DYNE-101 and DYNE-251: Moving from Bench to Clinic to Deliver Potentially Transformative Therapies in DM1 and DMD

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Ravi, *living with DMD*

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OUR MISSION

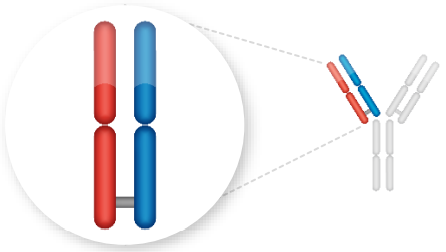
Life-transforming therapies

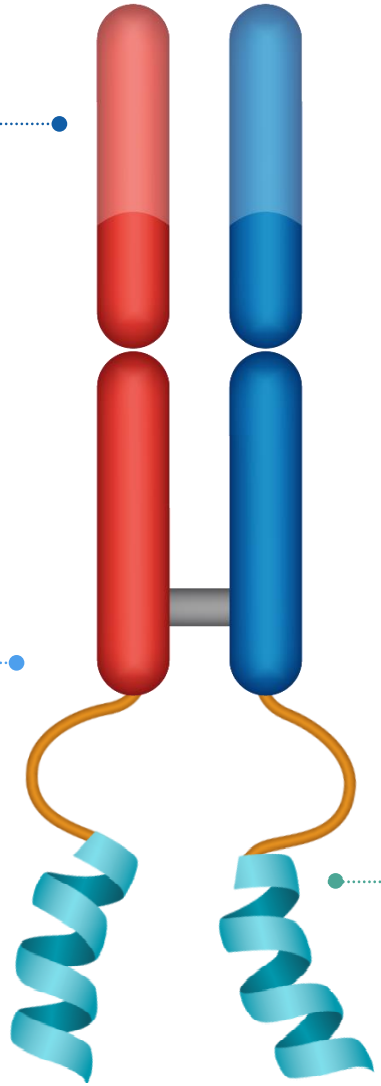
for patients with serious muscle diseases

Dyne's FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



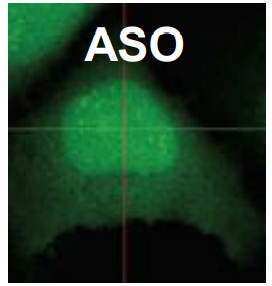


LINKER

Clinically validated, enables precise conjugation of multiple payloads to a single Fab

PAYLOAD

Modularity enables rational selection of payload to target the genetic basis of disease

