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Safety and Efficacy of DYNE-101 in Adults With DM1: Phase 1/2 ACHIEVE Trial Data

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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 a transferrin receptor 1 (TfR1)-binding antigen-binding fragment (Fab) 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]
- Initial data from this study showed dose-dependent muscle delivery of DYNE-101, consistent splicing correction, and meaningful improvements in multiple functional endpoints, as well as trends in improvement in patient-reported outcome (PRO) measures.[7]

METHODS

- ACHIEVE is a global, randomized, placebo-controlled study evaluating once-monthly or less frequent intravenous administrations of DYNE-101 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]
  - 56 participants have received DYNE-101 across 5 different doses/dose regimen cohorts in the MAD portion of the study (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]
  - In the MAD portion of the study, muscle biopsies were collected at baseline, 12 weeks, and 24 weeks.[7]
  - The primary endpoints are safety and tolerability.[6,7] Additional endpoints include pharmacokinetics and pharmacodynamics, including change from baseline in splicing, multiple assessments of muscle strength and function, and PROs, including Myotonic Dystrophy Health Index (MDHI).[6,7]
    - Splicing was assessed using the composite alternative splice index (CASI),[7] which quantifies RNA mis-splicing across a panel of 22 genes implicated in the pathophysiology of DM1. It has been shown to be a robust, reliable, and sensitive biomarker that captures the associations between RNA mis-splicing and physical strength and mobility, and has prognostic utility to predict future function in individuals with DM1.[8]
  - 6.8 mg/kg Q8W has been selected as the dose/dose regimen for the registrational expansion cohort of ACHIEVE.
  - Here we present 6-month efficacy data with 6.8 mg/kg Q8W from the placebo-controlled MAD period of the study. Safety data are as of December 6, 2024, and include all 56 participants dosed 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	18.7 (13.8)	26.5 (13.7)

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. DYNE-101 safety profile is favorable to date (summary of TEAEs)

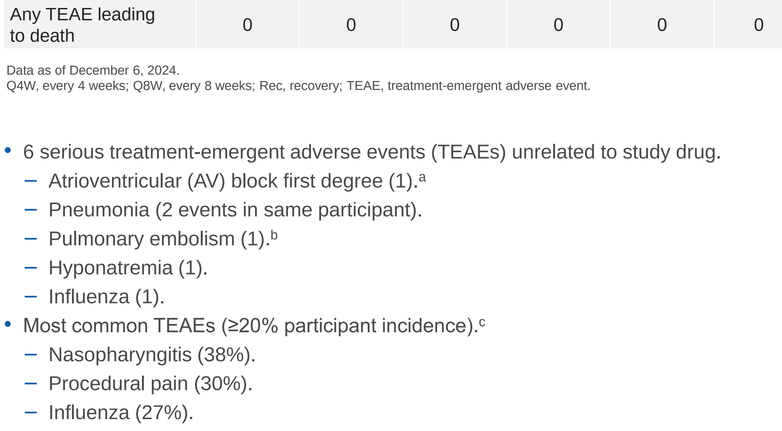
TEAE category	Participants with ≥1 TEAE – n (%)					
	1.8 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q8W N=8	5.4 mg/kg Q8W N=8	6.8 mg/kg Q8W N=8	Overall (N=56)
Any TEAE	16 (100)	16 (100)	8 (100)	8 (100)	8 (100)	56 (100)
Any related TEAE	9 (56)	9 (56)	2 (25)	3 (38)	6 (75)	29 (52)
Any serious 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 December 6, 2024.
Q4W, every 4 weeks; Q8W, every 8 weeks; Rec, recovery; TEAE, treatment-emergent adverse event.

- 6 serious treatment-emergent adverse events (TEAEs) unrelated to study drug.
  - Atrioventricular (AV) block first degree (1).[a]
  - Pneumonia (2 events in same participant).
  - Pulmonary embolism (1).[b]
  - Hyponatremia (1).
  - Influenza (1).
- Most common TEAEs (≥20% participant incidence).[c]
  - Nasopharyngitis (38%).
  - Procedural pain (30%).
  - Influenza (27%).
  - Infusion-related reaction (25%).
  - Diarrhea; headache (each 21%).
- 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.

