

HARMONIA Study Design: A Global Phase 3 Trial Assessing the Efficacy and Safety of Z-basivarsen in Myotonic Dystrophy Type 1

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Industry-Supported Research Highlights

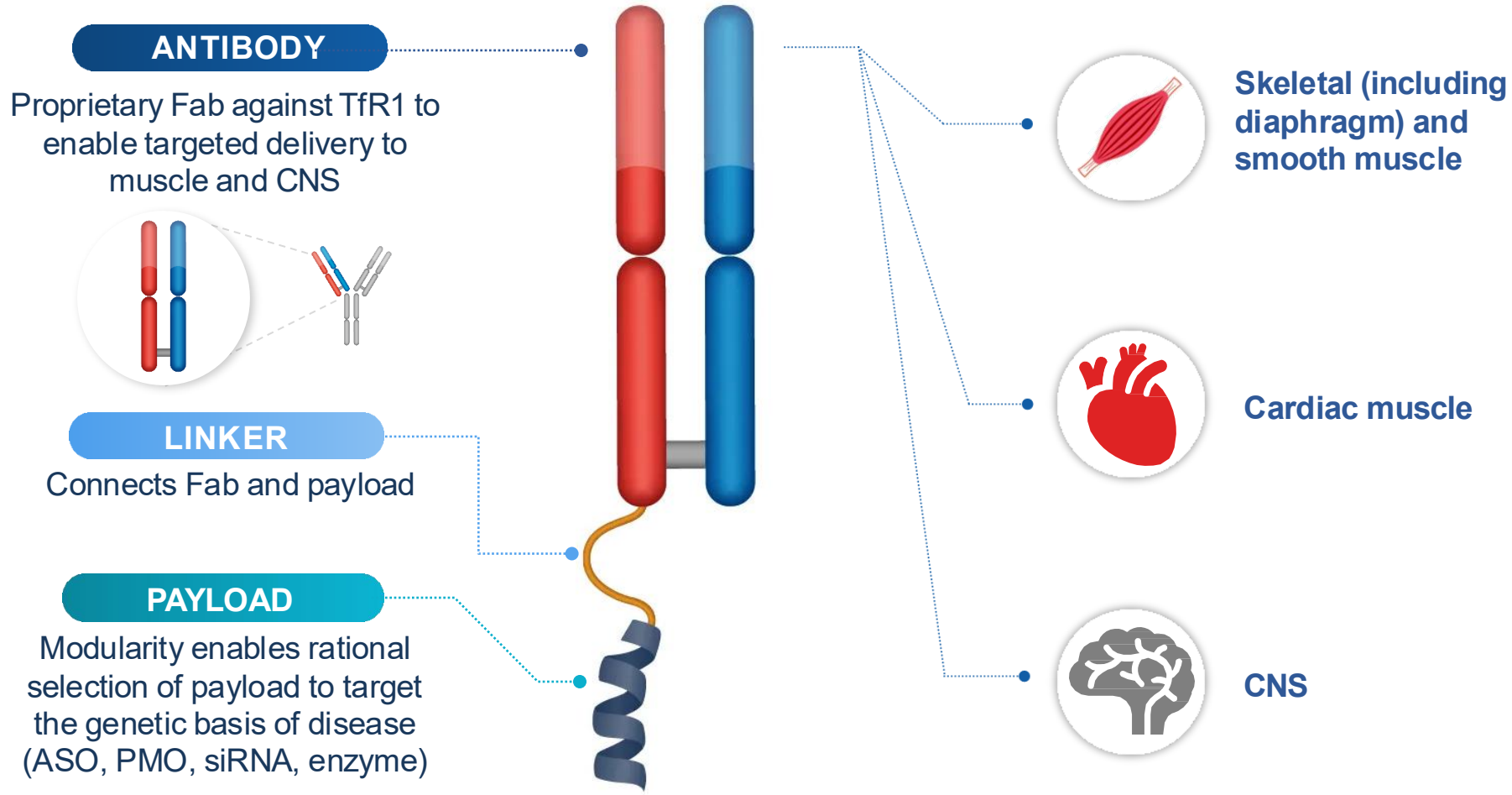
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Disclosures

- I am an employee of Dyne Therapeutics, Inc., and may hold stock in the company
- Zeleciment basivarsen (z-basivarsen, also known as DYNE-101) is an investigational medicine and has not received approval by the FDA, EMA, or any other regulatory authorities

EMA, European Medicines Agency; FDA, Food and Drug Administration.