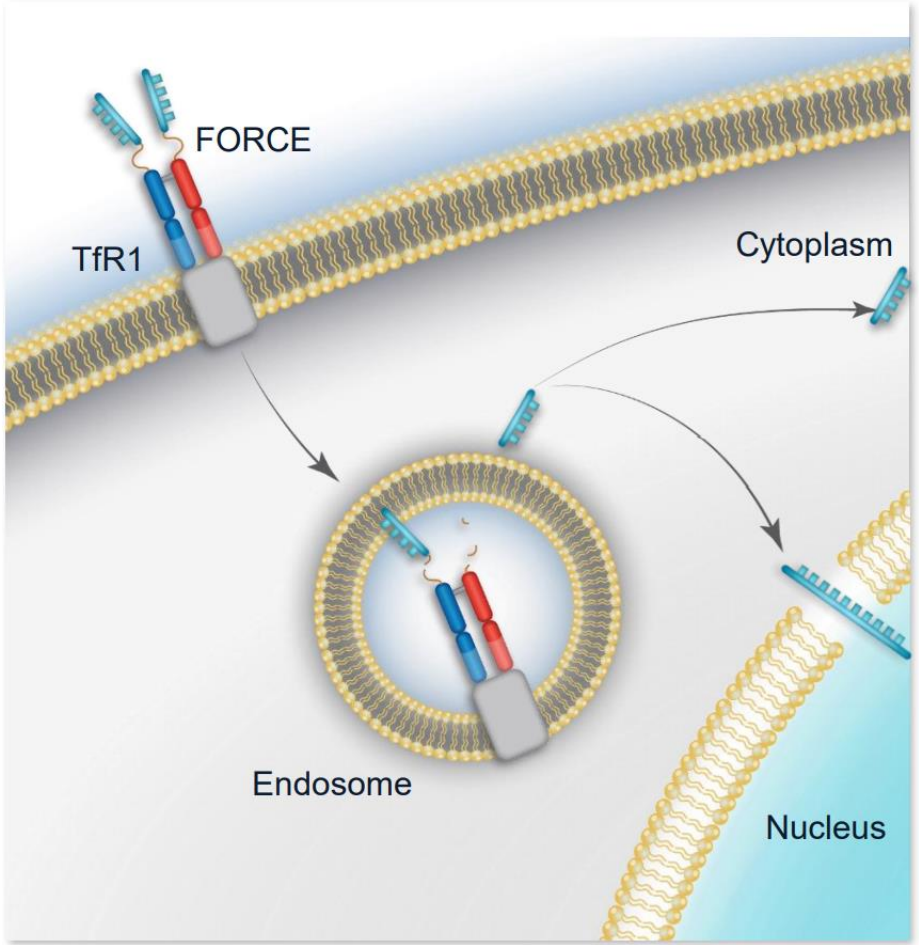


Nuclear localization

Cytoplasmic localization

Adapted from Ohrt T., et al. *Nucleic Acids Res* 2006;34:1369.

FORCE Platform Harnesses Cell Biology to Modify Disease



- Harnesses natural mechanism of TfR1 receptor-mediated delivery to transport therapeutics across the cell membrane
- Achieves endosomal escape without any membrane-destabilizing agents
- Distinctive pharmacokinetic profile creates opportunity for durable target engagement and wide therapeutic index

Developing Transformative Therapies for People Living with DM1

Overview

- Mutation in the *DMPK* gene
- Onset at any point, depending on DM1 phenotype
- Life expectancy of 45 - 60 years

Clinical Presentation

- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

Population

- >40,000 (US)
- >74,000 (Europe)

