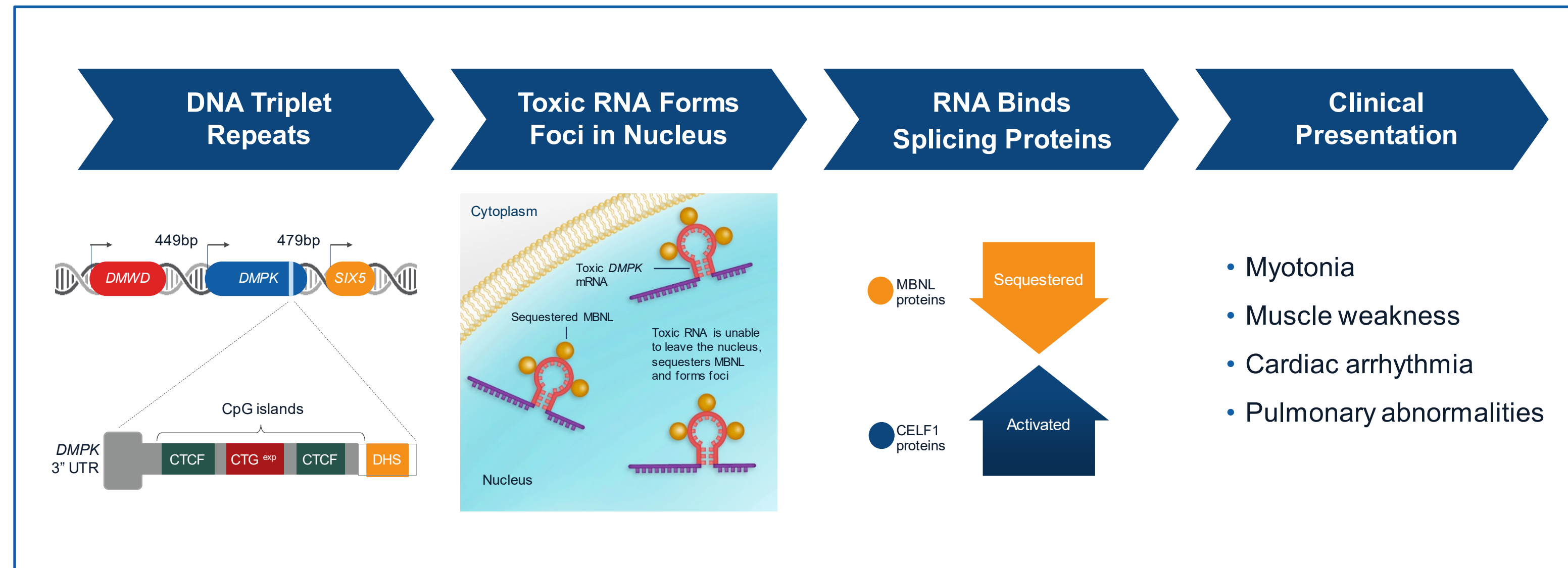


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BACKGROUND

- 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 dystrophin myotonia 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

