Preclinical Data Support the Initiation of the ACHIEVE Trial of DYNE-101 in Individuals With Myotonic Dystrophy Type 1 (DM1)

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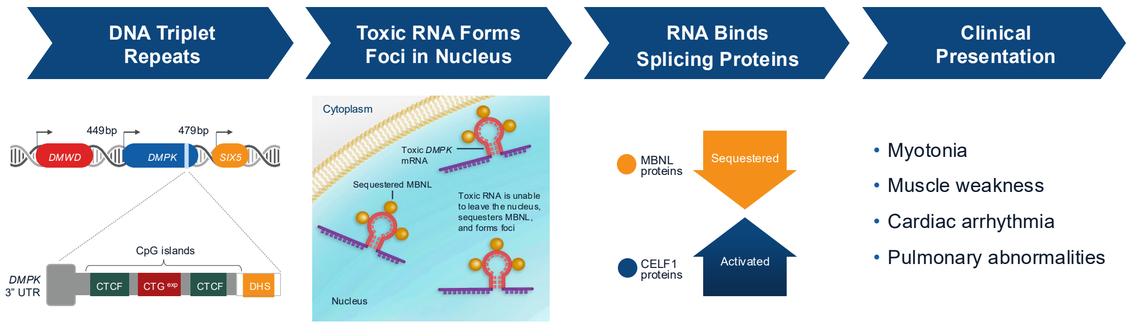
BACKGROUND

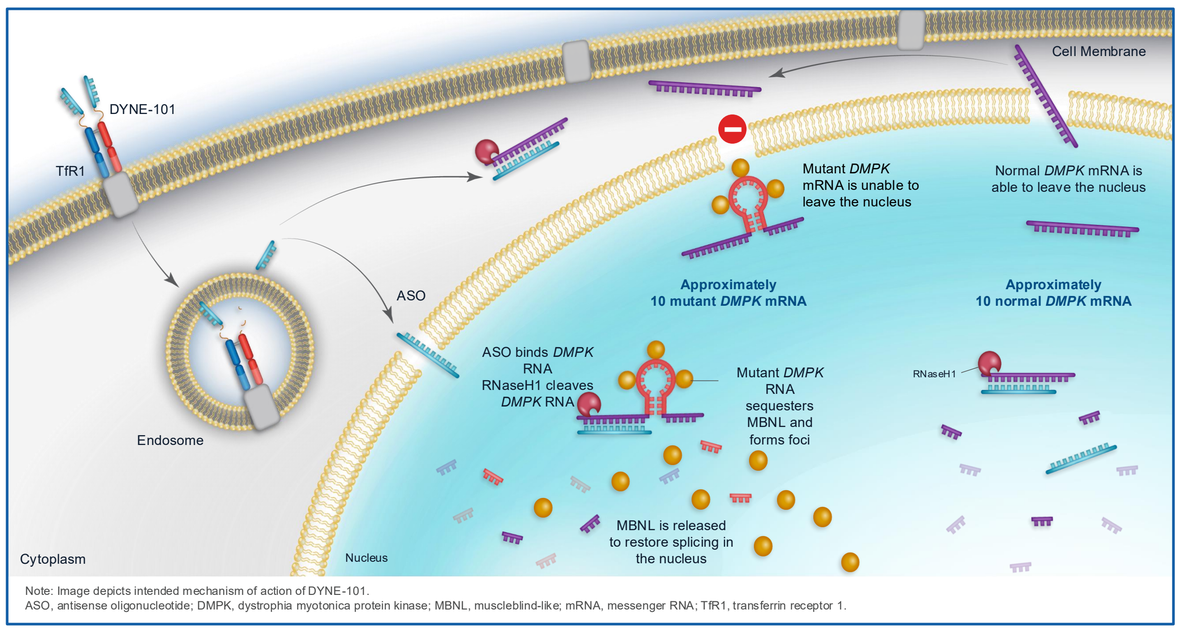
- Myotonic dystrophy type 1 (DM1) is a neuromuscular disorder with multisystemic involvement that is characterized by varying degrees of myotonia, impaired skeletal muscle function, skeletal muscle wasting, a broad spectrum of systemic symptoms, and high clinical inter- and intra-individual variability.[1,2]
- 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**).

Figure 1. Overview of spliceopathy in DM1[1-5]



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; mRNA, messenger RNA; SIX5, SIX Homeobox 5; UTR, untranslated region.

