#1171

DYNE-101 Targets the Underlying Cause of DM1 to Enable Multi-system Functional Improvement in the ACHIEVE Trial

Valeria Sansone[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[10], Huaihou Chen[10], Shauna Andersson[10], Douglas Kerr[10]
*Presenting author.
[1]Neurorehabilitation Unit, The NeMO Clinical Center and University of Milan, Milan, Italy; [2]Institute of Myology, Paris, France; [3]Newcastle University, Newcastle-Upon-Tyne, UK; [4]Manchester Academic Health Science Centre, Manchester, UK; [5]Radboud University Medical Center, Nijmegen, Netherlands; [6]Agostino Gemelli University Policlinic, Rome, Italy; [7]University of Auckland, Auckland, New Zealand; [8]Ludwig-Maximilians University, Munich, Germany; [9]University College London Hospitals, London, UK; [10]Dyne Therapeutics, Inc., Waltham, MA, USA

ACHIEVE

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 multisystem clinical manifestations.[1–3]
- No disease-modifying therapies are available, limiting treatment to symptom management.[4]
- 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 DYNE-101 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 DYNE-101, consistent splicing correction, and meaningful improvements in multiple functional endpoints.[7]

METHODS

- ACHIEVE is a global, randomized, placebo-controlled study evaluating once per two months or more frequent intravenous administrations of DYNE-101 in adults (18–49 years) with DM1. It consists of a placebo-controlled 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 DYNE-101 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), each with placebo control.[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 patient-reported outcomes (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.

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)

[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; Q8W, every 8 weeks; QMT, quantitative muscle testing; MDHI, Myotonic Dystrophy Health Index; SD, standard deviation; sec, seconds; vHOT, video hand opening time.

Table 2. Summary of TEAEs

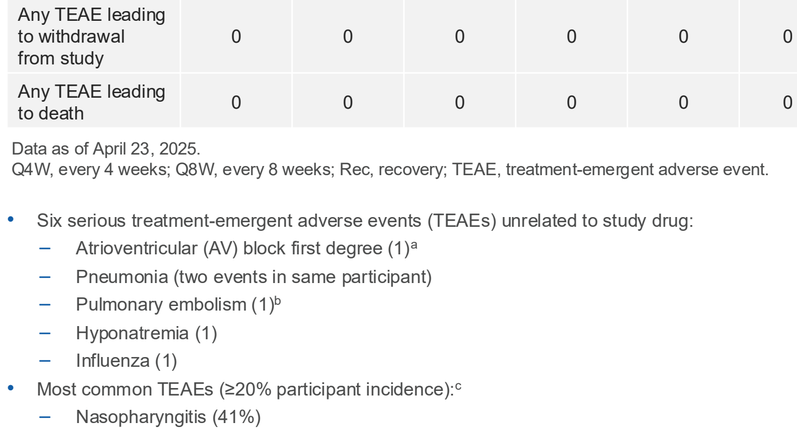
TEAE category	Participants with ≥1 TEAE – n (%)					
	1.8 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q8W N=8	5.4 mg/kg Q8W N=8	6.8 mg/kg Q8W N=8	Overall (N=56)
Any TEAE	16 (100)	16 (100)	8 (100)	8 (100)	8 (100)	56 (100)
Any related TEAE	9 (56)	10 (63)	3 (38)	6 (75)	6 (75)	34 (61)
Any serious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

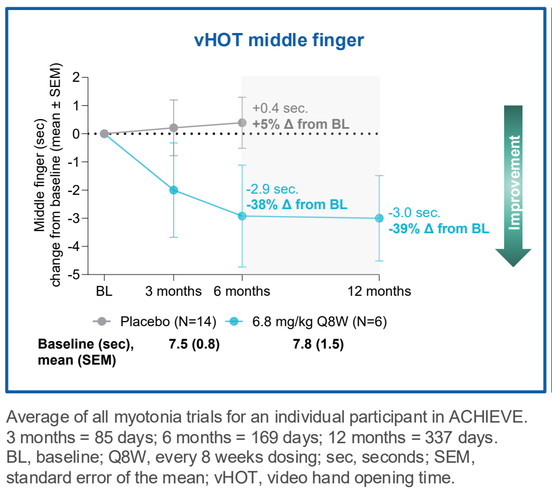
[a]Transient worsening of AV block in a participant with ongoing medical history of first-degree AV block; [b]Attributed to risk factors for pulmonary embolism; [c]All cohorts combined; preferred terms are reported.