The FORCE platform enables broad delivery to tissues relevant to disease pathophysiology



The FORCE platform 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.

Note: Figure depicts oligonucleotide payload.

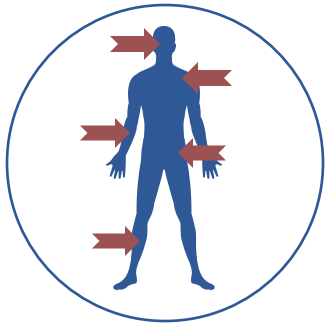
ASO, antisense oligonucleotide; CNS, central nervous system; Fab, fragment antigen binding; PMO, phosphorodiamidate morpholino oligomer; siRNA, small interfering RNA; TfR1, transferrin receptor 1.

Myotonic dystrophy type 1 (DM1)



Rare, progressive, genetic, neuromuscular disease with high morbidity and early mortality[1]

Occurs in ~9.27 individuals per 100,000 worldwide[2]



Heterogeneous multisystemic presentation that arises from a spliceopathy caused by CTG repeat expansions in *DMPK*[1,3]

Affects skeletal, cardiac and smooth muscle, as well as the eyes, endocrine system, and CNS[1,3]



Currently no approved disease-modifying therapies are available[4]

An increasing number of investigational therapies are in clinical development[4]

Individuals with DM1 desire therapies that can achieve functional improvements that enhance daily activities and quality of life[5]

CNS, central nervous system; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase.

1. Hagerman KA, et al. *Muscle Nerve.* 2019;59:457–464; 2. Liao Q, et al. *Neuroepidemiology*. 2022;56:163–173; 3. López-Martínez A, et al. *Genes (Basel)*. 2020;11:1109;
4. Rahm L, et al. *Nat Rev Neurol.* 2025;21:623–641; 5. White M. *Ther Innov Regul Sci.* 2020;54:775–778.

ACHIEVE multiple ascending dose (MAD) study

6-month placebo-controlled period (MAD cohorts)

- **6.8 mg/kg** N=8 (3:1) Q8W, placebo
- **5.4 mg/kg** N=8 (3:1) Q8W, placebo
- **3.4 mg/kg** N=16 (3:3:2) Q4W, recovery, placebo
- **3.4 mg/kg** N=8 (3:1) Q8W, placebo
- **1.8 mg/kg** N=16 (3:3:2) Q4W, recovery, placebo

Muscle biopsies at baseline, 12 weeks, and 24 weeks

Transition to 6.8 mg/kg*

Open-label extension (OLE)

Long-term extension (LTE)

Population

- Ages 18–49 years

Primary endpoints

- Safety and tolerability

Additional endpoints

- Pharmacokinetics
- Change from baseline of:
  - Splicing
  - *DMPK* RNA expression
  - Multiple assessments of muscle strength and function
  - Patient-reported outcomes, including MDHI

Data from the MAD portion of the ACHIEVE study was used to select the registrational dose of 6.8 mg/kg Q8W that is being evaluated in the Registrational Expansion Cohort of the study[1,2]

Doses provided refer to approximate antisense oligonucleotide component of DYNE-101. Recovery cohort Q4W × 2 doses then placebo for the remainder of the 24W placebo-controlled period. Q8W, every 8 weeks with a loading dose given 4 weeks after first dose of active drug. Additional endpoints include select secondary and exploratory endpoints. *Transition to 6.8 mg/kg dose occurs at non-uniform times during OLE or LTE.
DMPK, dystrophia myotonica protein kinase; MAD, multiple ascending dose; MDHI Myotonic Dystrophy Health Index; LTE, long-term extension; OLE, open-label extension; Q4W, every 4 weeks; RNA, ribonucleic acid; W, week.