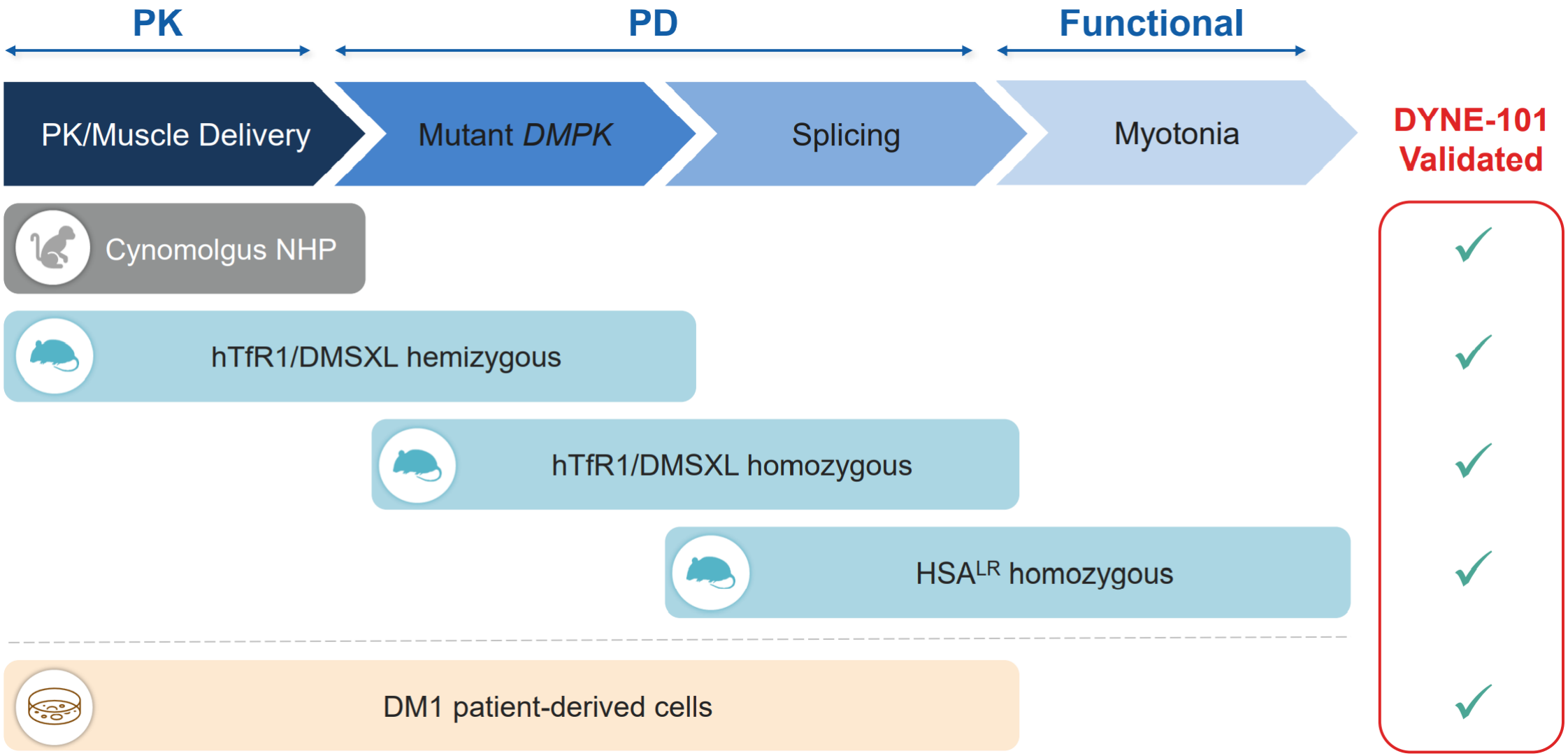
NO approved therapies

OUR APPROACH

Disease-Modifying Nuclear *DMPK* Knockdown

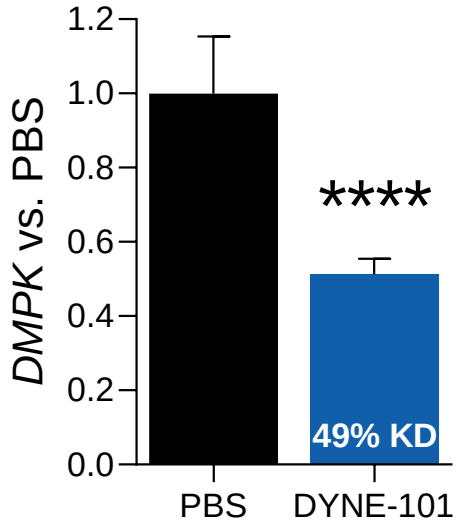
Targeting toxic gain of function *DMPK* RNA to potentially **stop or reverse** disease progression

Robust Preclinical Data Supporting the Potential of DYNE-101 to Drive Disease Modification in the Clinic