Figure 1. DYNE-101 at 6.8 mg/kg Q8W Led to Consistent Splicing Correction



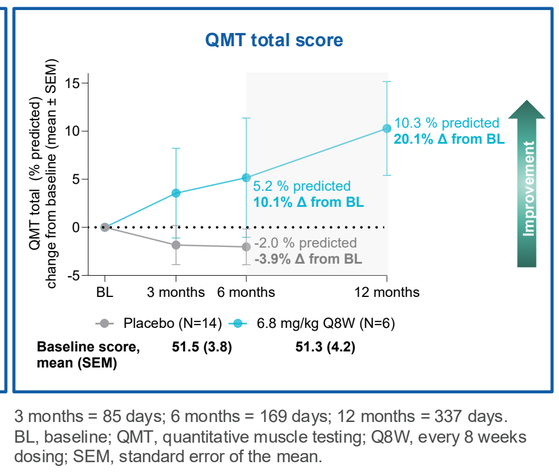
[a]All patients transitioned to treatment at Month 6; [b]One baseline sample in 6.8 mg/kg treatment group not included as the sample did not meet quality control criteria.
3 months = 85 days; 6 months = 169 days; 11 months = 309 days.
CASI, composite alternative splicing index; Q8W, every 8 weeks dosing; SEM, standard error of the mean.

Figure 2. Sustained vHOT Improvement at 6 and 12 Months



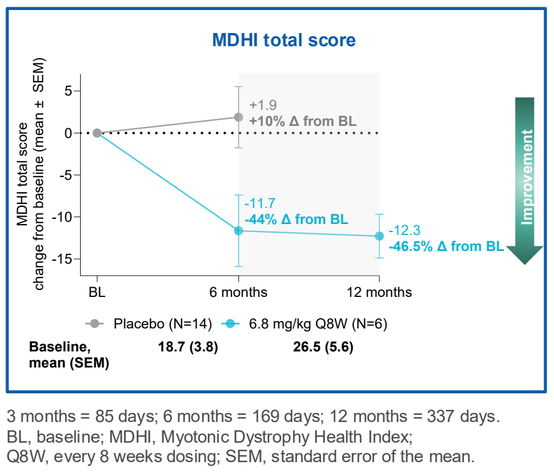
Average of all myotonia trials for an individual participant in ACHIEVE.
3 months = 85 days; 6 months = 169 days; 12 months = 337 days.
BL, baseline; Q8W, every 8 weeks dosing; sec, seconds; SEM, standard error of the mean; vHOT, video hand opening time.

Figure 3. Continued Improvement in Strength (QMT Total) through 12 Months



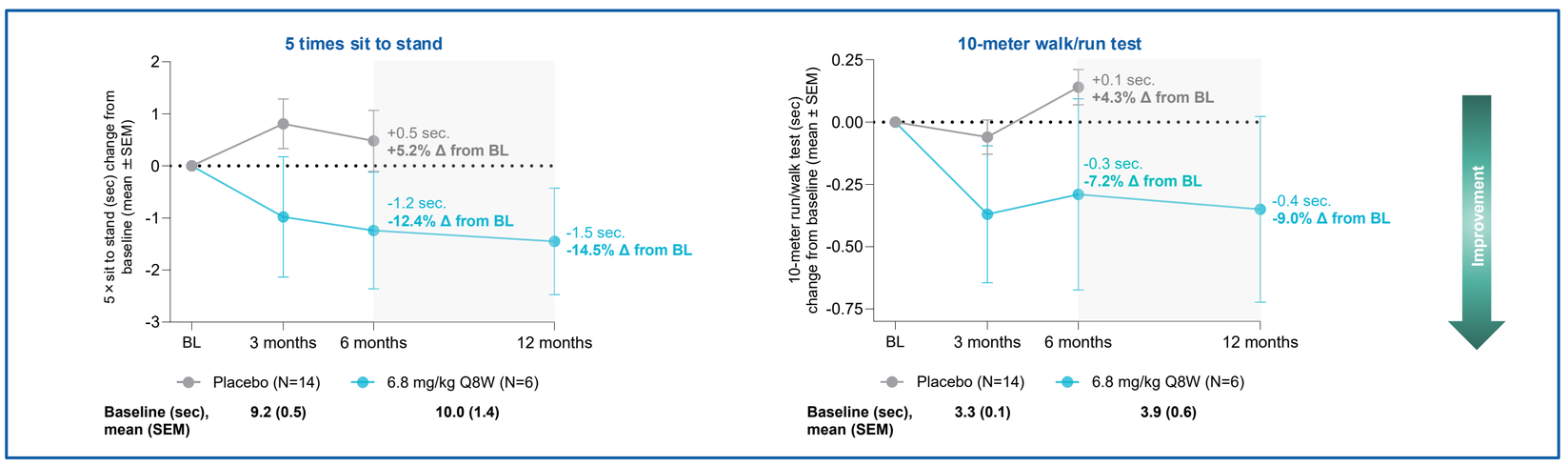
3 months = 85 days; 6 months = 169 days; 12 months = 337 days.
BL, baseline; QMT, quantitative muscle testing; Q8W, every 8 weeks dosing; SEM, standard error of the mean.

