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

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View on the Dyne Therapeutics publications website:

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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

HARMONIA

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

We are on a mission to deliver

FUNCTIONAL IMPROVEMENT

for individuals, families and communities

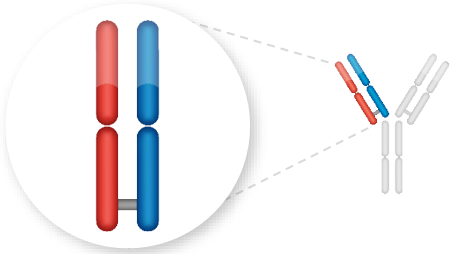
Functional improvement is best achieved by addressing the root cause of the disease across multiple organ systems

Dyne THERAPEUTICS

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

ANTIBODY

Proprietary Fab against TfR1 to enable targeted delivery to muscle and CNS

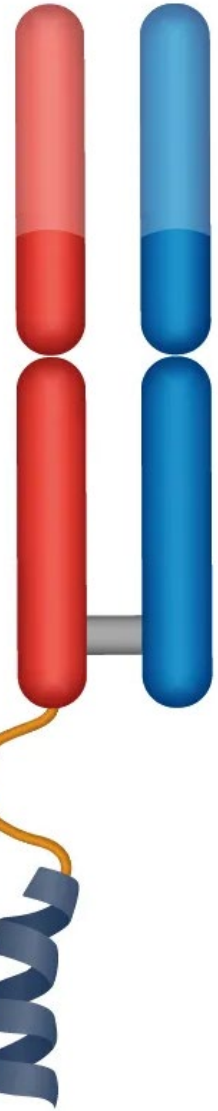


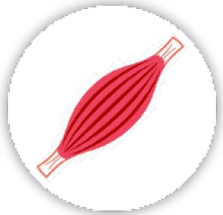
LINKER

Connects Fab and payload

PAYLOAD

Modularity enables rational selection of payload to target the genetic basis of disease (ASO, PMO, siRNA, enzyme)