Figure 2. DYNE-101 targets mutant nuclear *DMPK* RNA

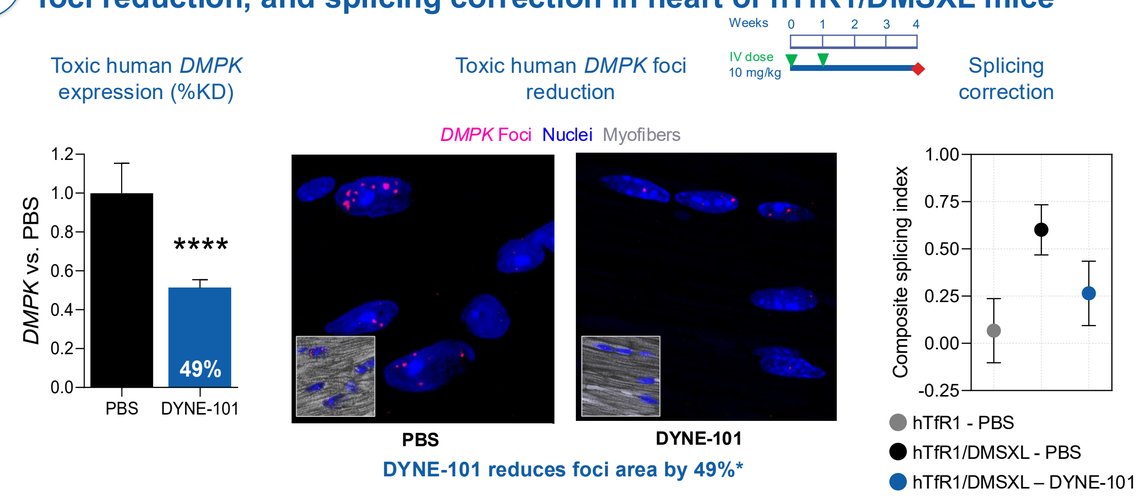


Note: Image depicts intended mechanism of action of DYNE-101.
ASO, antisense oligonucleotide; DMPK, dystrophia myotonica protein kinase; MBNL, muscleblind-like; mRNA, messenger RNA; TfR1, transferrin receptor 1.

- The Phase 1/2 ACHIEVE Study (NCT05481879) is designed to assess the safety, tolerability, pharmacodynamics, efficacy, and pharmacokinetics of multiple intravenous doses of DYNE-101 in adults with DM1.[8]
- Here we present preclinical data supporting the design, methodology, and initiation of the ACHIEVE Study.

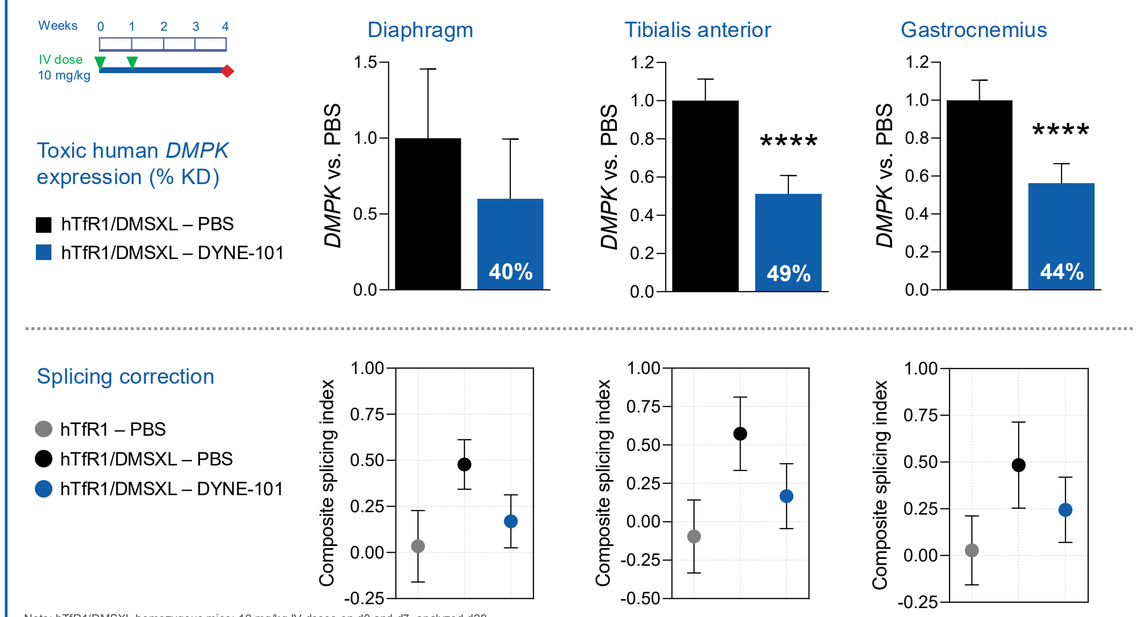
PRECLINICAL DATA

Figure 3. DYNE-101 demonstrated significant toxic human *DMPK* KD, foci reduction, and splicing correction in heart of hTfR1/DMSXL mice