Figure 4. Improvement in Patient-Reported Outcome Sustained at 6 and 12 Months



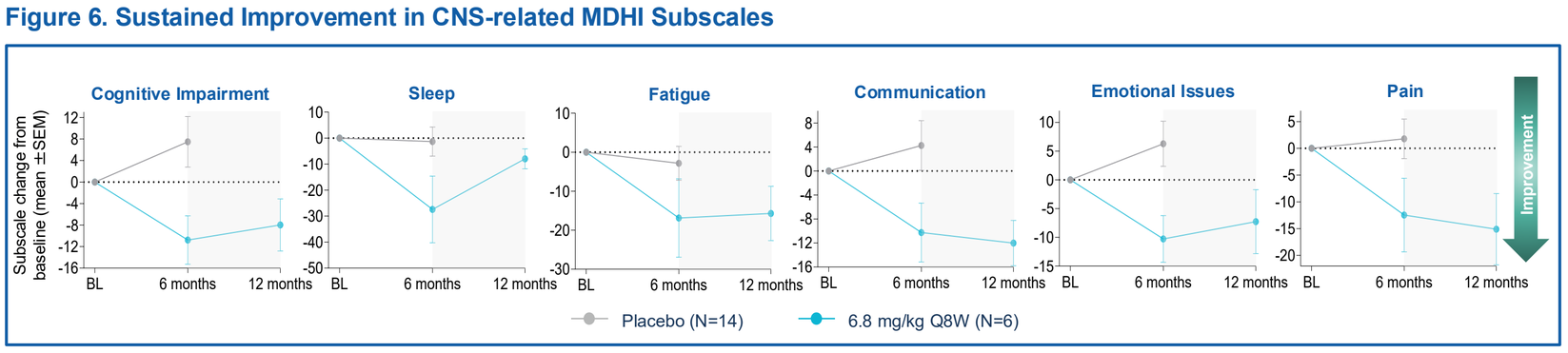
3 months = 85 days; 6 months = 169 days; 12 months = 337 days.
BL, baseline; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks dosing; SEM, standard error of the mean.

Figure 5. Benefit Across Multiple Timed Function Tests Sustained at 6 and 12 Months



3 months = 85 days; 6 months = 169 days; 12 months = 337 days.
BL, baseline; Q8W, every 8 weeks dosing; sec, seconds; SEM, standard error of the mean.

Figure 6. Sustained Improvement in CNS-related MDHI Subscales



Patient-reported outcomes 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; SEM, standard error of the mean.

CONCLUSIONS

- DYNE-101 shows a continued favorable safety profile,[a] with no serious related TEAEs.
- DYNE-101 addresses the underlying pathobiology (dysregulated splicing) 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.
- The MAD portion of ACHIEVE is completed; 6.8 mg/kg Q8W has been selected as the registrational dose/dose regimen of DYNE-101.

[a]Data as of April 23, 2025

REFERENCES

1. Lopez-Martinez A, et al. *Genes (Basel).* 2020;11:1109;
2. Pavićević DS, et al. *Biomed Res Int.* 2013;2013:391821;
3. Thornton CA. *Neurol Clin.* 2014;32:705–719;
4. Thornton CA, et al. *Curr Opin Genet Dev.* 2017;44:135–140;
5. Zanotti S, et al. Poster presented at: American Society of Gene and Cell Therapy Annual Meeting; May 16–20, 2023; Washington, USA. Abstract 82;
6. ClinicalTrials.gov. NCT05481879 (https://clinicaltrials.gov/ct2/show/NCT05481879);
7. Kools J, et al. Poster presentation at the World Muscle Society Annual Congress, Prague, Czechia, October 8–12, 2024. Poster 221P;

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 served as a paid consultant for Dyne Therapeutics and Avidity Biosciences (payments to institution), and receives research funding from PepGen Inc. 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 Olivia Atkinson of 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.

DYNE-101 is an investigational medicine being evaluated in the ongoing ACHIEVE trial and has not received approval by the FDA, EMA, or any other regulatory authorities.

2025 Neuromuscular Study Group Annual Scientific Meeting, Stresa, Italy, September 26, 2025