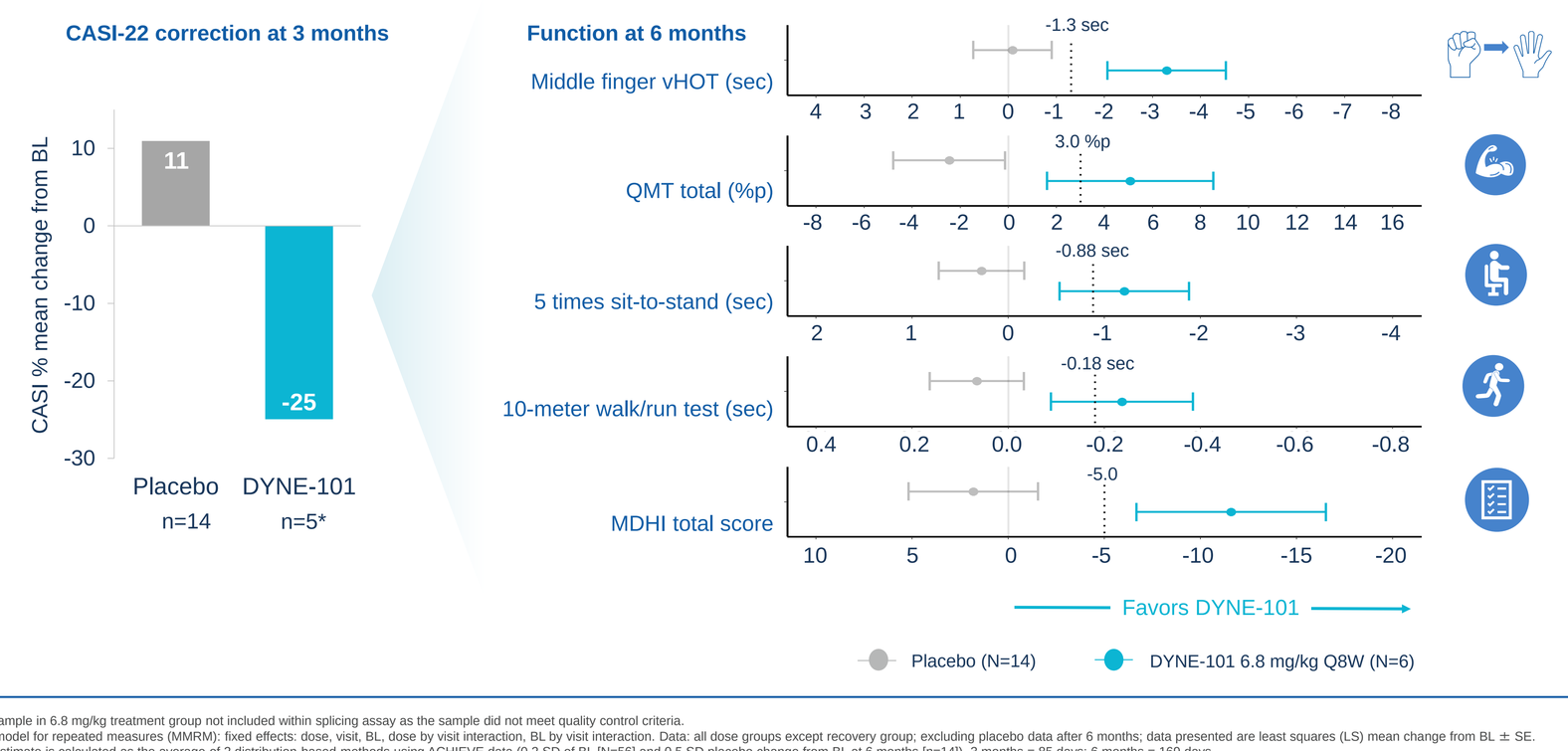
a. Transient worsening of AV block in a participant with ongoing medical history of first-degree AV block;
b. Attributed to risk factors for pulmonary embolism; c. All cohorts combined; preferred terms are reported.

Figure 1. DYNE-101 at 6.8 mg/kg Q8W addresses central pathobiology of DM1 at 3 months



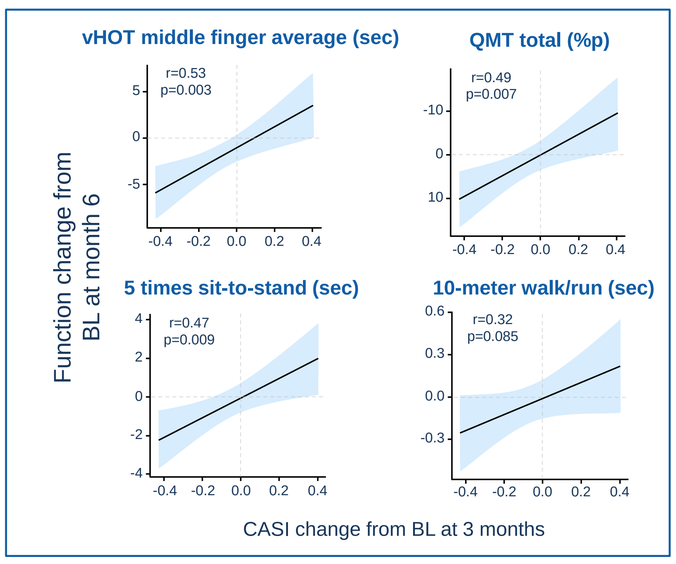
*1 baseline sample in 6.8 mg/kg treatment group not included as the sample did not meet quality control criteria. 3 months = 85 days.
ASO, antisense oligonucleotide; BL, baseline; SEM, standard error of mean.

