ACHIEVE Trial, a Randomized, Placebo-Controlled, Multiple Ascending Dose Study of DYNE-101 in Individuals With Myotonic Dystrophy Type 1 (DM1)

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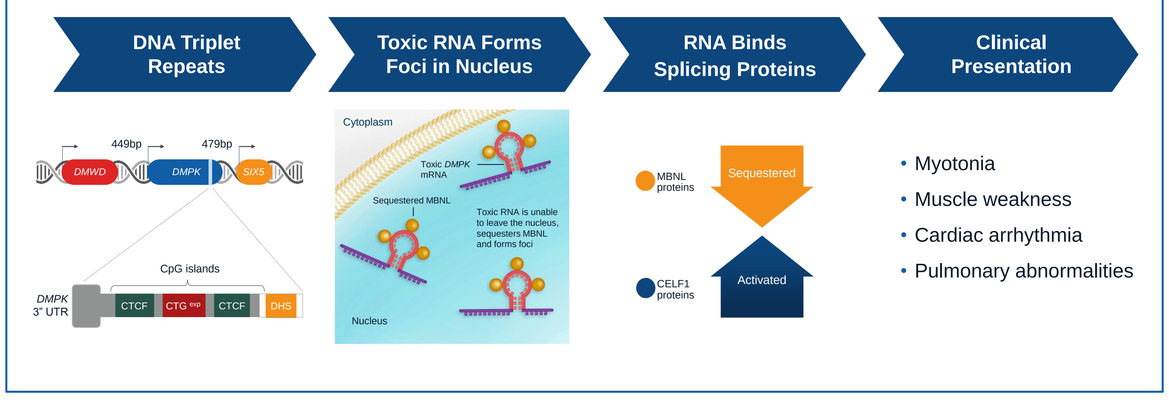
BACKGROUND

- Myotonic dystrophy type 1 (DM1) is a neuromuscular disorder with multisystemic involvement that is characterized by varying degrees of myotonia, impaired skeletal muscle function, skeletal muscle wasting, a broad spectrum of systemic symptoms, and high clinical inter- and intra-individual variability.[1,2]
- DM1 is caused by expansions of CUG repeats in the 3' untranslated region of the dystrophia myotonica protein kinase (*DMPK*) RNA.[3]
- The expanded CUG repeats form hairpin-loop structures that sequester splicing regulators into toxic nuclear foci, leading to a spliceopathy that drives DM1 clinical manifestations (**Figure 1**).[4,5]
- No disease-modifying therapies are available, limiting treatment to symptom management.[6]
- DYNE-101 is an investigational therapeutic designed to target the mutant nuclear *DMPK* RNA for RNase-H1–mediated degradation by an antisense oligonucleotide (ASO); the ASO is joined by a clinically validated valine-citrulline linker to an antigen-binding fragment (Fab) that targets the human transferrin receptor 1 (hTfR1), which is expressed on muscle (**Figure 2**).[7]

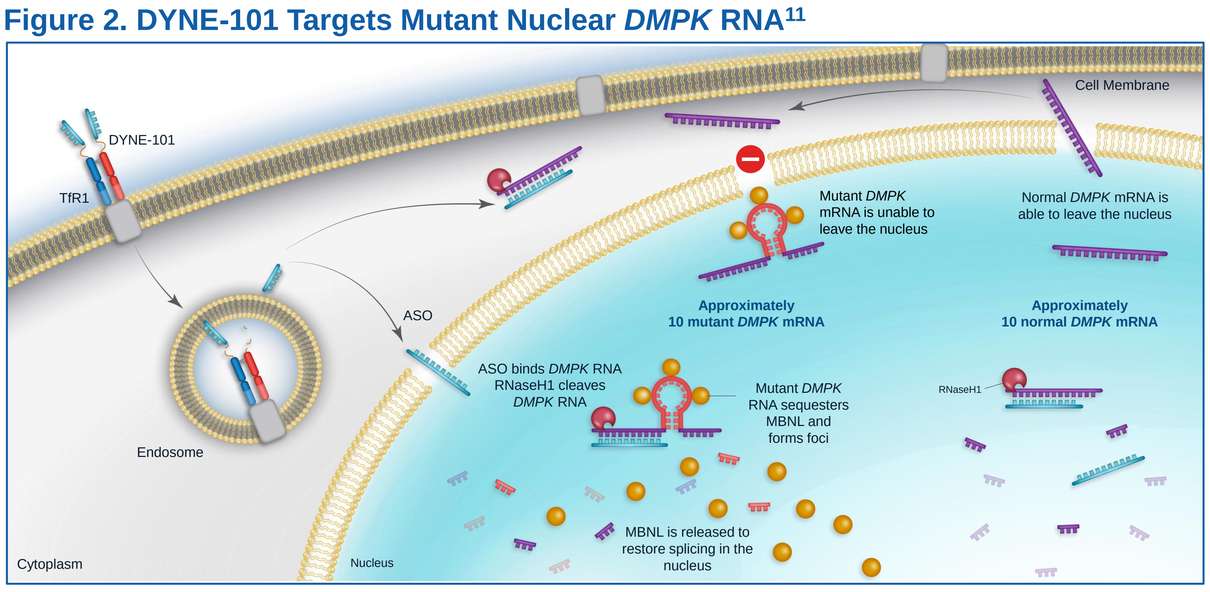
Figure 1. Overview of Spliceopathy in DM1[10]