Skeletal (including diaphragm) and smooth muscle

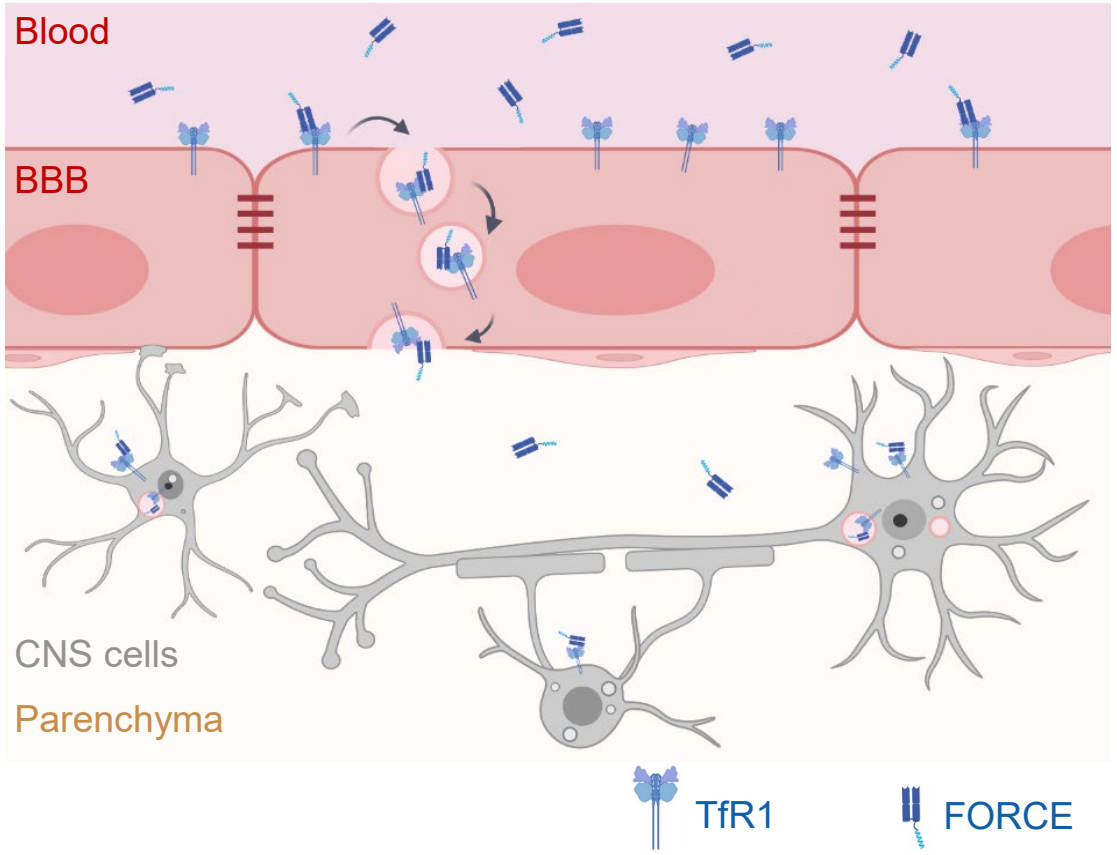
Cardiac muscle

CNS

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

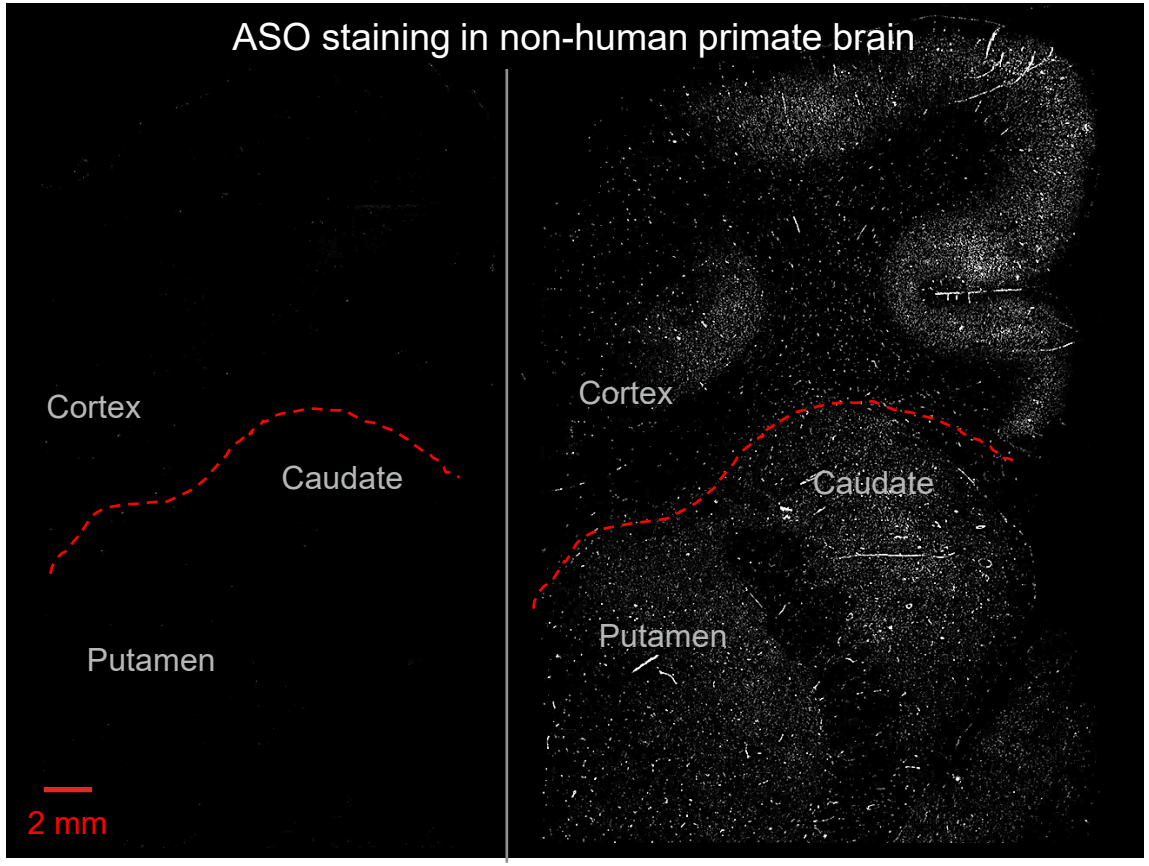
The FORCE platform can cross the blood-brain-barrier and achieve widespread brain delivery

TfR1-mediated transcytosis: potential for crossing the BBB



Naked ASO, IV
No ASO delivery

FORCE, IV
Widespread ASO delivery



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.

