Long-Term Functional Improvement With Zeleciment Basivarsen in the Phase 1/2 ACHIEVE Trial

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ACHIEVE

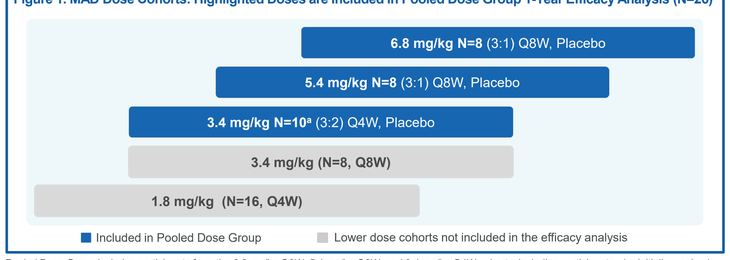
BACKGROUND

- Myotonic dystrophy type 1 (DM1) is a rare neuromuscular disorder with multisystem presentation. It is caused by expansion of cytosine, thymine, and guanine repeats in the 3' untranslated region of the dystrophia myotonica protein kinase (*DMPK*) gene. Messenger RNA (mRNA) transcribed from the mutated gene forms hairpin-loop structures that sequester splicing regulators into toxic nuclear foci, leading to widespread dysregulation of RNA splicing (spliceopathy) that drives the multisystemic clinical manifestations of the disorder[1–3]
- No disease-modifying therapies are currently available for DM1, limiting treatment to symptom management[4]
- Zeleciment basivarsen ("z-basivarsen," also known as DYNE-101) is an investigational therapeutic for DM1, consisting of an antigen-binding fragment that targets the transferrin receptor 1 conjugated to an antisense oligonucleotide designed to target mutant nuclear *DMPK* mRNA to correct spliceopathy[5]
- The safety and efficacy of z-basivarsen are being investigated in the phase 1/2 ACHIEVE trial (NCT05481879; EudraCT number 2022-000889-18) and the phase 3 HARMONIA trial (NCT07486934)[6-8]
- Data from the multiple ascending dose (MAD) portion of ACHIEVE have previously shown dose-dependent muscle delivery of z-basivarsen, consistent DMPK knockdown and splicing correction, and durable improvements in myotonia, muscle strength and function, and patient-reported outcomes (PROs)[7,9]

METHODS

- The ACHIEVE MAD study is a global, randomized, placebo-controlled study of intravenous z-basivarsen in adults (18–49 years) with DM1, comprising a MAD period (24 weeks), an open-label extension (24 weeks), and a long-term extension (96 weeks)
- In the MAD portion, 56 participants received z-basivarsen across five 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)
- Primary endpoints are safety and tolerability. Additional endpoints include myotonia, muscle strength and function, and PROs, including the Myotonic Dystrophy Health Index (MDHI)
- A previous long-term analysis included N=6 assigned to 6.8 mg/kg (registrational dose) at baseline[9]; to evaluate efficacy in a larger sample, we analyzed 12-month data in a Pooled Dose Group (N=26; **Figure 1**)
  - The Pooled Dose Group includes a mixture of dose exposures and does not reflect the effect of maintaining 6.8 mg/kg for the entire treatment duration
  - Only 8/26 participants in the Pooled Dose Group received the registrational dose for the full 12 months analyzed, and most did not receive the registrational dose during this timeframe
- Here, we present 12-month MAD data for the 6.8 mg/kg cohort and the Pooled Dose Group; additionally, data from the Pooled Dose Group were compared with DM1 natural history data from patients enrolled in the ongoing, prospective END-DM1 study[10,11]
  - Safety data presented herein are cumulative from the ACHIEVE MAD participants as of April 20, 2026

Figure 1. MAD Dose Cohorts: Highlighted Doses are Included in Pooled Dose Group 1-Year Efficacy Analysis (N=26)



Pooled Dose Group includes participants from the 6.8 mg/kg Q8W, 5.4 mg/kg Q8W, and 3.4 mg/kg Q4W cohorts, including participants who initially received placebo within those cohorts and subsequently received active treatment. The participants who originally received placebo were re-baselined to the visit prior to their first active dose. 6.8 mg/kg and 5.4 mg/kg dose cohorts were treated with Q8W, every 8 weeks with a loading dose given 4 weeks after first dose of active drug.
[a]Patients assigned to recovery were not included in this analysis.
MAD, multiple ascending dose; Q4W, every 4 weeks; Q8W, every 8 weeks.