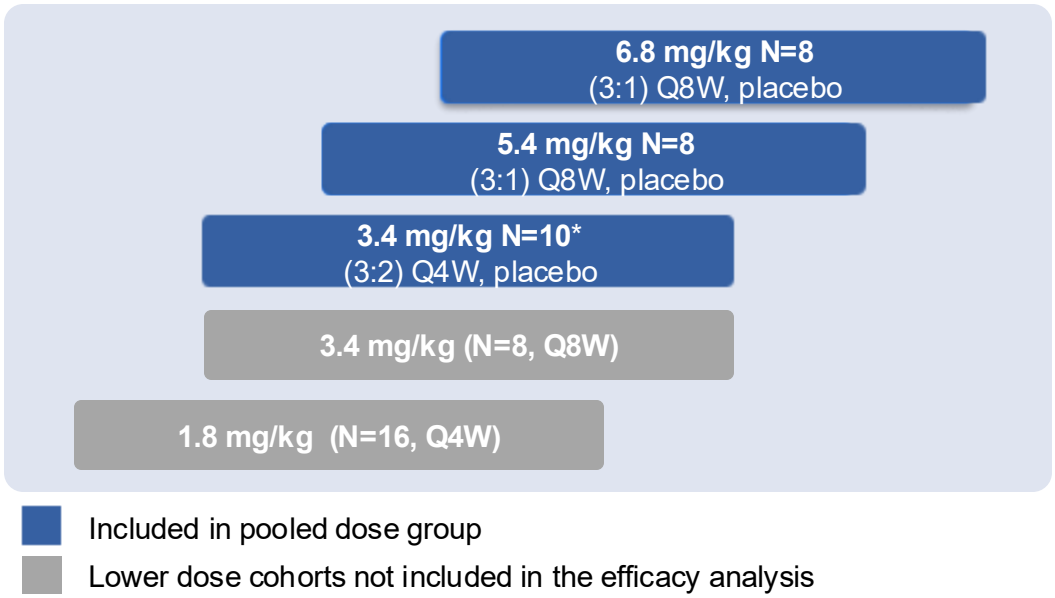
1. Lilleker J. 2025 Annual MDA Clinical and Scientific Conference. March 16-19, Dallas, TX; 2. Sansone V, et al. Poster presentation at the Annual International Congress of the WMS, Vienna, Austria, October 7–11, 2025. Poster 380P.

ACHIEVE

ACHIEVE MAD study: Efficacy analysis of pooled dose group

- Previous long-term analysis included N=6 assigned to 6.8 mg/kg (registrational dose) at baseline[1]
- To determine if similar trends hold in a larger sample, we analyzed 12-month efficacy of a pooled dose group (N=26)
- 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

Pooled dose group 1-year efficacy analysis



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. *Patients assigned to recovery were not included in this analysis.
MAD, multiple ascending dose; Q4W, every 4 weeks; Q8W, every 8 weeks.

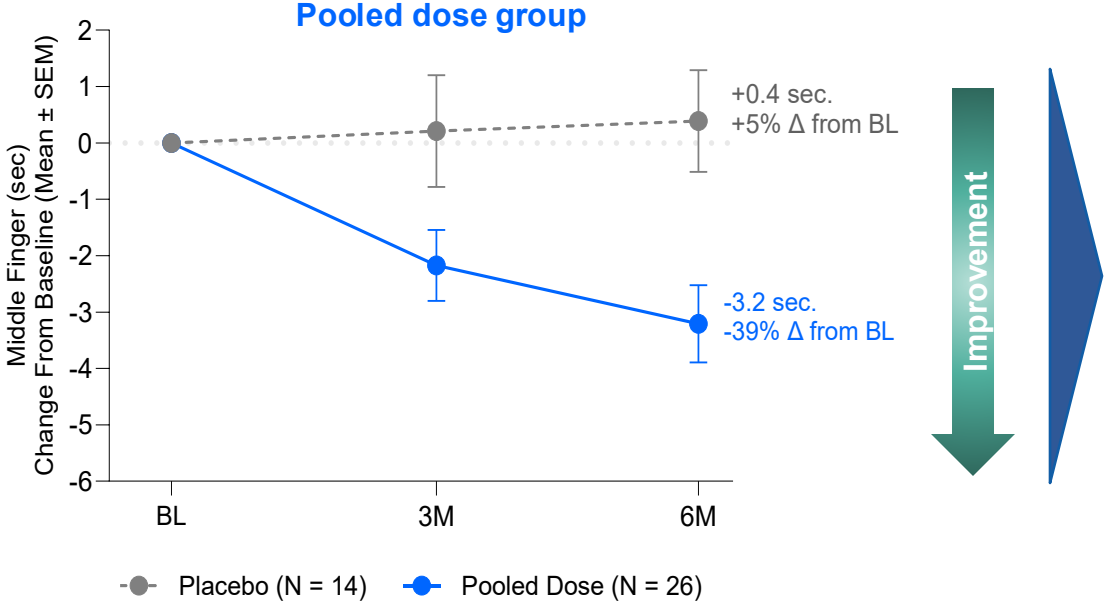
1. Sansone V, et al. Poster presentation at the Annual International Congress of the WMS, Vienna, Austria, October 7–11, 2025. Poster 380P.

