

# A Randomized, Placebo-Controlled, Multiple Ascending Dose Study Assessing Safety, Tolerability, Pharmacodynamics, Efficacy, and Pharmacokinetics of DYNE-101 Administered to Participants with Myotonic Dystrophy Type 1

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This study has been transitioned to CTIS with ID 2023-510353-42-00 check the CTIS register for the current data. The purpose of this first-in-human study is to evaluate the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics...

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruiting
<b>Health condition type</b>	Musculoskeletal and connective tissue disorders congenital
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON56459

### Source

ToetsingOnline

### Brief title

ACHIEVE study

### Condition

- Musculoskeletal and connective tissue disorders congenital
- Muscle disorders
- Neuromuscular disorders

### Synonym

DM1, Myotonic Dystrophy Type 1

## Research involving

Human

## Sponsors and support

**Primary sponsor:** Dyne Therapeutics, Inc.

**Source(s) of monetary or material Support:** Dyne Therapeutics;Inc.

## Intervention

**Keyword:** antisense oligonucleotide, DM1, DYNE-101, Myotonic Dystrophy Type 1

## Outcome measures

### Primary outcome

Number and proportion of participants with treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), TEAEs considered related to study drug, and TEAEs leading to discontinuation from study drug and discontinuation from the study

### Secondary outcome

Change from baseline in splicing index in skeletal muscle tissue

Change from baseline in DMPK RNA expression in muscle tissue

Change from baseline in hand grip relaxation time by a dynamometer

Change from baseline in myotonia as measured by vHOT

Change from baseline in Quantitative Myometry Testing (QMT)

Change from baseline in 10-meter walk/run test (10-MWRT)

Change from baseline in stair ascend/descend test

Change from baseline in 5 times sit to stand (5×STS)

Change from baseline in 9 Hole Peg Test (9 HPT)

Maximum observed plasma drug concentration (C<sub>max</sub>)

Time to maximum observed plasma drug concentration (t<sub>max</sub>)

Area under the plasma-drug concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC<sub>last</sub>)

AUC extrapolated to time infinity (AUC\*)

Apparent terminal phase elimination rate constant (\*Z)

Apparent terminal elimination half-life (t\*)

Plasma clearance (CL)

Volume of distribution at the terminal phase (V<sub>z</sub>), if appropriate

Volume of distribution at steady state (V<sub>ss</sub>), if appropriate

Tissue ASO concentration

Incidence of antidrug antibodies (ADAs)

## Study description

### Background summary

Although clinical care recommendations have been established, no curative or disease modifying treatments for DM1 are currently available. This limits treatment to management of symptoms (Ashizawa et al. 2018, Johnson et al. 2019). Thus, the development of new therapies is important to address this significant unmet need.

DYNE-101 is an antigen-binding fragment (Fab) drug conjugate (FDC) designed to deliver a gapmer antisense oligonucleotide (ASO) therapeutic to muscle tissue for the treatment of myotonic dystrophy type 1 (DM1), an autosomal dominant, serious, rare, progressive, and degenerative neuromuscular disease.

DYNE-101 targets the DMPK RNA and is expected to reduce levels of DMPK transcripts harboring the toxic expansion of CUG repeats that cause DM1 pathology. This effect is predicted to lead to the release of MBNL proteins and consequently correct the splicing defects that drive the manifestation of DM1 in muscle tissue.

DYNE-101 was developed with a Fab that is optimized to target human transferrin receptor 1 (TfR1), conjugated via a clinically validated linker to an oligonucleotide that is specific to the human DMPK RNA. DYNE-101 was proven to

be highly efficacious at reducing DMPK RNA in multiple DM1 pharmacology models in vitro and in vivo.

## **Study objective**

This study has been transitioned to CTIS with ID 2023-510353-42-00 check the CTIS register for the current data.

The purpose of this first-in-human study is to evaluate the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple ascending doses (MADs) of DYNE-101 administered intravenously (IV) to participants with DM1. This study is designed to identify the therapeutic dose and regimen to be used in the long-term extension (LTE) and future studies.