CELF1, CUGBP Elav-Like Family Member 1; CTCF, chromatin insulator CCCTC-binding factor; CTG, cytosine-thymine-guanine; DHS, DNase I hypersensitivity site; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; DMWD, dystrophia myotonica-containing WD repeat motif; MBNL, muscleblind-like; SIX5, SIX Homeobox 5; UTR, untranslated region.

- Preclinical work in the hTfR1/DMSXL mouse model of DM1 established that DYNE-101 corrected manifestations of myotonic dystrophy in cardiac and skeletal muscle and demonstrated pharmacological properties that translate from mice to cynomolgus monkeys.[8]
- DYNE-101 was well tolerated in a 13-week Good Laboratory Practices toxicology study in cynomolgus monkeys.[8]
- The Phase 1/2 ACHIEVE trial (NCT05481879) is designed to assess the safety, tolerability, pharmacodynamics, efficacy, and pharmacokinetics of multiple intravenous doses of DYNE-101 in adults with DM1.[9]
- Here we present the design and methodology of the ACHIEVE trial.

Figure 2. DYNE-101 Targets Mutant Nuclear *DMPK* RNA[11]



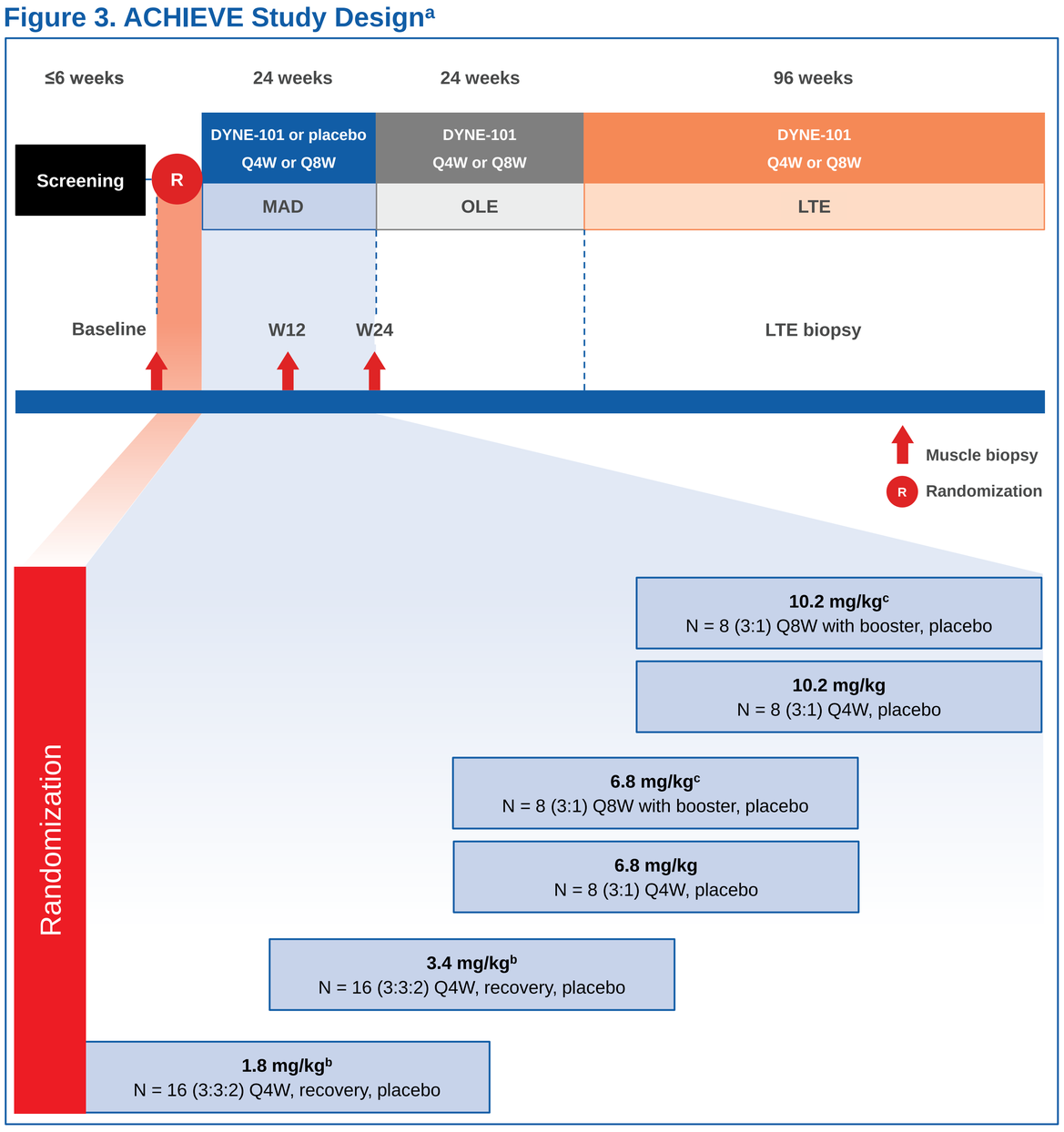
Note: Image depicts intended mechanism of action of DYNE-101.
ASO, antisense oligonucleotide; DMPK, dystrophia myotonica protein kinase; MBNL, muscleblind-like; TfR1, transferrin receptor 1.