RESULTS

Table 1. Baseline Characteristics

Mean (SD)	Placebo (N=14)	6.8 mg/kg Q8W (N=6)	Pooled Dose Group (N=26)
Age (years)	32.6 (9.6)	37.2 (9.7)	35.6 (8.0)
BMI (kg/m^2)	24.4 (4.7)	23.4 (5.6)	22.7 (3.9)
CASI-22	0.68 (0.20)	0.74 (0.25)	0.73 (0.19)
CTG repeats	597 (246)	542 (191)	527 (243)
vHOT (middle finger) (sec)	7.5 (3.0)	7.8 (3.8)	8.2 (4.4)
QMT total (% predicted)	51.5 (14.3)	51.3 (10.4)	48.0 (14.3)
Hand grip (% predicted)	44.8 (16.9)	49.0 (12.9)	41.5 (16.3)
10-meter walk/run (sec)	3.34 (0.48)	3.94 (1.56)	3.99 (1.49)
5 times sit-to-stand (sec)	9.24 (2.03)	9.98 (3.33)	10.20 (3.94)
MDHI total[a]	18.7 (13.8)	26.5 (13.7)	24.4 (19.8)

Pooled Dose Group includes participants from the 6.8 mg/kg Q8W, 5.4 mg/kg Q8W, and 3.4 mg/kg Q4W cohorts, including participants who initially received placebo within those cohorts and subsequently received active treatment. The participants who originally received placebo were re-baselined to the visit prior to their first active dose. Only 8/26 participants in the Pooled Dose Group received the registrational dose for the full 12 months analyzed, and most did not receive the registrational dose during this timeframe.
[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; MAD, multiple ascending dose; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks; QMT, quantitative muscle testing; SD, standard deviation; sec, seconds; vHOT, video hand opening time.

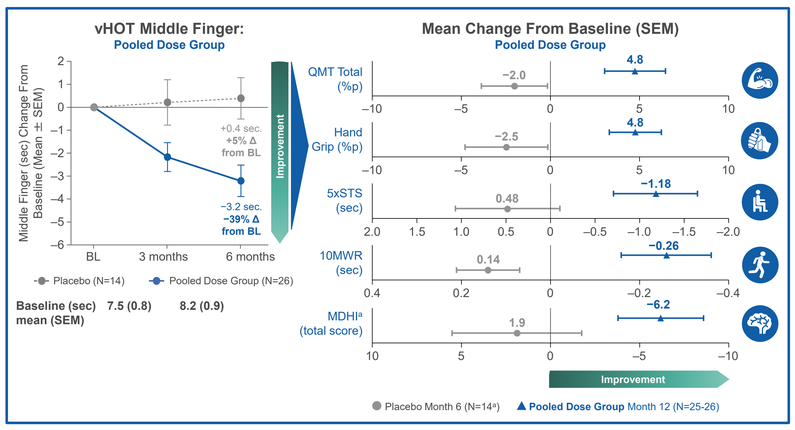
Table 2. Summary of Treatment-Emergent Adverse Events (TEAEs)

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	10 (62.5)	10 (62.5)	4 (50)	6 (75)	7 (87.5)	37 (66.1)
Any serious TEAE	5 (31.3)	0	2 (25)	1 (12.5)	0	8 (14.3)
Any serious related TEAE	0	0	0	0	0	0
Any TEAE leading to withdrawal from study	0	0	0	2 (25)	0	2[a] (3.6)
Any TEAE leading to death	0	0	0	0	0	0

- **10 serious TEAEs unrelated to study drug**
  - Atrioventricular block first degree (1)[b]
  - Pneumonia (2 events in same participant)
  - Pulmonary embolism (1)[c]
  - Hyponatremia (1)
  - Influenza B virus test positive (1)
  - Fall (1)
  - Gastroenteritis (1)
  - Meningioma (1)
  - Uterine leiomyoma (1)
- **Most common TEAEs (≥30% participant incidence)[d]**
  - Infusion-related reaction (50%)[e]
  - Nasopharyngitis (46.4%)
  - Diarrhea (35.7%)
  - Headache (33.9%)
  - Procedural pain (33.9%)
  - Influenza (32.1%)
  - Back pain (30.4%)
- **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**