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Pooled efficacy data continue to support vHOT as an early indicator of functional improvement

vHOT middle finger

Pooled dose group

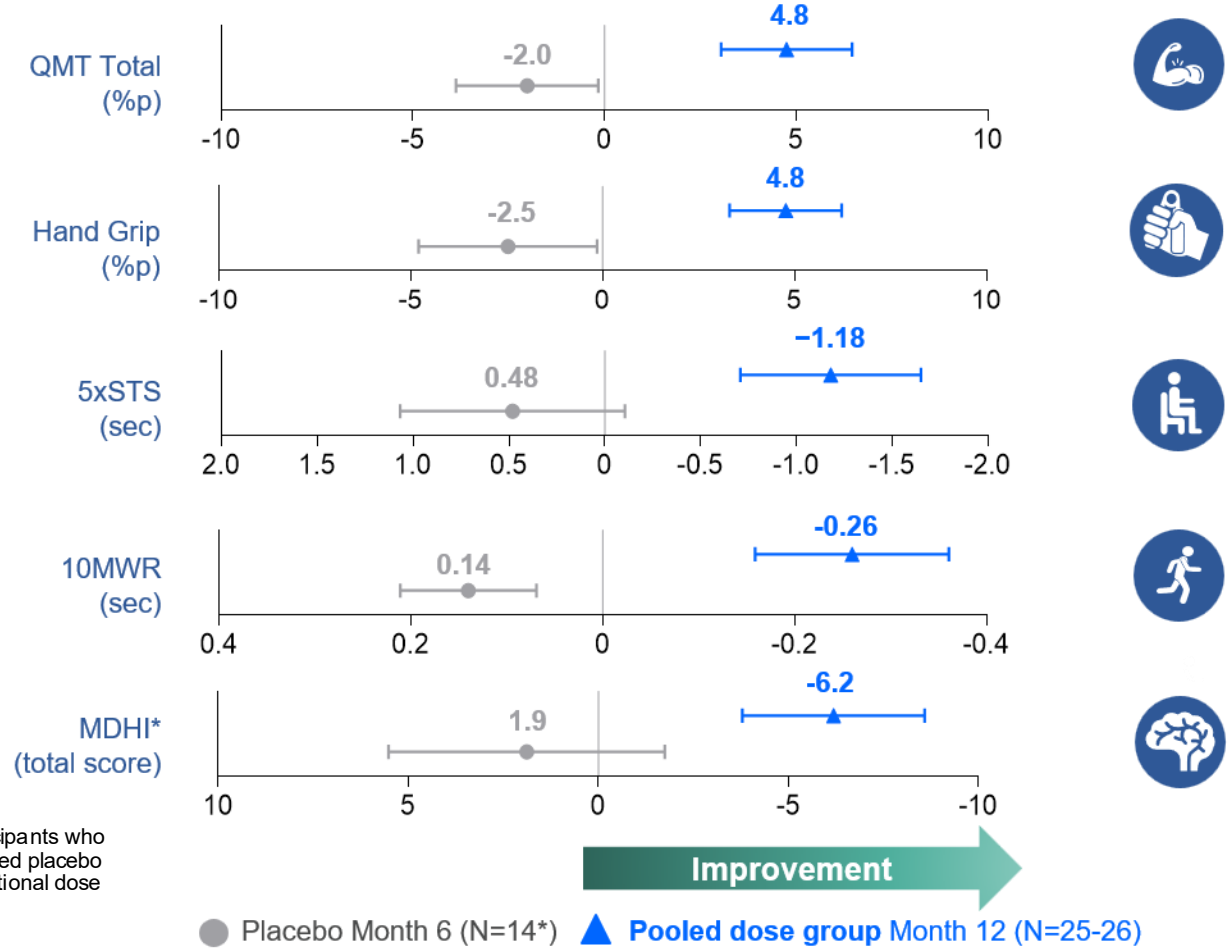


Baseline (sec), mean (SEM)	**7.5 (0.8)**	**8.2 (0.9)**

As of April 20, 2026, z-basivarsen administered in the MAD showed a favorable safety profile with no serious related TEAEs

Mean change from baseline (SEM)

Pooled dose group



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.
*MDHI, N=13. Percent mean change from baseline = (mean change from baseline/baseline mean)× 100. 6 months = 169 days; 12 months = 337 days.
%p, percent predicted; 5xSTS, five times sit-to-stand; 10MWR, 10-meter walk/run; 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.

ACHIEVE

Next steps for z-basivarsen development

ACHIEVE

Goal of registrational expansion cohort:

- Assess correction of underlying spliceopathy using vHOT as a measure of hand myotonia and function
- Designed to support accelerated approval in the US

Status:
Fully enrolled with 71 participants; data expected in Q1 2027

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Designed in partnership with the DM1 community
Goal of Phase 3 study:

- Primary endpoint is 5xSTS, a responsive and reliable endpoint with functional relevance to activities of daily living