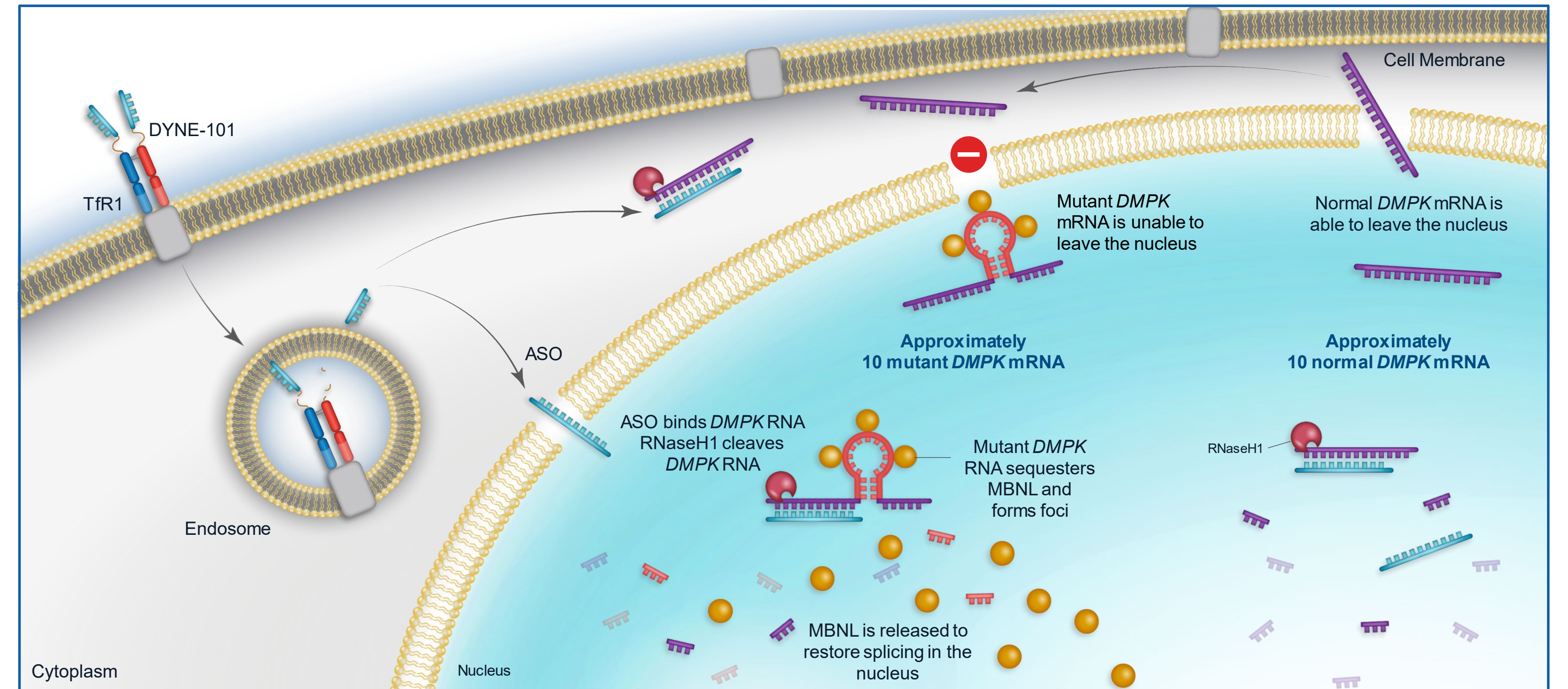
Figure 1. Overview of Spliceopathy in DM1¹⁰



CELF1, CUGBP Elav-Like Family Member 1; CTCF, chromatin insulator C/EBP-binding factor; CTG, cytosine-thymine-guanine; DHS, DNase I hypersensitivity site; DM1, myotonic dystrophy type 1; DMPK, dystrophin myotonia protein kinase; DMWD, dystrophin myotonia-containing WD repeat motif; MBNL, muscleblind-like; SDS, 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* RNA¹¹