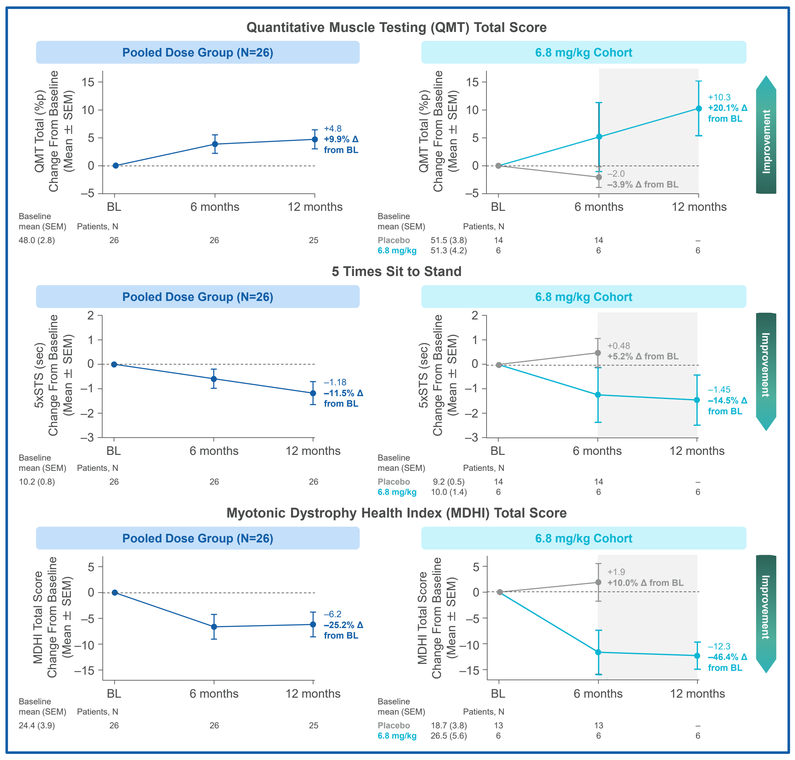
Data as of April 20, 2026.
[a]TEAEs leading to study withdrawal were IRRs that resolved within 2–3 days in 2 participants who had received z-basivarsen for over 12 months. [b]Transient worsening of atrioventricular (AV) block in a participant with ongoing medical history of first-degree AV block. [c]Attributed to risk factors for pulmonary embolism. [d]All cohorts combined. [e]Most IRRs were mild or moderate in severity.
IRR, infusion-related reactions; Q4W, every 4 weeks; Q8W, every 8 weeks; Rec, recovery; TEAE, treatment-emergent adverse event.

Figure 2. Pooled Efficacy Data From ACHIEVE Continue to Support vHOT as an Early Indicator of Functional Improvement



For information on the Pooled Dose Group, see footnotes in Table 1.
Percent mean change from baseline = (mean change from baseline/baseline mean) x 100. 6 months = 169 days; 12 months = 337 days.
[a]MDHI, N=13.
%p, percent predicted; 10MWR, 10-Meter Walk/Run; 5xSTS, 5 Times Sit to Stand; BL, baseline; M, months; MDHI, Myotonic Dystrophy Health Index; Q4W, every 4 weeks; Q8W, every 8 weeks; QMT, quantitative muscle testing; sec, seconds; SEM, standard error of the mean; vHOT, video hand opening time.

Figure 3. Improvement in Strength, Motor Function, and Patient-Reported Disease Burden Is Sustained at 12 Months

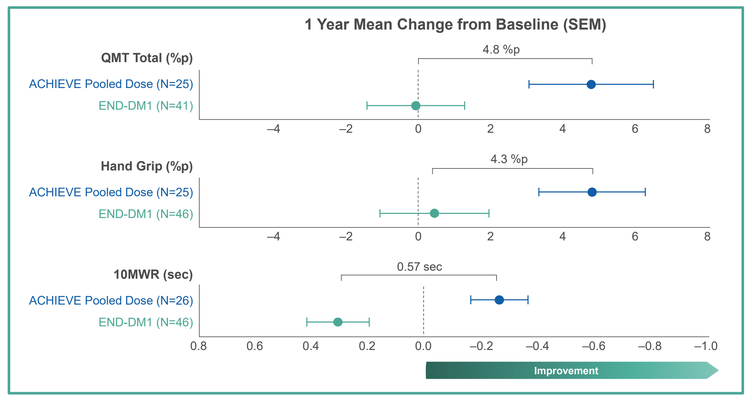


For information on the Pooled Dose Group, see footnotes in Table 1.
Percent mean change from baseline = (mean change from baseline/baseline mean) x 100. 6 months = 169 days; 12 months = 337 days.
5xSTS, 5 Times Sit to Stand; %p, percent predicted; BL, baseline; MDHI, Myotonic Dystrophy Health Index; Q4W, every 4 weeks; Q8W, every 8 weeks; QMT, quantitative muscle testing; sec, seconds; SEM, standard error of the mean.

