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HARMONIA Study Design: A Global Phase 3 Trial Assessing the Efficacy and Safety of Zeleciment Basivarsen in Myotonic Dystrophy Type 1 (DM1)

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HARMONIA

BACKGROUND

- Myotonic dystrophy type 1 (DM1) is a rare, progressive, genetic, neuromuscular disorder in which a spliceopathy caused by CTG repeat expansions in the myotonic dystrophy protein kinase (*DMPK*) gene drives heterogenous multisystemic manifestations (muscular, central nervous system [CNS] and non-muscular) resulting in substantial disease burden and early mortality[1–5]
- No disease-modifying therapies are currently available, limiting treatment to symptom management[6,7]
- High unmet need exists for a treatment that addresses the underlying cause of DM1 in systems where patients report the most impact, including muscle and CNS[4]
- ACHIEVE (NCT05481879) is an ongoing global, randomized, placebo-controlled, Phase 1/2 clinical trial evaluating the safety and efficacy of zeleciment basivarsen (z-basivarsen, also known as DYNE-101) in adults aged 18–65 years with DM1[8]
  - ACHIEVE consists of a multiple ascending dose (MAD) period (24 weeks [completed]), followed by an open-label extension (OLE) period (24 weeks), and long-term extension (LTE) period (168 weeks)[8,9]
  - Data from the MAD portion of ACHIEVE demonstrated that z-basivarsen was associated with trends toward functional improvement across diverse clinical measures, including myotonia, muscle strength and function, and patient-reported outcomes[9]
  - Based on the benefit–risk profile observed in the MAD portion of ACHIEVE, the selected dose regimen of 6.8 mg/kg Q8W is currently being evaluated in the registrational expansion cohort (REC), with change from baseline in hand myotonia and function as measured by video hand opening time (vHOT) at 6 months versus placebo being assessed as the primary endpoint[10]
    - As of April 20, 2026, the 6.8 mg/kg dose of z-basivarsen administered Q8W in the MAD showed a favorable safety profile with no serious related TEAEs, based on approximately 143 patient-years of follow-up[11]
- Building on the ongoing REC of ACHIEVE, HARMONIA is a Phase 3 study assessing the efficacy, safety, and tolerability of z-basivarsen in individuals with DM1

DM1 pathophysiology and z-basivarsen mechanism of action

- DM1 is caused by CTG repeat expansion in the *DMPK* gene, ultimately leading to multisystemic spliceopathy[12]
- Mutant *DMPK* messenger RNA (mRNA) forms a hairpin structure that aggregates into toxic nuclear foci in multiple cell types (including those in muscle and brain), sequestering members of the muscleblind-like (MBNL) family of splicing factors within the nucleus and leading to splicing dysregulation (spliceopathy), which is the molecular hallmark of DM1[12]
- Z-basivarsen is an investigational therapeutic that consists of a transferrin receptor 1 (TfR1)-binding antigen-binding fragment (Fab) conjugated to an antisense oligonucleotide (ASO) that targets mutant nuclear *DMPK* RNA for degradation with the goal of correcting the underlying spliceopathy that causes disease manifestations[13–16]
  - TfR1 is highly expressed on the surface of muscle cells and brain capillary endothelial cells that form the blood–brain barrier, enabling broad delivery to cells within both muscle and the CNS[13,17]