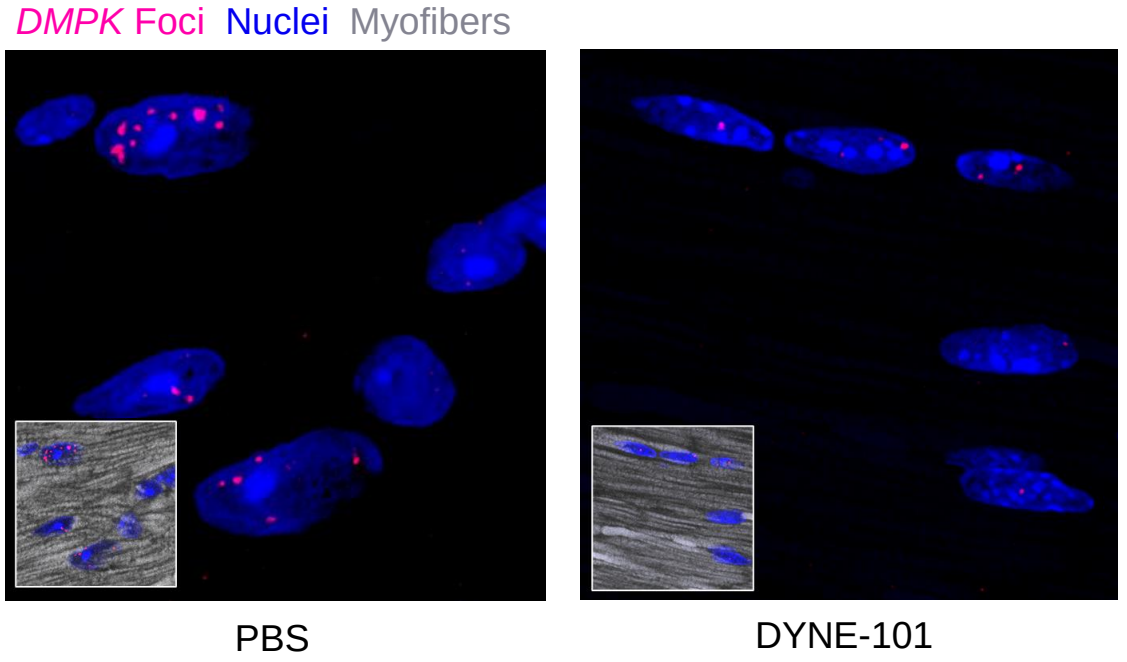


DYNE-101 Demonstrated Toxic *DMPK* KD, Foci Reduction and Splicing Correction in Heart of hTfR1/DMSXL Homozygous Model

Toxic Human *DMPK* RNA KD

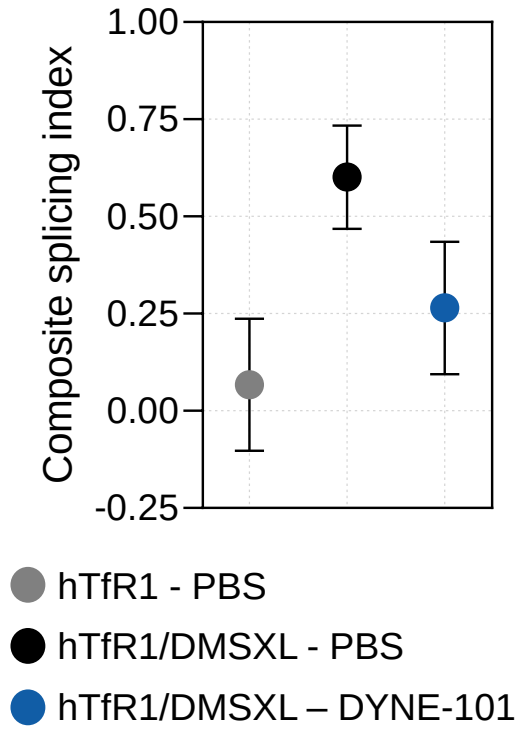


Toxic Human *DMPK* Foci Reduction



DYNE-101 reduces foci area by 49%*

Splicing Correction



Note: hTfR1/DMSXL homozygous model. 2 x 10 mg/kg on d0 and d7, analyzed d28.
Composite splicing index includes changes in *Ldb3* exon (E) 11, *Mbnl2* E6, and *Nfix* E7. Data are mean ± SD, n = 6 - 7.; * p <0.05; **** p < 0.0001.

DYNE-101 Achieved *DMPK* Knockdown & Well Tolerated in NHPs

Robust WT *DMPK* KD Achieved in Skeletal, Cardiac and Smooth Muscles

- Up to 70% *DMPK* KD at 2 months with low monthly dosing

13-Week GLP Toxicology Study[1]

- No dose limiting toxicity observed up to a maximally feasible dose[2]
- No changes in cardiac, respiratory, neurologic or ophthalmic endpoints
- No effect on kidney function
- No effect on liver function
- No effect on coagulation
- NOAEL was identified at the highest dose tested

Notes: 1. Based on conclusions of report from third-party CRO. 2. Dosed once every three weeks.
NOAEL: No-observed-adverse-effect level