Primary objective:

To evaluate the safety and tolerability of multiple IV doses of DYNE-101 administered to participants with DM1

Secondary objectives:

To evaluate the effect of multiple intravenous doses of DYNE-101 administered to participants with DM1 on muscle tissue

To evaluate change in muscle parameters after multiple doses of DYNE-101 administered to participants with DM1

To evaluate plasma and muscle tissue PK following multiple intravenous doses of DYNE 101 administered to participants with DM1

To evaluate the immunogenicity of multiple intravenous doses of DYNE-101 administered to participants with DM1

## **Study design**

This is a MAD study with a 24-week double-blinded, placebo controlled period to assess the safety, tolerability, PD, efficacy, and PK of DYNE-101 administered IV to participants with DM1. The study consists of dose escalation across 4 ascending dose levels. Participants who receive dose level 1 will follow an every 4 weeks (Q4W) dosing regimen (Cohort 1). For dose level 2 participants in Cohort 2A will receive dose level 2 Q4W, while participants in Cohort 2B will receive dose level 2 every 8 weeks (Q8W) with a booster dose on Days 29 and 197. Cohort 2B will begin enrollment after the last participant is enrolled in Cohort 2A. Participants who receive dose levels 3 and 4 will follow a Q4W dosing regimen (Cohorts 3A and 4A) and/or Q8W dosing regimen with a booster dose on Days 29 and 197 (Cohorts 3B and 4B). The purpose of the booster dose is to accelerate achievement of steady-state concentrations.

All participants will undergo a Screening Period of up to 60 days, a 24-week Placebo-Controlled Period (with first dose on Day 1), a 24-week DYNE-101 Treatment Period (starting on Day 169), and an LTE (starting when the dose is

administered at the Day 337 Visit and ending on Day 1009).

This study plans to open cohorts at 4 dose levels. Dose levels 1 will enroll (ie, randomize) 16 participants. Dose level 2 will enroll 24 participants (16 in Cohort 2A and 8 in Cohort 2B). Dose levels 3 and 4 may enroll up to 16 participants each. That is a total of 72 participants (54 active and 18 placebo). In addition, up to 16 participants may be enrolled as part of 1 or 2 expansion cohorts, and up to 2 participants per cohort may be replaced. That means up to 106 participants may be enrolled in this study.

## **Intervention**

Participants in Cohorts 1 and 2A will be randomized 3:3:2 to receive study drug during the Placebo-Controlled Period as follows:

- Six participants will receive 6 active repeat doses of DYNE-101 Q4W.
- Six participants will receive 2 active repeat doses of DYNE-101 on Days 1 and 29 followed by 4 repeat doses of placebo Q4W. These participants will inform the PK and PD parameters extrapolated from nonclinical species.
- Four participants will receive 6 repeat doses of placebo Q4W.

During the Placebo-Controlled Period, participants in Cohort 2B (Q8W) will be randomized 3:1 to receive either DYNE-101 or placebo Q8W with a booster dose on Day 29. For dose levels 3 and 4, after obtaining data from the first cohort of the previous dose level (ie, Cohort 2A or Cohort 3A/Cohort 3B, as applicable), the Dose Evaluation Committee (DEC) will provide a recommendation to the Safety Management Committee (SMC) whether to open a Q4W dosing regimen (Cohorts 3A and 4A), a Q8W dosing regimen with a booster on Day 29 (Cohorts 3B and 4B), or both for dose levels 3 and 4. During the Placebo-Controlled Period, participants in Cohorts 3A and 4A will be randomized 3:1 to receive either DYNE-101 or placebo Q4W. Participants in Cohorts 3B and 4B will be randomized 3:1 to receive either DYNE-101 or placebo Q8W with a booster dose on Day 29.