METHODS

STUDY DESIGN AND PATIENT POPULATION

- ACHIEVE is a Phase 1/2, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study.[9]
- This study includes a MAD/placebo-controlled period (24 weeks), an open-label extension period (OLE, 24 weeks), and a long-term extension (LTE) period (96 weeks; **Figure 3**).[9]
  - Approximately 64 patients aged 18 to 49 years will be enrolled into 4 cohorts of ascending doses of DYNE-101: 1.8, 3.4, 6.8, and 10.2 mg/kg (doses refer to ASO component of DYNE-101).[9]
  - Patients who receive 1.8 or 3.4 mg/kg DYNE-101 will be dosed every 4 weeks (Q4W), and patients who receive 6.8 or 10.2 mg/kg DYNE-101 will be dosed Q4W or every 8 weeks (Q8W) with booster.[9]
  - All patients will receive the highest safe and tolerable dose of DYNE-101 during the OLE and LTE periods.[9]

Figure 3. ACHIEVE Study Design[a]



[a]Doses provided refer to ASO component of DYNE-101.
[b]Patients in the recovery cohort will receive 2 doses of DYNE-101 Q4W then placebo for the remainder of the 24-week placebo-controlled period.
[c]DYNE-101 Q8W with booster includes Q4W × 3 doses then Q8W dosing.
ASO, antisense oligonucleotide; LTE, long-term extension; MAD, multiple ascending dose; OLE, open-label extension; Q4W, dosing every 4 weeks; Q8W, dosing every 8 weeks; W12, week 12; W24, week 24.

1 PRIMARY OUTCOME MEASURE[9]

- Number of participants with treatment-emergent adverse events (through study completion, up to week 145)

2 SELECT SECONDARY OUTCOME MEASURES[9]

- Change from baseline in Splicing Index in skeletal muscle tissue (up to week 97)
- Change from baseline in *DMPK* RNA expression in muscle tissue (up to week 97)
- Change from baseline in hand grip relaxation time (up to week 145)
- Change from baseline in quantitative myometry testing (QMT; [up to week 145])
- Change from baseline in 10-meter walk/run test (10-MWRT; [up to week 145])
- Change from baseline in stair-ascend/descend test (up to week 145)
- Change from baseline in 5 times sit to stand (5 × STS; [up to week 145])
- Change from baseline in 9-hole peg test (9-HPT; [up to week 145])
- Pharmacokinetic endpoints

Inclusion Criteria[9]

- ❑ Diagnosis of DM1 with trinucleotide repeat size >100
- ❑ Age at onset of DM1 muscle symptoms ≥12 years
- ❑ Clinically apparent myotonia equivalent to hand opening time of at least 2 seconds in the opinion of the Investigator
- ❑ Hand grip strength and ankle dorsiflexion strength averaged from both sides ≥20th and ≤80th percentile for age, sex, and height at screening
- ❑ Able to complete 10MWT, stair ascend/descend, and 5XSTS test at screening without the use of assistive devices such as canes, walkers, or orthoses

Exclusion Criteria[9]

- ❑ 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 the study
- ❑ History of anaphylaxis
- ❑ Medical condition other than DM1 that would significantly impact ambulation or participation in functional assessments
- ❑ Treatment with medications that can improve myotonia within a period of 5 half-lives of the medication prior to performing screening assessments
- ❑ Electrocardiogram (ECG) with the QTcF ≥450 ms in men and QTc ≥460 in women, PR ≥240 ms, left bundle-branch block, or a conduction defect, which is clinically significant in the opinion of the Investigator
- ❑ Percent predicted forced vital capacity (FVC) <50%
- ❑ 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

Note: Other inclusion and exclusion criteria may apply.
DM1, myotonic dystrophy type 1; QTc, corrected QT interval; QTcF, corrected QT interval by Fridericia's formula.

CONCLUSIONS

- DYNE-101 reduced mutant *DMPK* RNA expression and corrected splicing defects in skeletal and cardiac muscles of hTfR1/DMSXL mice.[8]
- DYNE-101 reduced wild-type *DMPK* RNA in skeletal and cardiac muscles of cynomolgus monkeys, demonstrating translatability to higher species.[8]
- DYNE-101 was well tolerated in a 13-week GLP toxicology study in cynomolgus monkeys.
- The Phase 1/2 ACHIEVE study will inform further development of DYNE-101 for the treatment of DM1.

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