIEVE trial (NCT05481879; EudraCT number 2022-000889-18).[6,7]
- 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.[7]

METHODS

- ACHIEVE is a global, randomized, placebo-controlled study evaluating once per two months 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).[6,7]
  - In the MAD portion of ACHIEVE:
    - 56 participants received z-basivarsen across five different doses/dose regimen cohorts (1.8 mg/kg every 4 weeks [Q4W], 3.4 mg/kg Q4W or every 8 weeks [Q8W], 5.4 mg/kg Q8W, and 6.8 mg/kg Q8W).[6,7]
    - The primary endpoints were safety and tolerability.[6,7] Additional endpoints included pharmacokinetics and pharmacodynamics, multiple assessments of muscle strength and function, myotonia, and PROs, including Myotonic Dystrophy Health Index (MDHI).[6,7]
  - 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 period of the study. Safety data are as of April 23, 2025, and include all 56 participants dosed in the MAD portion of ACHIEVE through 6.8 mg/kg Q8W.

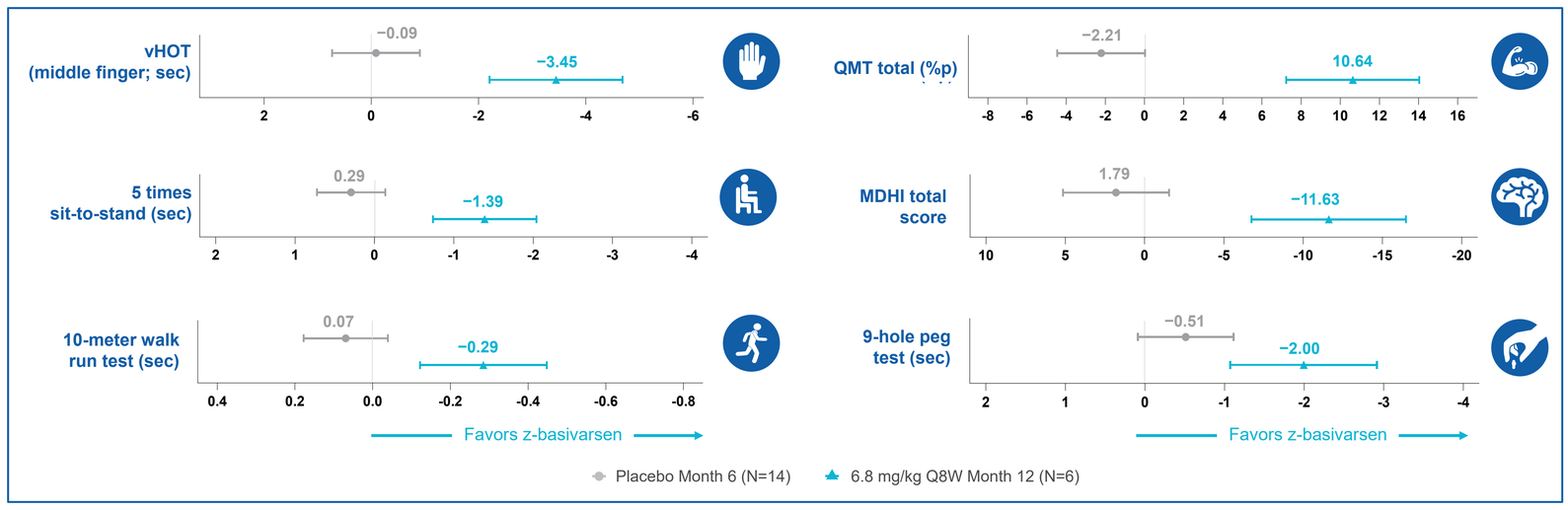
RESULTS

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)

[a]Scored 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.

Figure 1. Z-basivarsen Led to Functional Improvement Across Several Clinical Measures



MDHI, myotonic dystrophy health index; Q8W, every 8 weeks dosing; QMT quantitative muscle testing; sec, second; SEM, standard error of the mean; vHOT, video hand opening time.
Mixed model for repeated measures (MMRM) fixed effects: dose, visit, baseline, dose by visit interaction, baseline by visit interaction. All dose groups except recovery group; excluding placebo data after 6 months; Data presented are least squares (LS) mean change from baseline ± SEM; 6 months = 169 days, 12 months = 337 days.