Diagram adapted from Pulgar VM. *Front Neurosci.* 2019;12:1019 and Liu K, et al. *Sci Rep.* 2016;6:21019, and created using BioRender.com.

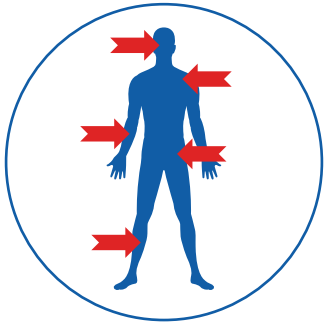
ASO, antisense oligonucleotide; BBB, blood–brain barrier; CNS, central nervous system; IV, intravenous; TfR1, transferrin receptor 1.

Zanotti S. Presentation at the 26th American Society of Gene and Cell Therapy Annual Meeting. May 17, 2023. Los Angeles, USA. Abstract 82.

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]



Heterogenous 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, heart, endocrine system, and CNS[1,3]

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

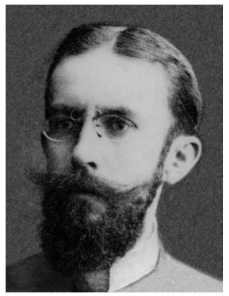
An increasing number of investigational therapies are in clinical development[4]

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.

Progress and developments in myotonic dystrophy type 1



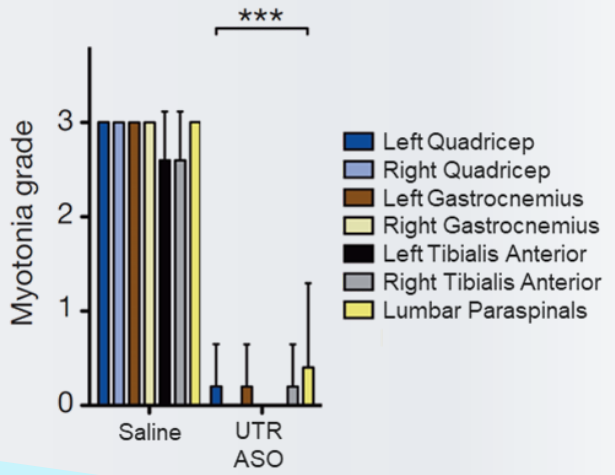
1909
Hans Steinert clinically defines myotonic dystrophy[1]

2000
DM1 mouse model demonstrates RNA gain of function in disease pathogenesis[3]

2012
Systemic ASO treatment shown to reverse myotonia in a mouse model of DM1[5]

- Dose-dependent partial reversal of myotonia observed within just 2 weeks of administration
- Effects of UTR-directed ASO on myotonia were maintained 1 year after initial treatment course

Myotonia grade after 1 year in *HSA*^{LR} mice treated with SC ASO for 4 weeks[5]



Clinical development

1992
Unstable CTG region identified[2]

2003
Role of MBNL1 and spliceopathy identified[4]

2014
First clinical trial of naked ASO therapy for DM1 begins[6]

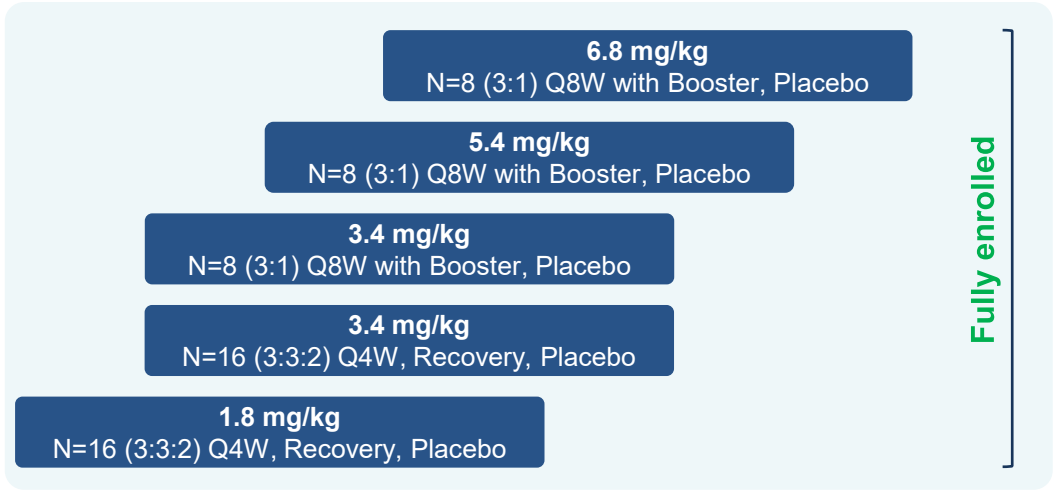
2021–22
Clinical trials of conjugated ASO therapies begin[7]