Figure 2. Splicing correction with DYNE-101 at 3 months resulted in meaningful functional improvements at 6 months



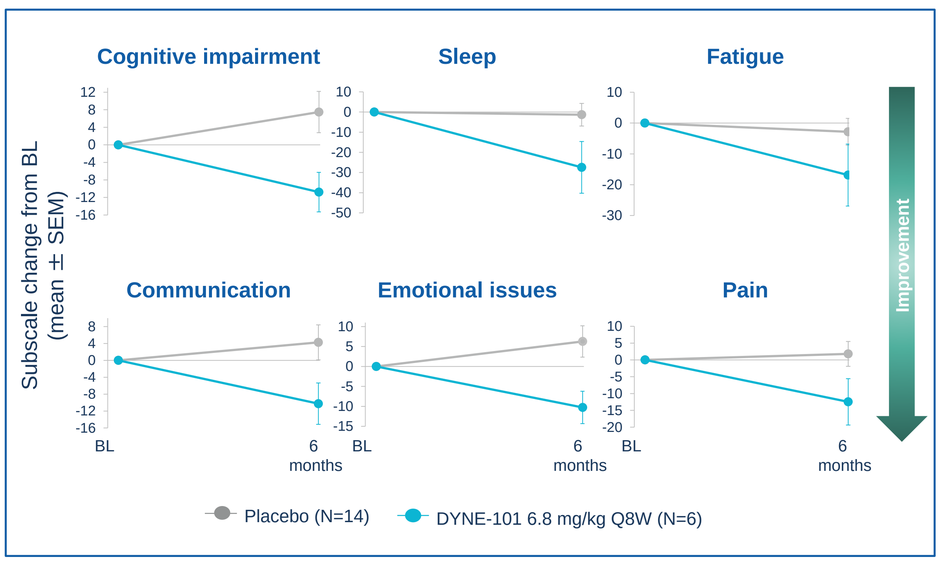
*1 BL sample in 6.8 mg/kg treatment group not included within splicing assay as the sample did not meet quality control criteria.
Mixed model for repeated measures (MMRM): fixed effects: dose, visit, BL, dose by visit interaction, BL by visit interaction. Data: all dose groups except recovery group; excluding placebo data after 6 months; data presented are least squares (LS) mean change from BL ± SE.
MCID estimate is calculated as the average of 2 distribution-based methods using ACHIEVE data (0.2 SD of BL [N=56] and 0.5 SD placebo change from BL at 6 months [n=14]). 3 months = 85 days; 6 months = 169 days.
BL, baseline; CASI, composite alternative splicing index; MCID, minimal clinically important difference; MDHI, Myotonic Dystrophy Health Index; Q4W, every 4 weeks; Q8W, every 8 weeks; QMT, quantitative muscle testing; SD, standard deviation; SE, standard error; sec, seconds; vHOT, video hand opening time.

Figure 3. Splicing correction at 3 months predicted functional benefit at 6 months



Shown are linear regression lines and correlation analysis for pooled 3.4 mg/kg Q4W, 5.4 mg/kg Q8W and 6.8 mg/kg Q8W, and placebo. Band for model predicted mean with 95% CI. 3 months = 85 days; 6 months = 169 days.
BL, baseline; CASI, composite alternative splicing index; CI, confidence interval; Q4W, every 4 weeks; Q8W, every 8 weeks; QMT, quantitative muscle testing; sec, seconds.

Figure 4. Improvement in CNS subscales indicates encouraging PRO trends



PROs collected at BL and 6 months (169 days).
BL, baseline; CNS, central nervous system; PRO, patient-reported outcome; Q8W, every 8 weeks; SEM, standard error of mean.

CONCLUSIONS

- DYNE-101 is designed to target mutant nuclear *DMPK* RNA with the goal of correcting the abnormal splicing to improve the multisystem disease manifestations of DM1.[1,5]
- DYNE-101 shows a continued favorable safety profile,[a] with no serious related TEAEs.
- DYNE-101 addresses the underlying pathobiology (dysregulated splicing) of DM1, and at 6.8 mg/kg Q8W has demonstrated clinically meaningful improvements on measures of strength, mobility, and PROs, including central nervous system manifestations.
- Splicing correction at 3 months was predictive of functional benefit at 6 months.
- 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 December 6, 2024.

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DISCLOSURE INFORMATION

Daniel Wolf, Chris Mix, Soma Ray, Baoguang Han, and Douglas Kerr are employees of Dyne Therapeutics and may hold stock in the company;
James B. Lilleker has participated in advisory boards and/or conference support/presentations for Roche, Sanofi, and Dyne Therapeutics;
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; Joost Kools has nothing to disclose; Giullaume Bassez and Marika Pane have nothing to disclose; Richard H. Roxburgh has nothing to disclose; 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; Valeria Sansone has received compensation for intellectual and teaching activities from Dyne Therapeutics, Avidity Biosciences, Roche, Biogen, Novartis, and Lupin Pharmaceuticals.

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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.

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