ACHIEVE Trial Informed by Input from Multiple Stakeholders

Global, Multi-disciplinary KOL & Regulatory Input

- Overall design for the MAD portion in patients ages 18 to 49
- Splicing, myotonia, measures of strength & function, key safety considerations
- Natural history data to contextualize clinical trial data for patients and families, clinicians, payers, regulators

Global Advocacy Leaders, Patient and Caregiver Input

- Considerations for trial selection
- Clinical trial protocol and visit schedule
- Minimizing patient burden during trial conduct
- Ensuring support and education to patients and families

Phase 1/2 Clinical Trial to Evaluate DYNE-101 in Patients with DM1

Population

- Adult patients living with DM1
- Ages 18 to 49 years
- ~64 adult participants

Primary Endpoints

- Safety and tolerability

Key Secondary Endpoints

- Pharmacokinetics
- Change from baseline of:
  - Splicing
  - *DMPK* RNA expression
  - Multiple assessments of muscle strength and function

Stages of ACHIEVE

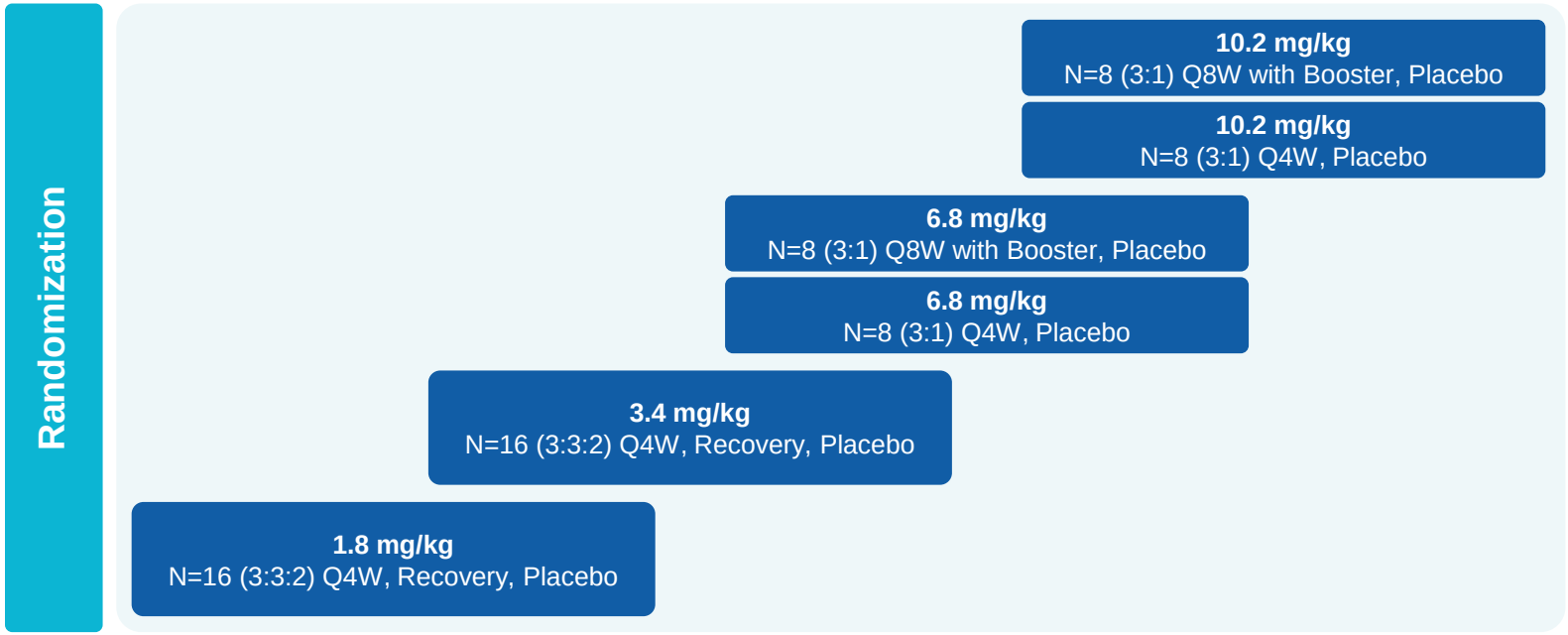
- Multiple Ascending Dose (MAD): 24 weeks
- Open-Label Extension (OLE): 24 weeks
- Long-Term Extension (LTE): 96 weeks