2025
Composite SI score shown to correlate with common clinical outcome measures for DM1[8]

*** P<0.0001 ASO vs saline (two-way ANOVA).
ASO, antisense oligonucleotide; CTG, cytosine-thymine-guanine trinucleotide repeat; DM1, myotonic dystrophy type 1; MBNL, muscleblind-like protein; SC, subcutaneous; SI, Splice Index; UTR, untranslated region.
1. Steinberg H, et al. *Nervenarzt*. 2008;79(8):965–970; 2. Brook JD, et al. *Cell*. 1992;68(4):799–808; 3. Mankodi A, et al. *Science*. 2000;289(5485):1769–1773;
4. Kanadia RN, et al. *Science*. 2003;302(5652):1978–1980; 5. Wheeler TM, et al. *Nature*. 2012;488(7409):111–115; 6. Thornton CA, et al. *Lancet Neurol*. 2023;22(3):218–228;
7. Pascual-Gilabert M, et al. *Drug Discov Today*. 2023;28(3):103489; 8. Provenzano M, et al. *J Clin Invest*. 2025;135(4):e185426.

ACHIEVE: Phase 1/2 study of zeleciment basivarsen (z-basivarsen, also known as DYNE-101) in adults with DM1

Placebo-controlled period (MAD cohorts)



Transition to 6.8 mg/kg[1]

Open-label extension (OLE)

Long-term extension (LTE)