Table 2. Summary of TEAEs

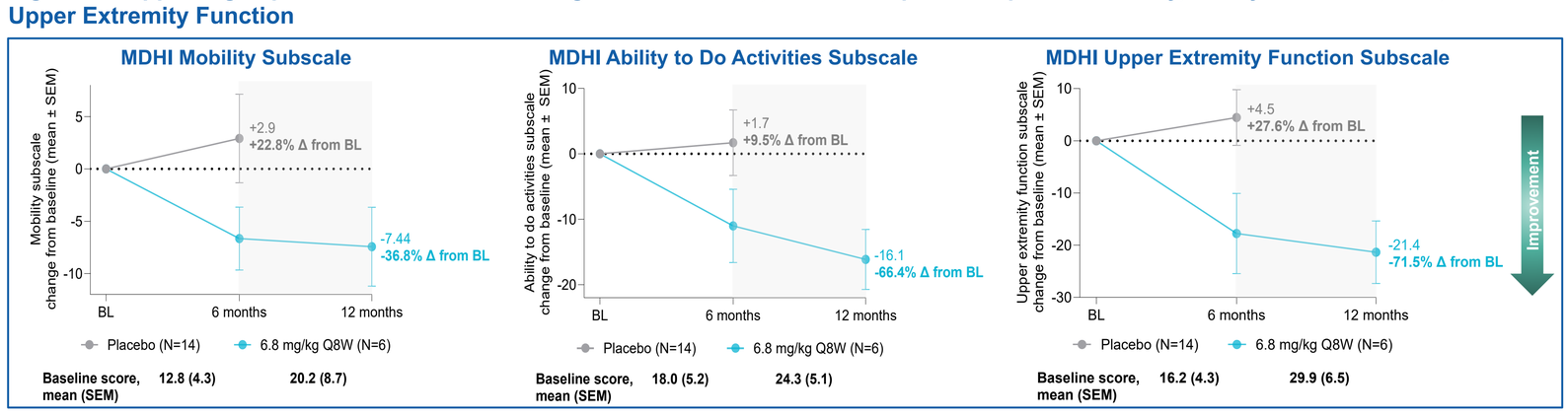
TEAE category	Participants with ≥1 TEAE – n (%)					
	1.8 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q8W N=8	5.4 mg/kg Q8W N=8	6.8 mg/kg Q8W N=8	Overall (N=56)
Any TEAE	16 (100)	16 (100)	8 (100)	8 (100)	8 (100)	56 (100)
Any related TEAE	9 (56)	10 (63)	3 (38)	6 (75)	6 (75)	34 (61)
Any serious TEAE	4 (25)	0	1 (13)	0	0	5 (9)
Any serious related TEAE	0	0	0	0	0	0
Any TEAE leading to withdrawal from study	0	0	0	0	0	0
Any TEAE leading to death	0	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 ~2.5x greater than the upper limit of normal
- No participants have demonstrated persistent related anemia or thrombocytopenia

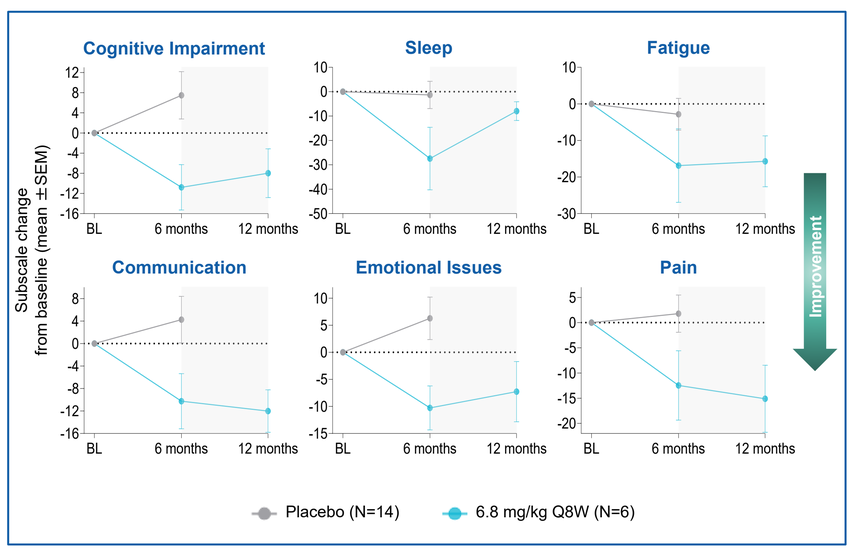
[a]Transient worsening of AV block in a participant with ongoing medical history of first-degree AV block; [b]Attributed to risk factors for pulmonary embolism; [c]All cohorts combined; preferred terms are reported.