- Assess and confirm multisystem functional improvement
- Support global access and reimbursement

Status:
Enrolling globally, including Asia, Europe, and North America

5xSTS, five times sit-to-stand; DM1, myotonic dystrophy type 1; vHOT, video hand opening time.

The 5xSTS test is a functionally meaningful endpoint in DM1

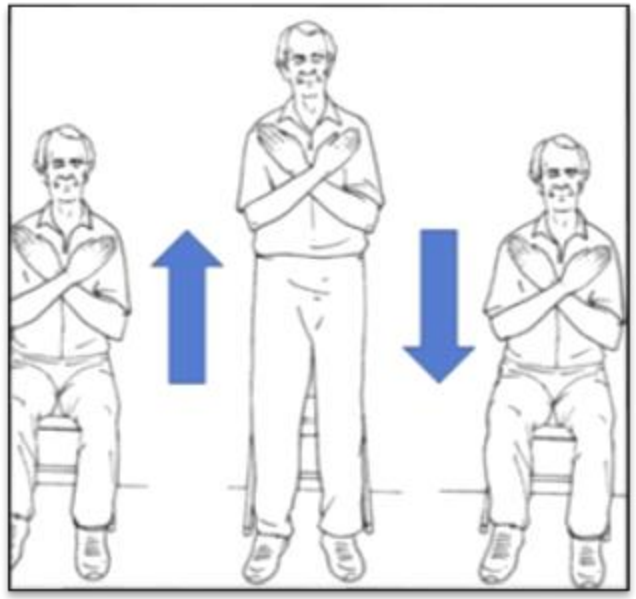
Five times sit-to-stand (5xSTS) quantifies the ability to perform **repeated sit to stand transfers** (lower extremity function, balance/postural control, functional mobility, stamina, and trunk muscle engagement)[1]

5xSTS assesses fall risk[1]

- 5xSTS independent **predictor of falls**[1]
- DM1 patients have **~7–10× increased risk of falls** vs healthy controls[2,3]
  - ~40% of DM1 falls result in injury
  - Risk ratio ~11–17% for associated fractures

"I recently fell down a staircase and got a concussion… It'd be nice not to fall. But I just celebrate every month that I don't fall...".

Adult with DM1



Measures ability to perform activities of daily living

5xSTS requires engagement of trunk muscles

- **Fat infiltration of trunk muscles in DM1** associated with decreases in[2]
  - Muscle strength
  - Mobility and balance
  - Respiratory function
- **Respiratory failure**, most common cause of death in DM1, can be due to skeletal muscle weakness[4,5]

5xSTS, five times sit-to-stand; DM1, myotonic dystrophy type 1.