Population

- Ages 18–49 years

Primary endpoints

- Safety and tolerability

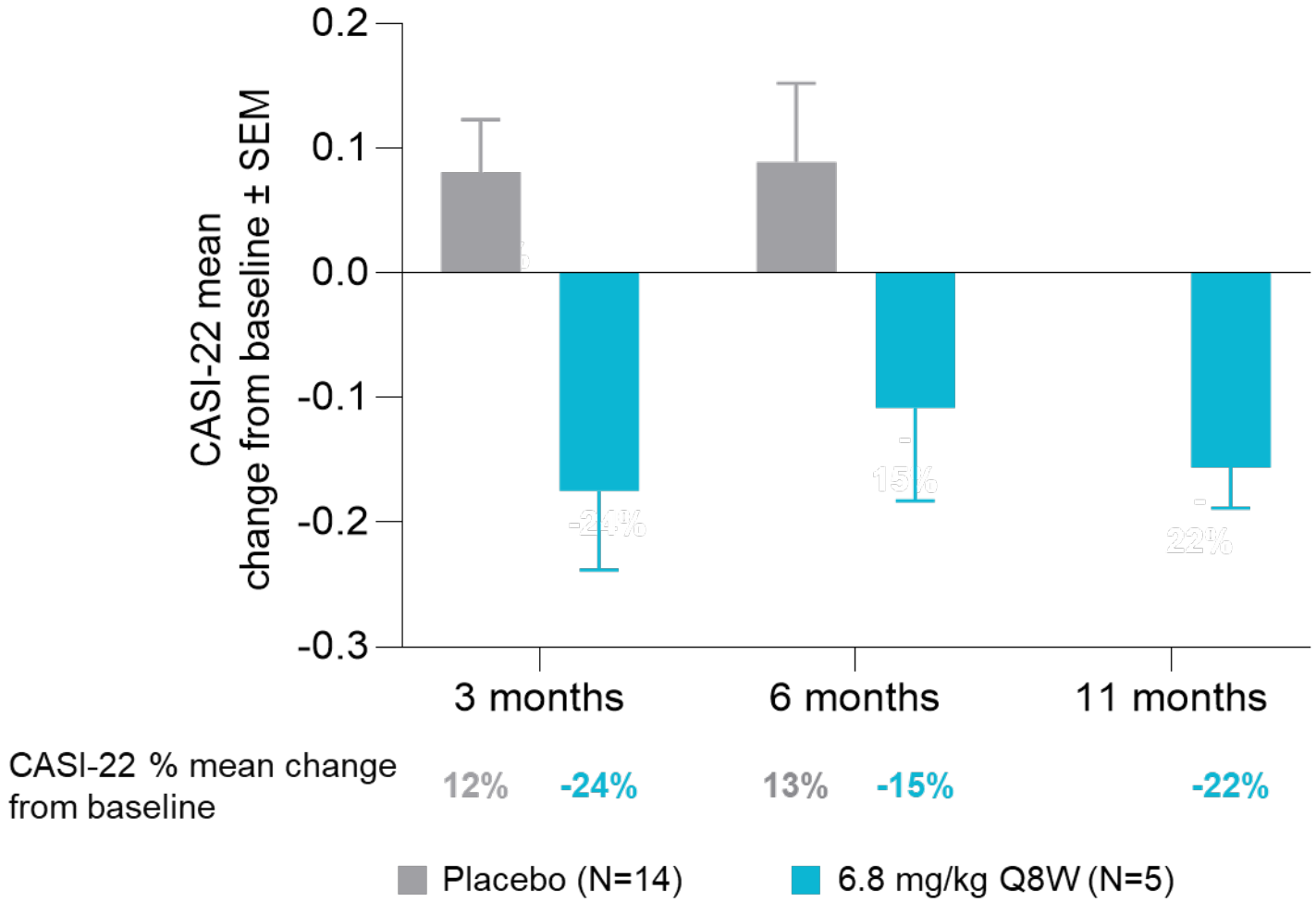
Additional endpoints

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

Registrational dose and dose regimen selected at 6.8 mg/kg Q8W

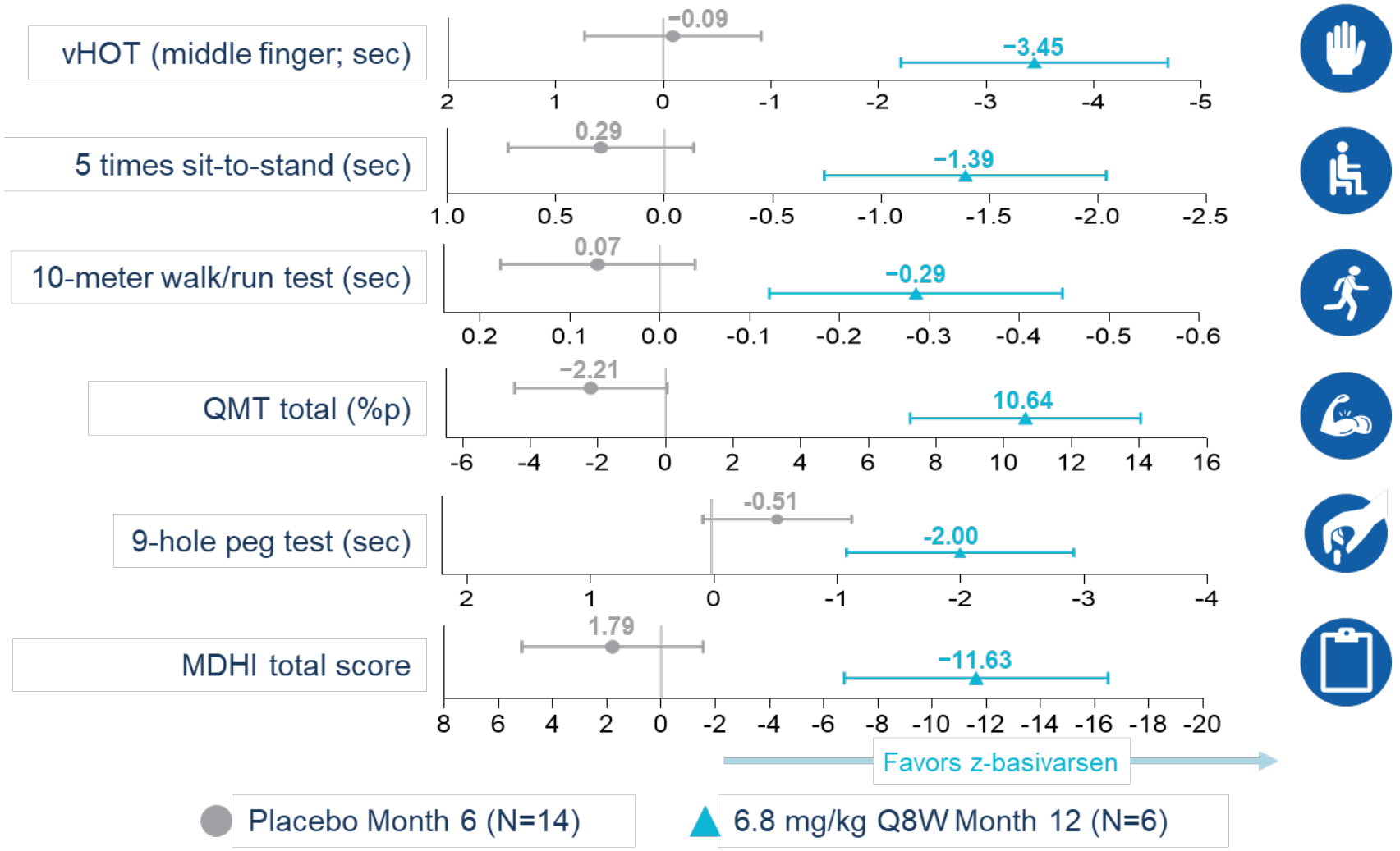
Doses provided refer to antisense oligonucleotide component of z-basivarsen. Recovery cohort Q4W ×2 doses then placebo for the remainder of the 24W placebo-controlled period.
Q8W with booster includes Q4W ×3 doses then Q8W dosing. Additional endpoints include select secondary and exploratory endpoints.
1. Transition to 6.8 mg/kg dose occurs at non-uniform times during OLE or LTE.
DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; MAD, multiple ascending dose; MDHI, Myotonic Dystrophy Health Index; Q4W, every 4 weeks; Q8W, every 8 weeks.
Lilleker J, et al. Presentation at the Annual MDA Clinical and Scientific Conference, Dallas, USA, March 16–19, 2025