Figure 2. Supporting Improvement in Muscle Strength and Function, Patients Reported Improved Mobility, Ability to Do Activities, and Upper Extremity Function



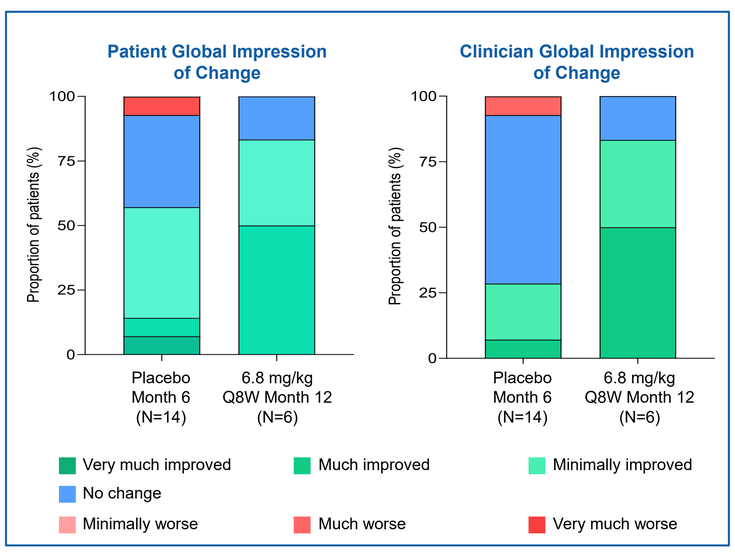
BL, baseline; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks dosing; SEM, standard error of the mean. 6 months = 169 days; 12 months = 337 days.

Figure 3. Sustained Improvement in CNS-related MDHI Subscales



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.
PROs including MDHI collected at baseline, 6 months (169 days), and 12 months (337 days).

Figure 4. Questionnaires Showed Improvements in Patient and Clinician Impressions of Global Functioning From Baseline



Q8W, every 8 weeks dosing.
6 months = 169 days; 12 months = 337 days.

CONCLUSIONS

- Z-basivarsen shows a continued favorable safety profile,[a] with no serious related TEAEs.
- Z-basivarsen targets the underlying cause of DM1 to enable functional improvement in multi-systems in the ACHIEVE trial, including improvement in measures of myotonia, muscle strength and function, and PROs.
- Key clinical outcomes are supported by patient-reported improvement in muscle strength, function and ability to do activities.

[a]Data 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, Kedrion, and Sanofi. He has participated as a scientific advisor for Amicus Therapeutics Inc., Argenx, Astellas, Bayer, Pepgen, Sanofi, Spark, and Taysha. He declares no stocks or shares; Christopher Turner has acted as a consultant for PepGen and Vertex Pharmaceuticals; Soma Ray, Huaihou Chen, Shauna Andersson, and Douglas Kerr are employees of Dyne Therapeutics and may hold stock in the company.

ACKNOWLEDGMENTS

This study was funded by Dyne Therapeutics. Medical writing and editorial support was provided by Obsidian Healthcare Group Ltd, UK. This support was funded by Dyne Therapeutics. The authors wish to thank the clinical trial investigators and site coordinators and, most importantly, all the participants, families, and caregivers for their willingness to participate in this clinical trial, which was sponsored by Dyne Therapeutics.

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.

Muscular Dystrophy Association Clinical and Scientific Conference (MDA), Orlando, Florida, USA, March 8–11, 2026

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