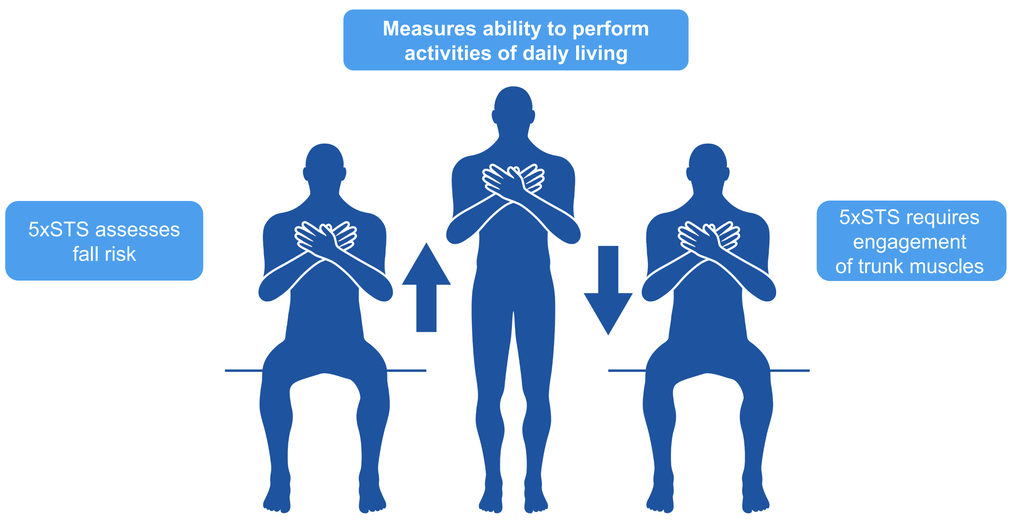
OVERALL STUDY AIM

- HARMONIA is a Phase 3, placebo-controlled, randomized, double-blind study powered to detect the multisystemic efficacy, safety, and tolerability of z-basivarsen administered intravenously to individuals with DM1 aged ≥16 years

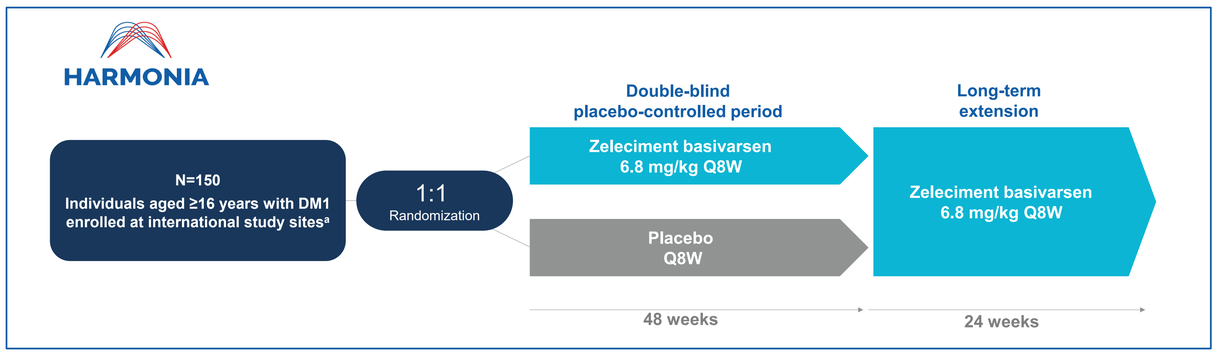
TRIAL DESIGN

- The ACHIEVE REC utilizes vHOT for the primary endpoint, as a direct measure of myotonia and function and as a potential early indicator of multisystemic functional improvement due to correction of underlying spliceopathy[8–11,18,19]
- Designed with patient and physician input, HARMONIA aims to capture the broader, multisystemic impact of treatment, and utilizes 5xSTS for the primary endpoint, reflecting a functionally meaningful measure that is highly relevant to individuals with DM1[20,21]
  - 5xSTS is a reliable and responsive measure of the ability to perform sit-to-stand transfers and reflects functions highly meaningful to individuals with DM1, including lower extremity strength, balance control, mobility, stamina, and trunk muscle engagement[20,21]
  - Additionally, 5xSTS has been shown to be an independent predictor of falls[22] and provides important clinical information related to the ability to perform activities of daily living[21]
  - In addition to 5xSTS, HARMONIA will include a broad set of secondary and exploratory endpoints designed to capture the multisystemic impact of z-basivarsen, including effects on the CNS

5xSTS may provide a potential measure for functional improvement in DM1[21]



HARMONIA study design



a. Additional eligibility criteria apply as per protocol. Q8W, every 8 weeks.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria[a]

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

Exclusion criteria[a]

- 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

a. Additional eligibility apply; b. 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.

TRIAL 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[a]
- DM1-ACTIV^C total score[a]
- PGI-C and CGI-C
- PGI-S and CGI-S

Safety

- Safety and tolerability

A suite of exploratory endpoints will assess multiple domains of CNS impact in DM1, including use of clinical outcome assessments, patient-reported outcomes, and actigraphy

a. 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, Clinician Global Impression of Change; CGI-S, Clinician Global Impression of Severity; CNS, central nervous system; DM1, myotonic dystrophy type 1; DM1-ACTIV^C, DM1 Activity and Participation scale for clinical use; 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.

CONCLUSIONS

- HARMONIA reflects input from the DM1 community and leading physicians and is designed to evaluate z-basivarsen in a Phase 3 setting
- The primary endpoint is the 5xSTS test, which is intended to assess functional mobility relevant to sit-to-stand performance
- 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

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DISCLOSURE INFORMATION

Sowmya Chary, Soma Ray, Shuli Yu, and Douglas Kerr are employees of Dyne Therapeutics and may hold stock in the company.

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Zeleciment basivarsen (z-basivarsen, also known as DYNE-101) 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.