Z-basivarsen led to consistent splicing correction



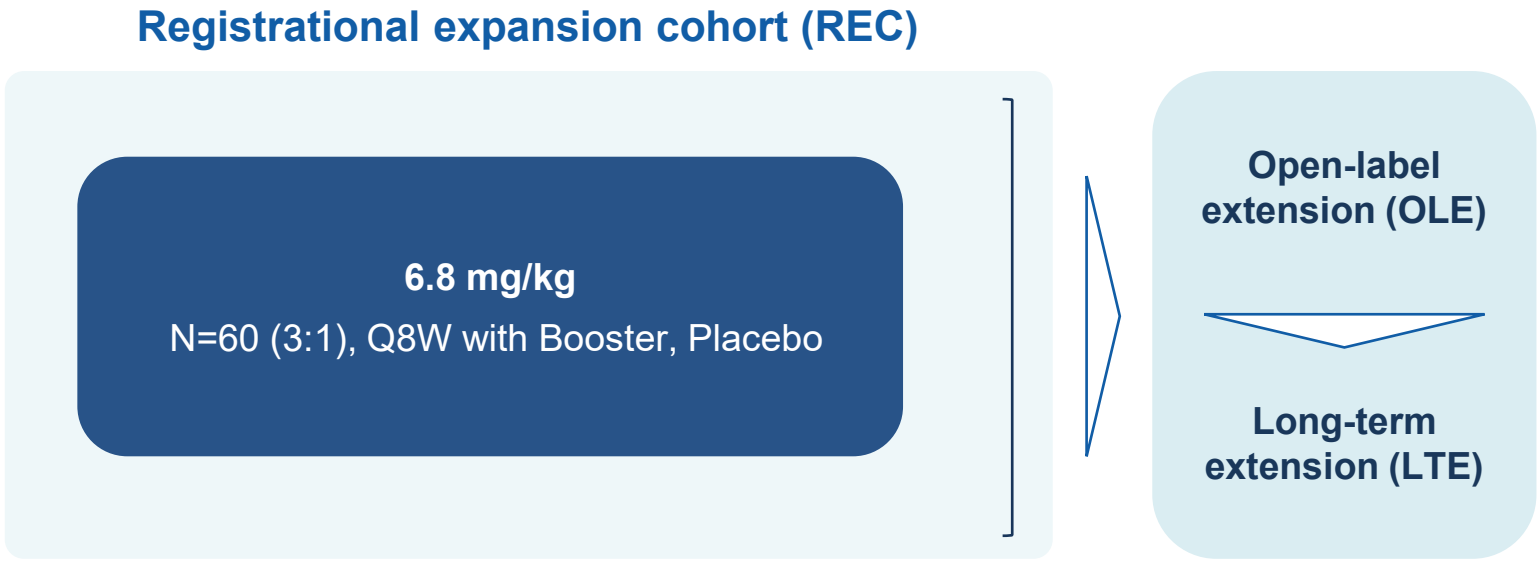
All patients transitioned to treatment at Month 6. Multiple aliquot approach, all aliquots are tested and median taken across those with valid results, up to 4. One baseline sample in 6.8 mg/kg treatment groups not included within splicing assay as the sample did not meet QC criteria. Percent mean change, calculated as mean change from baseline divided by baseline mean. 3 months = 85 days; 6 months = 169 days; 11 months = 309 days.
CASI, composite alternative splicing index; DMPK, dystrophia myotonica protein kinase; SEM, standard error of the mean; Q8W, every 8 weeks.
Sansone V, et al. Supplementary data from poster presentation at the Annual International Congress of the WMS, Vienna, Austria, October 7–11, 2025. Poster 380P.