1. Muñoz-Bermejo L, et al. *Biology (Basel)*. 2021;10:510; 2. Berends J, et al. *Neuromuscul Disord*. 2019;29:758–765; 3. Jiménez-Moreno AC, et al. *Neuromuscul Disord.* 2018;28(3):229–235; 4. Solbakken G, et al. *BMC Neurol*. 2019;19:135; 5. Alsaggaf R, et al. *Muscle Nerve*. 2025;71:229–236.

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Beyond myotonia: Establishing a potential benchmark measure for functional improvement in DM1

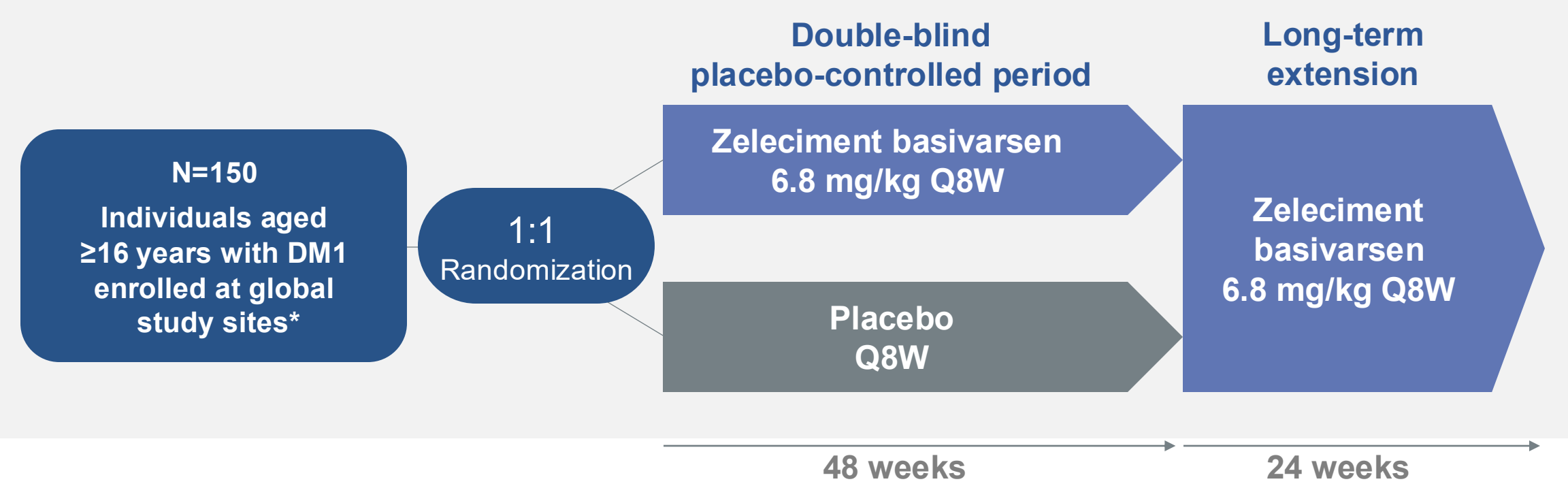
	vHOT	5xSTS
Reliable *Reproducible and accounts for population heterogeneity*	✓	✓
Responsive *Demonstrates responsiveness and ability to detect change over a reasonable timeframe*	✓	✓
Functionally meaningful *Reflects impact of disease severity and treatment*	◐	✓
Applicable to activities of daily living *Captures functional improvements that enhance quality of life*	◐	✓

5xSTS provides a comprehensive functional measure of outcomes in DM1 clinical trials

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DM1, myotonic dystrophy type 1; 5xSTS, five times sit-to-stand; vHOT; video hand opening time.

HARMONIA: Phase 3 study design



In addition to the primary endpoint of change in 5xSTS from baseline to Week 49, secondary and exploratory endpoints will broadly assess multisystem impact, including the CNS

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*Additional eligibility criteria apply as per protocol.
5xSTS, five times sit-to-stand test; CNS, central nervous system; DM1, myotonic dystrophy type 1; Q8W, every 8 weeks.