Starting on Day 169, all participants, including those previously receiving placebo, will receive treatment with DYNE-101 during the DYNE-101 Treatment Period and during the 96-week LTE. Participants in Cohorts 1, 2A, 3A and 4A will receive DYNE-101 Q4W. Participants in Cohorts 2B, 3B and 4B will receive DYNE-101 Q8W. To mirror the booster dosing regimen in the Placebo-Controlled Period, a booster dose of DYNE 101 will be administered on Day 197 of the DYNE-101 Treatment Period to participants originally randomized to placebo (Figure 1 of the protocol). To maintain the blind of the randomized treatment that was administered during the Placebo-Controlled Period, a corresponding dose of placebo will be administered on Day 197 of the DYNE-101 Treatment Period to participants originally randomized to DYNE-101.

## **Study burden and risks**

Participants in all cohorts and all dosing schemes will undergo 4 needle biopsies of the tibialis anterior: 3 needle muscle biopsies during the Placebo-Controlled Period and 1 biopsy during the DYNE-101 Treatment Period.

The first 2 participants enrolled at each dose level will serve as a sentinel pair, one receiving DYNE-101 and the other receiving placebo. After dose administration to the second participant in the sentinel pair, a 7-day safety and tolerability observation period will begin, after which the DEC will review all accumulated data from the study to determine whether the remainder of the participants at that dose level can be enrolled and provide a recommendation to the SMC for approval. The remaining participants will receive their first dose of study drug in a staggered fashion, such that only 1 participant receives a first dose of study drug on a given day.

The DEC will review all the accumulated data from the study after all participants in the first cohort of each dose level have completed 4 weeks after the first dose of study drug to make a recommendation to the SMC whether the next higher dose level cohort may be enrolled. Increases to the next higher dose level will not exceed a 2 fold increment. The maximum dose administered will not exceed 75 mg/kg. The DEC may recommend to the SMC that the next cohort may be enrolled at a lower dose or longer interval (Q8W) based on emerging data. In addition, 1 optional expansion cohort with N = 16 participants or 2 optional expansion cohorts with N = 8 participants each may be enrolled at the recommendation of the DEC with final decision by the SMC. The doses selected for these cohorts may use either a Q4W or a Q8W (with boosters) dosing regimen, and the dose level will not exceed the highest dose level previously studied. Participants in the lower dose cohorts may undergo 1 or more changes to the dose level or frequency as recommended by the DEC and endorsed by the DEC after they have completed the muscle biopsy at the Day 169 visit.

For the expansion cohorts, the dose level may not exceed that which was previously studied and for which all participants have completed the Placebo-Controlled Period. Thus, expansion cohorts will not include a sentinel pair.

## Contacts

### Public

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US

### Scientific

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US

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

### Inclusion criteria

1. Age 18 to < 50 years, at the time of signing the informed consent.
2. Diagnosis of DM1 confirmed by molecular genetics with trinucleotide repeat size > 100.
3. Age of onset of DM1 muscle symptoms  $\geq$  12 years
4. Clinically apparent myotonia equivalent to hand opening time of at least 2 seconds in the opinion of the Investigator
5. Hand grip strength and ankle dorsiflexion strength
  - a. Hand grip strength averaged from both sides  $\geq$  20% and  $\leq$  80% ( $\pm$  5%) predicted for age, sex, and height at screening
  - b. Ankle dorsiflexion strength averaged from both sides  $\geq$  20% and  $\leq$  80% ( $\pm$ 10%) predicted for age, sex, and height at screening.Note: two sets of functional assessments must be performed during the Screening period. Participants must meet inclusion criterion #5 on both sets of functional assessments for study eligibility.
6. Able to complete 10MWT, stair ascend/descend, and 5xSTS at screening without the use of assistive devices such as canes, walkers, or orthoses. The use of submalleolar orthoses and inserts or supports that do not extend above the malleolus are permitted during testing
7. Body mass index (BMI) < 35kg/m<sup>2</sup>
8. If being treated with testosterone, on a stable replacement dose for 30 days prior to screening
9. Participants must agree to follow protocol-specified contraception guidance as described in Section 10.4.