In the ACHIEVE trial, z-basivarsen led to functional improvement across several clinical measures



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.
MDHI, myotonic dystrophy health index; Q8W, every 8 weeks; QMT quantitative muscle testing; SEM, standard error of the mean; vHOT, video hand opening time.
Sansone V, et al. Poster presentation at the Annual International Congress of the WMS, Vienna, Austria, October 7–11, 2025. Poster 380P.

ACHIEVE registrational expansion cohort (REC)



Population

- Ages 18–65 years

Primary endpoints

- Change in myotonia (vHOT) at Week 25

Additional endpoints

- Change from baseline of:
  - Splicing
  - Multiple assessments of muscle strength and function
  - Patient-reported outcomes, including MDHI

Doses provided refer to antisense oligonucleotide component of z-basivarsen. Q8W with booster includes Q4W x 3 doses then Q8W dosing. Additional endpoints include select secondary and exploratory endpoints.
DM1, myotonic dystrophy type 1; MDHI, Myotonic Dystrophy Health Index; Q4W, every 4 weeks; Q8W, every 8 weeks; REC, registrational expansion cohort; vHOT, video hand opening time.
ClinicalTrials.gov. NCT05481879.

Z-basivarsen clinical development plan

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:
Currently enrolling in US, Europe, UK, Australia, and New Zealand

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Goal of Phase 3 study:

- Assess and confirm multisystem functional improvement
- Support global access and reimbursement

Status:
Sites initiating globally

Designed in partnership with the DM1 community

- ✓ Enrollment criteria
- ✓ Assessments
- ✓ PROs
- ✓ Study logistics (e.g. travel)

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DM1, myotonic dystrophy type 1; PRO, patient-reported outcome; vHOT, video hand opening time.

Framework for primary endpoint consideration

	vHOT
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*	

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DM1, myotonic dystrophy type 1; vHOT, video hand opening time.

The 5xSTS test is a functionally meaningful endpoint in DM1

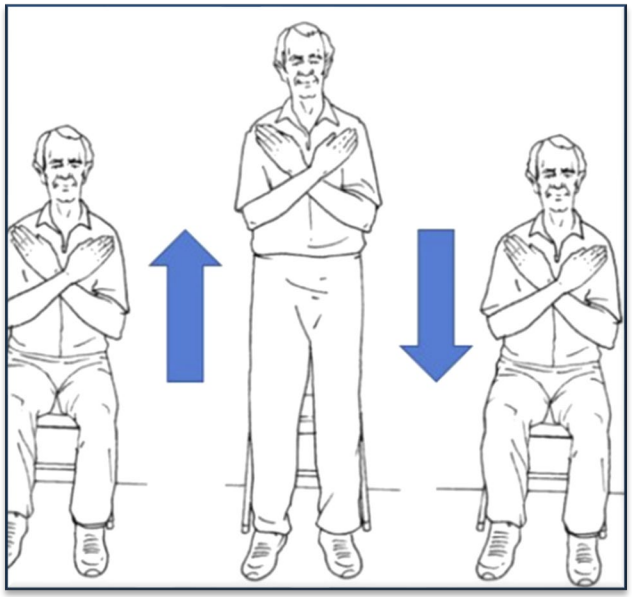
Five Times Sit-to-Stand (5xSTS) quantifies the ability to perform **repeated sit to stand transfers** (lower extremity function, balance/postural control, functional mobility, stamina, and trunk muscle engagement)[1]

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]
  - 50% 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]

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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;
2. Solbakken G, et al. *BMC Neurol*. 2019;19:135; 3. Alsaggaf R, et al. *Muscle Nerve*. 2025;71:229–236.