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

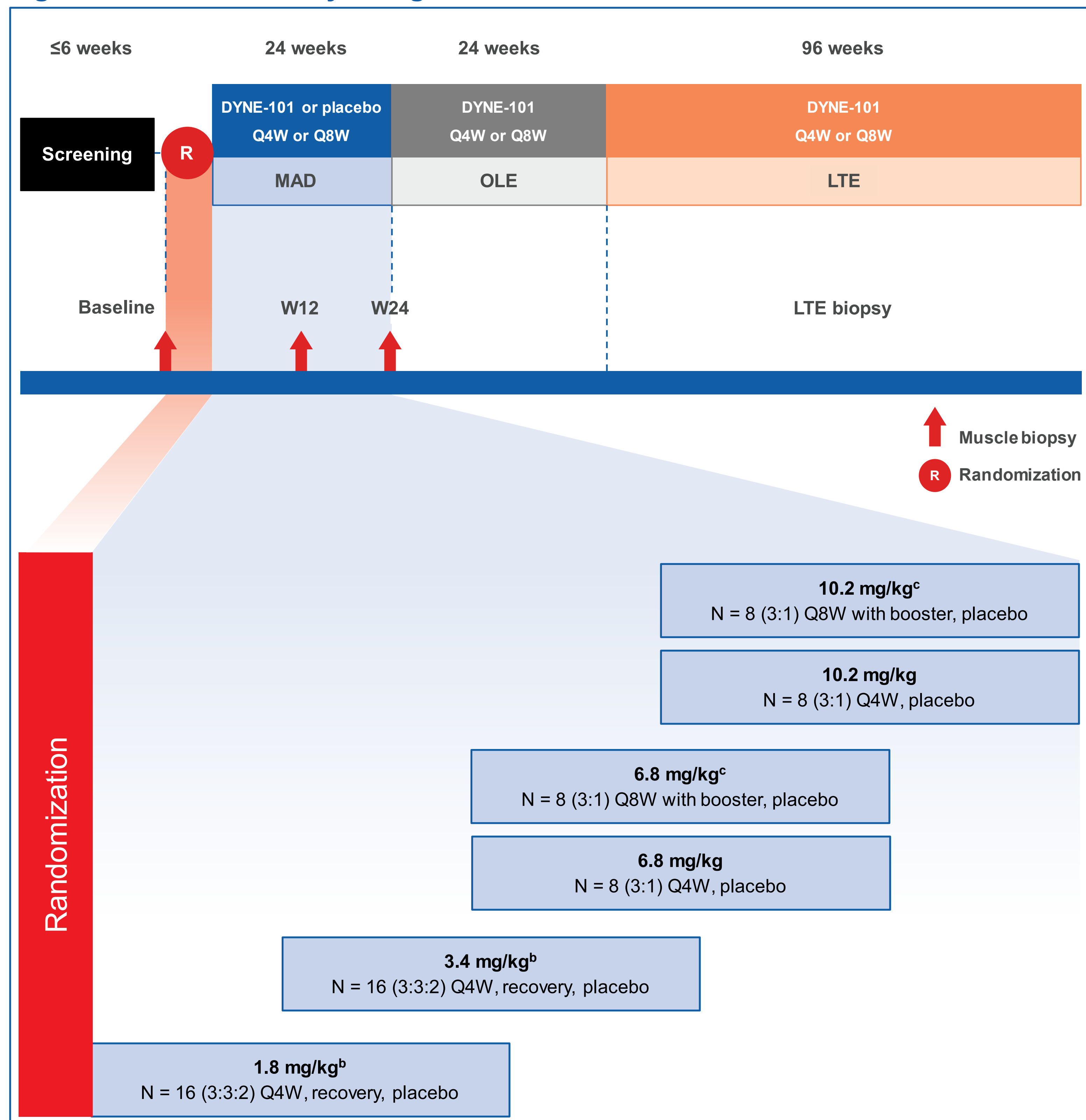
METHODS



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



^aDoses provided refer to ASO component of DYNE-101. ^bPatients in the recovery cohort will receive 2 doses of DYNE-101 Q4W then placebo for the remainder of the 24-week placebo-controlled period. ^cDYNE-101 Q8W with booster includes Q4W × 3 doses then Q8W dosing. ^dASO, 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.

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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1

PRIMARY OUTCOME MEASURE⁹

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

2

SELECT SECONDARY OUTCOME MEASURES⁹

- 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 Criteria⁹

- 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 Criteria⁹

- 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 QTcF ≥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 Fredericia's formula.

REFERENCES

- De Antonio M, et al. *Orphanet J Rare Dis*. 2019;14(1):122. doi:10.1186/s13023-019-1088-3.
- Pavičević DS, et al. *Biomed Res Int*. 2013;2013:391821. doi:10.1155/2013/391821.
- Thornton CA. *Neurol Clin*. 2014;32(3):705-719.
- Chau A, Kalsotra A. *Dev Dyn*. 2015;244(3):377-390.
- Pascual-Gilbert M, et al. *Drug Discov Today*. 2021;26(7):1765-1772.
- Thornton CA, et al. *Curr Opin Genet Dev*. 2017;44:135-140.
- Zanotti S, et al. Poster presented at: International Congress of Myology; September 12-15, 2022; Nice, France.
- Zanotti S. Oral presentation at: Annual Meeting of the American Society of Gene & Cell Therapy; May 16-19, 2022; Washington DC.
- ClinicalTrials.gov. NCT05481879. Accessed February 3, 2022. <https://clinicaltrials.gov/ct2/show/NCT05481879>.
- López-Martínez A, et al. *Genes (Basel)*. 2020;11(9):1109. doi:10.3390/genes11091109.
- Zanotti S. Oral presentation at: Annual Meeting of the American Society of Gene & Cell Therapy; May 11-14, 2021; virtual congress.