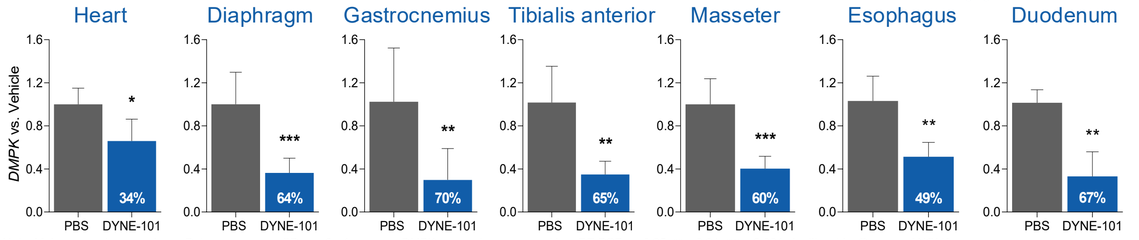
Note: hTfR1/DMSXL homozygous mice; 10 mg/kg IV doses on d0 and d7, analyzed d28.
Composite splicing index includes changes in *Ldb3* exon (E) 11, *Mbnl2* E6, and *Nfix* E7.[7] Data are mean ± SD, n = 6 – 7 per arm. *DMPK* expression measured by qRT-PCR.
*p<0.05; ****p<0.0001 significant by *t*-test.
hTfR1/DMSXL mice express the hTfR1 and a human *DMPK* gene with > 1000 CTG repeats (DMSXL) that is representative of a severe DM1 phenotype.[8]
DMPK, dystrophia myotonica protein kinase; IV, intravenous; KD, knockdown; PBS, phosphate-buffered saline; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

Figure 4. DYNE-101 demonstrated toxic human *DMPK* KD and splicing correction in skeletal muscle of hTfR1/DMSXL mice



Note: hTfR1/DMSXL homozygous mice; 10 mg/kg IV doses on d0 and d7, analyzed d28.
Composite splicing indices include *Bin1* E11, *Insr* E11, *Ldb3* E11, *Mbnl2* E6, *Nfix* E7, and *Ttn* E313 mis-splicing measured by qRT-PCR. Data are mean ± SD; n = 4 - 7. *DMPK* expression measured by qRT-PCR.
**** p<0.0001 by *t*-test.
DMPK, dystrophia myotonica protein kinase; IV, intravenous; KD, knockdown; PBS, phosphate buffered saline; qRT-PCR, real-time quantitative reverse transcription polymerase chain reaction; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

Figure 5. Repeat monthly dosing of DYNE-101 in NHPs achieved significant WT *DMPK* KD demonstrating translatability to higher species



Note: Male cynomolgus monkeys. Data are mean ± SD; n = 3 - 4 per arm. *DMPK* expression measured by qRT-PCR. p<0.05; **p<0.01; ***p<0.001 significant by One-way ANOVA.
DMPK, dystrophia myotonica protein kinase; IV, intravenous; KD, knockdown; NHP, non-human primate; WT, wild-type; PBS, phosphate-buffered saline; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