People with DM1 have impaired 5xSTS scores over each decade of life and scores decline more quickly compared to those without DM1

DM1 impact on 5xSTS when compared to unaffected individuals in same decade of life: Multicenter observational study of DM1 (MOS-DM1/POP) vs 5xSTS scores of unaffected individuals[1,2]

Impairment detected at each decade analyzed	High degree of impairment detected across each decade	Accelerated rate of decline across decades
On average, people with DM1 had slower 5xSTS scores than people without DM1 regardless of decade analyzed*	People with DM1 had 5xSTS times that were on average between ~>5–9 seconds slower than people without DM1*	DM1 appears to have a greater impact on 5xSTS impairment over time when compared to aging alone†

Data from DM1 Natural History utilized with permission of Charles Thornton, University of Rochester.
*Impairment in mean 5xSTS scores detected at each decade analyzed when comparing those with DM1 to age decade matched unaffected individuals.
†Comparison of 5xSTS change in affected and unaffected populations.
5xSTS, five times sit-to-stand; DM1, myotonic dystrophy type 1; SD, standard deviation.
1. Clinicaltrials.gov. NCT02308657; 2. Bohannon, et al. *Isokinetic Exer Sci*. 2010;18(4):235–240.

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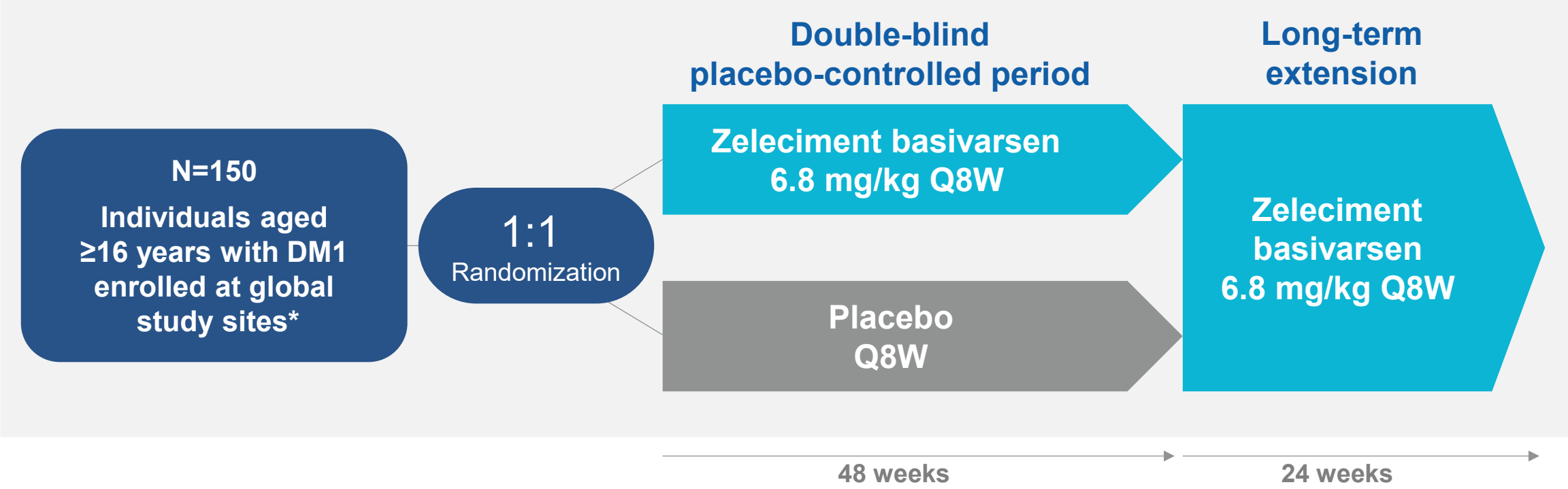
DM1, myotonic dystrophy type 1; 5xSTS, five times sit-to-stand vHOT; video hand opening time.

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 & 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

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*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.

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

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*MDHI and DM1-ACTIVE^{C} endpoints measured as change from baseline at Week 49.
5xSTS, five times sit-to-stand; 10MWR, 10-meter walk-run test; 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.

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 & 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 now being initiated at international locations

For more information

- Speak to your local MSL in the USA or contact medinfo@dyne-tx.com
- Visit dynemedicalcentral.com to receive more information about DM1 and other neuromuscular diseases

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

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

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HARMONIA