Divergence From Natural History

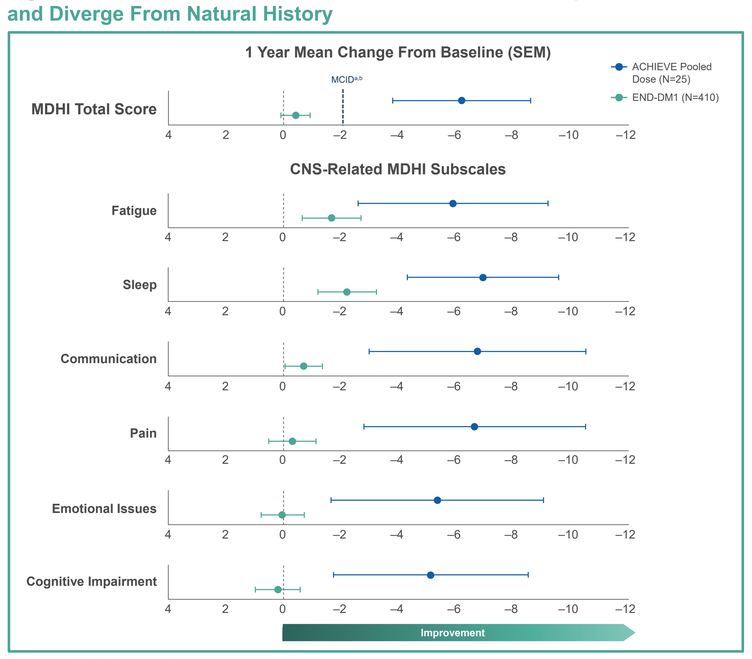
- Parameters for propensity matching included age, sex, and measures of strength and function
  - Propensity-matched baseline characteristics for the END-DM1 Cohort (N=49) and ACHIEVE Pooled Dose Group (N=26) can be viewed in the supplemental materials

Figure 4. ACHIEVE Pooled Dose Group Improves From Baseline and Diverges From Natural History in Strength and Ambulation



Thank you to END-DM1 Executive Committee for reviewing and approving use of this analysis.
N's reflect number of participants with assessments at baseline and Year 1. END-DM1 remains ongoing. 12 months = 337 days.
The 5xSTS assessment was not included in the original END-DM1 protocol.
For information on the Pooled Dose Group, see footnotes in Table 1.
%p, percent predicted; 5xSTS, 5 Times Sit to Stand; 10MWR, 10-Meter Walk/Run; DM1, myotonic dystrophy type 1; Q4W, every 4 weeks; Q8W, every 8 weeks; QMT quantitative muscle testing; sec, second; SEM, standard error of the mean.

Figure 5. MDHI Total Score and CNS-Related Subscales Improve at 1 Year and Diverge From Natural History



Thank you to END-DM1 Executive Committee for reviewing and approving use of this analysis.
For information on the Pooled Dose Group, see footnotes in Table 1.
[a]Sansone V, et al. *Muscle & Nerve*. 2026:1–11. [b]MDHI Total Score MCID values by Sansone et al. 2026 were calculated utilizing an anchor-based approach with the domain delta questionnaire related to "overall health" at Year 2 upon study completion. MCID values ranged from 4.71 to -2.06. The mean change in MDHI Total Score for the ACHIEVE pooled dose group also exceeds MDC ESch-based proposed by Sansone et al. 2026.
CNS, central nervous system; DM1, myotonic dystrophy type 1; MCID, minimal clinically important difference; MDC, minimal detectable change; MDHI, Myotonic Dystrophy Health Index; SEM, standard error of the mean.

CONCLUSIONS

- Z-basivarsen showed a continued favorable safety profile, with no serious related TEAEs through April 20, 2026
- The 6.8 mg/kg cohort demonstrated durable functional improvement in myotonia, motor function, and strength[8]
- Data continues to support vHOT as an early indicator of functional improvement
- Pooled dose analysis (N=26) showed functional improvement at 1 year, with consistent efficacy trends observed across endpoints
- Participants reported improvements in disease burden, including CNS-related impacts
- Z-basivarsen–treated participants showed divergence from natural history across functional and strength outcomes, as well as in functional improvements in MDHI total score

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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; Karlien Mul has acted as a consultant for Dyne Therapeutics and Avidity Biosciences (payments to institution), and receives research funding from PepGen; Guillaume Bassez, Marika Pane, and Richard H Roxburgh have nothing to disclose; Jordi Diaz-Manera has received funding for participating on advisory boards and 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; Benedikt Schoser has received unrestricted research grants from Amicus, Astellas, Roche, Mangold Foundation, AMOA 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; Allison Kreuzer, Alexandra Lovett, Soma Ray, Huaihou Chen, Shauna Andersson, and Douglas Kerr are employees of Dyne Therapeutics and may hold stock in the company.

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