10. Female participants must not be pregnant or breastfeeding
11. Capable of giving signed informed consent as described in Section 10.1.3 of the protocol, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol
12. Willingness and ability of participant to comply with and tolerate scheduled visits, dosing administration plan, and study assessments, including multiple needle muscle biopsy procedures over the duration of the study

## **Exclusion criteria**

1. Previous or ongoing medical condition, medical history, physical findings, or laboratory abnormalities that in the opinion of the Investigator could affect safety, make it unlikely that dosing schedule and follow-up will be correctly completed, and/or impair the assessment and interpretation of study results
2. History of major surgical procedure within 12 weeks prior to the start of investigative product administration or an expectation of a major surgical procedure (eg, implantation of cardiac defibrillator) during course of the study
3. History of anaphylaxis
4. History of clinically significant liver disease or ongoing treatment for liver disease
5. History of clinically significant hematologic disease or have any of the following hematologic results at Screening: platelets or hemoglobin below the lower limit of normal for age and sex.
6. History of clinically significant kidney disease, ongoing treatment for kidney disease (treatment for hypertension is permitted) or estimated glomerular filtration rate (eGFR) < 60 mL/min as calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Cystatin C Equation (Inker et al. 2012) at screening
7. Active malignancy or history within the last 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
8. Recent history (within previous 12 months) of drug or alcohol abuse
9. Medical condition other than DM1 that would significantly impact ambulation or participation in functional assessments
10. Current insulin-dependent diabetes mellitus or uncontrolled diabetes mellitus, congestive heart failure, symptomatic cardiomyopathy, symptomatic coronary artery disease, multiple sclerosis, or other serious medical illness
11. Second- or third-degree heart block, symptomatic first-degree heart block, atrial flutter, atrial fibrillation, ventricular arrhythmias, pacemakers, implanted defibrillator, or is receiving medication for treatment of cardiac arrhythmia



12. Treatment with medications that can improve myotonia of clinical functional endpoints within a period of 5 half-lives of the medication prior to performing screening assessments. May include but not limited to mexiletine, phenytoin, carbamazepine, procainamide, disopyramide, ranolazine, flecainide, lamotrigine, nifedipine, acetazolamide, clomipramine, imipramine, amitriptyline, taurine, quinine, or metformin.
13. Use of anticoagulant such as warfarin or a direct oral anticoagulant (eg, dabigatran) due to the increased risk of bleeding
14. Current treatment with immunosuppressive therapy
15. Receipt of another investigational drug, biologic agent, or device within 5 half-lives (if known) of the agent, or within 4 months prior to the start of Screening, whichever is longer. Individuals previously treated with oligonucleotide therapies (including small interfering RNA [siRNA]) may be eligible if the last dose of the investigational drug was received  $\geq 3$  years ago
16. ECG with the corrected QT interval by Fridericia's Formula (QTcF)  $\geq 450$  ms in men and QTcF  $\geq 460$  ms in women, PR  $\geq 240$  ms, left bundle-branch block, or a conduction defect, which is clinically significant in the opinion of the Investigator
17. Percent predicted forced vital capacity (FVC)  $< 50\%$
18. History of tibialis anterior biopsy within 3 months of Day 1 or planning to undergo tibialis anterior biopsies during study period for reasons unrelated to the study
19. Inability, or impaired ability, to complete study procedures and/or complete the study, due to physical or cognitive impairment, in the judgment of the Investigator
20. Inability to undergo venipuncture successfully or tolerate venous access

## Study design

### Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

### Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-03-2023
Enrollment:	5
Type:	Actual

## Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	DYNE-101
Generic name:	DYNE-101

## Ethics review

Approved WMO	
Date:	21-09-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO	
Date:	20-12-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO	
Date:	23-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO	
Date:	29-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO	
Date:	05-06-2023
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	13-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	27-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	14-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

Register	ID
EU-CTR	CTIS2023-510353-42-00
EudraCT	EUCTR2022-000889-18-NL
ClinicalTrials.gov	NCT05481879
CCMO	NL81751.000.22