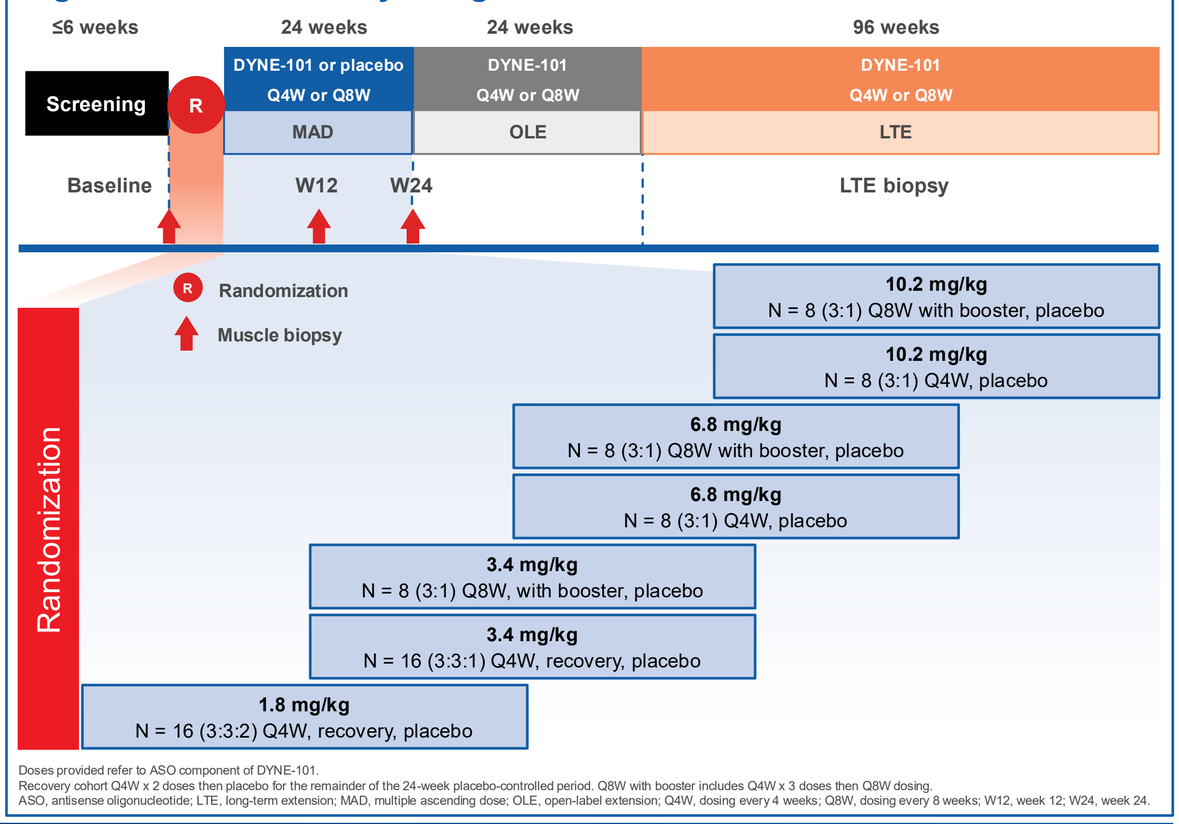
DYNE-101 was well tolerated in a 13-week NHP GLP toxicology study[a]

- No dose-limiting toxicity observed up to a maximally feasible dose[b]
- No changes in cardiac, respiratory, neurologic, or ophthalmic endpoints
- No effect on kidney or liver function, and no effect on coagulation
- NOAEL was identified at the highest dose tested

[a]Based on conclusions of report from third-party CRO.
[b]Dosed once every three weeks.
CRO, contract research organization; GLP, Good Laboratory Practice; NHP, non-human primate; NOAEL, no-observed-adverse-effect level.

ACHIEVE CLINICAL TRIAL

Figure 6. ACHIEVE Study Design



Doses provided refer to ASO component of DYNE-101.
Recovery cohort Q4W x 2 doses then placebo for the remainder of the 24-week placebo-controlled period. Q8W with booster includes Q4W x 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.

STUDY DESIGN AND PATIENT POPULATION[9]

- ACHIEVE is a Phase 1/2, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) trial.
- 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 6**).
  - Approximately 72 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).
  - Patients who receive 1.8 mg/kg DYNE-101 will be dosed every 4 weeks (Q4W), and patients who receive 3.4, 6.8 or 10.2 mg/kg DYNE-101 will be dosed Q4W or every 8 weeks (Q8W) with booster.
  - All patients will receive the highest safe and tolerable dose of DYNE-101 during the OLE and LTE periods.

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 video hand opening time (vHOT; 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

CONCLUSIONS

- **DYNE-101 reduced mutant *DMPK* RNA expression and corrected splicing defects in skeletal and cardiac muscles of hTfR1/DMSXL mice.**
- **DYNE-101 reduced wild type *DMPK* RNA in skeletal and cardiac muscles of cynomolgus monkeys, demonstrating translatability to higher species.**
- **DYNE-101 was well tolerated in a 13-week Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys.**
- **Initial data from the MAD portion of the ACHIEVE Study are expected in H2 2023.**

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