HARMONIA: Key inclusion and exclusion criteria

Selected inclusion criteria*

- Age ≥16 years
- DM1 confirmed by molecular genetics with trinucleotide repeat size >100
- Able to complete the following independently:†
  - Walk 10 meters
  - 5xSTS
- BMI <35 kg/m^2

Selected exclusion criteria*

- Known diagnosis of congenital DM1
- History of major surgical procedure within 12 weeks of start of screening (exception: pacemaker or defibrillator)
- Use of GLP-1 agonist/incretin medications within a period of 5 half-lives prior to screening assessments

Key changes from ACHIEVE[1]

- Inclusion of individuals 16–17 years and removal of upper age limit
- Onset of muscle symptoms at age ≥12 years no longer specified (however, congenital DM1 diagnosis remains exclusionary)
- Participants with controlled insulin-dependent diabetes are eligible
- Pacemakers and defibrillators are no longer exclusionary

*Additional eligibility apply. †Inserts or supports that do not extend above the ankle are permitted.
5xSTS, five times sit-to-stand; BMI, body mass index; DM1, myotonic dystrophy type 1; GLP-1, glucagon-like peptide 1.
1. ClinicalTrials.gov. NCT05481879.

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HARMONIA: Study endpoints

Primary endpoint

Change from baseline in 5xSTS at Week 49

Selected secondary endpoints

Change from baseline in muscle function tests at Week 49

- vHOT (middle finger)
- QMT total
- 10MWR
- 9-hole peg test

Patient- and clinician-reported outcomes

- MDHI*
- DM1-ACTIV^{C} total score*
- PGI-C and CGI-C
- PGI-S and CGI-S

Safety

- Safety and tolerability

*MDHI and DM1-ACTIV^{C} endpoints measured as change from baseline at Week 49.
5xSTS, five times sit-to-stand; 10MWR, 10-meter walk-run; CGI-C, clinical global impression of change; CGI-S, clinical global impression of severity; DM1, myotonic dystrophy type; DM1-ACTIV^{C}, DM1 activities and participation scale; MDHI, myotonic dystrophy health index; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; QMT, quantitative muscle testing; vHOT, video hand-opening time.

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HARMONIA: CNS endpoints

People with DM1 report considerable CNS symptoms, marking a significant unmet need[1]

Cognition	Behavior/personality	Emotional issues	Fatigue/sleep	EDS/sleep
>50%[2]	~50%[1]	60%[1]	93%[1]	93%[1]

HARMONIA will include a broad set of endpoints designed to assess CNS impact, including:



CogState

Clinical outcome assessment designed to measure multiple aspects of cognitive health



MDHI subscales

CNS-related subscales, including emotional issues, sleep, fatigue, cognitive impairment, pain and communication



FDSS

Fatigue and excessive daytime sleepiness scale: a patient-reported outcome



Actigraphy

Data may include parameters of sleep and physical activity



Biomarkers

Analyses may include blood- and/or urine-based measures

CNS, central nervous system; DM1, myotonic dystrophy type 1; EDS, excessive daytime sleepiness; FDSS, fatigue and excessive daytime sleepiness scale; MDHI, myotonic dystrophy health index.

1. Hagerman KA, et al. *Muscle Nerve.* 2019;59(4)457–464; 2. Fujino H, et al. *Muscle Nerve.* 2018;57(5):742–748.

Summary

- HARMONIA has been designed alongside the DM1 community and leading physicians, and is intended to be a field-defining Phase 3 study
- The primary endpoint is the 5xSTS test, a reliable, responsive, functionally meaningful endpoint that is relevant to activities of daily living
- A broad set of secondary and exploratory endpoints will evaluate the impact of z-basivarsen on multisystemic functional improvement, including the CNS
- Clinical study sites for HARMONIA are enrolling globally, including in Asia, Europe, and North America

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5xSTS, five times sit-to-stand; CNS, central nervous system; DM1, myotonic dystrophy type 1.

Acknowledgments

- The authors wish to thank the ACHIEVE investigators and site staff, ACHIEVE participants and their families, and the DM1 community/advocates/HCPs who have provided input to the HARMONIA protocol and initiation activities

View on the Dyne Therapeutics publications website:
Functional Improvement With Zeleciment Basivarsen in the Phase 1/2 ACHIEVE Trial

Poster

Supplement

HARMONIA

DM1, myotonic dystrophy type 1; HCP, healthcare professional.