Safety, Tolerability & Splicing Data Expected in H2 2023

Multiple Ascending Dose Stage of ACHIEVE

ACHIEVE

Global, Randomized, Placebo-Controlled Stage Evaluating Once Monthly or Less Frequent Administration of DYNE-101 in ~64 Adult Patients Living with DM1



MAD Study Details

- IV administration of DYNE-101 or placebo every 4 weeks or every 8 weeks
- Muscle biopsies: Baseline, 12 weeks, 24 weeks
- Patients in MAD study escalated to highest tolerable dose in OLE and LTE

Global Strategy & Adaptive Trial Design Enable Rapid Achievement of Potentially Registrational Clinical Data

Doses provided refer to ASO component of DYNE-101. Recovery cohort Q4W x 2 doses then placebo for the remainder of the 24W placebo-controlled period. Q8W with booster includes Q4W x 3 doses then Q8W dosing.

Building a Global DMD Franchise of Transformative Therapies

Overview

- Mutation in the *DMD* gene that encodes for dystrophin
- Onset in first few years of life
- Life expectancy ~30 years

Clinical Presentation

- Muscle weakness
- Progressive loss of function
- Loss of ambulation
- Respiratory/cardiac failure

Population

- ~12,000 - 15,000 (US)
- ~ 25,000 (Europe)

Current Approved Exon 51 Therapies Only Increased Dystrophin Production <1%

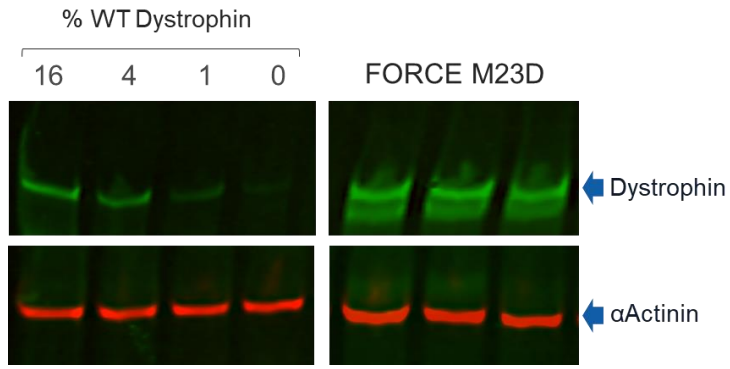
OUR APPROACH

Best-in-class Targeted Exon Skipping

Increase dystrophin expression and enable less frequent dosing to potentially **stop or reverse disease progression**

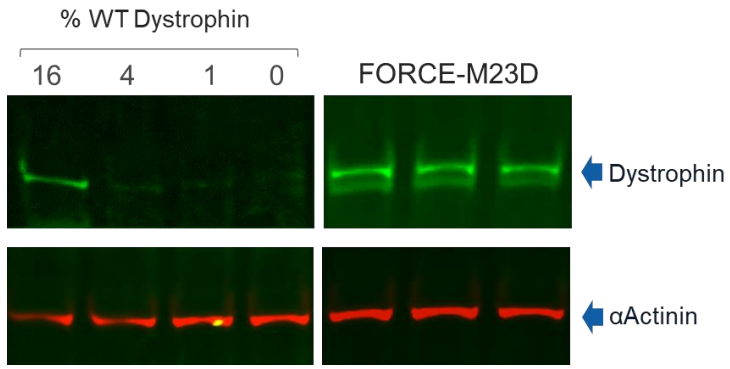
FORCE Achieved Robust and Durable Dystrophin Expression and Sarcolemma Localization in Muscle

Quadriceps



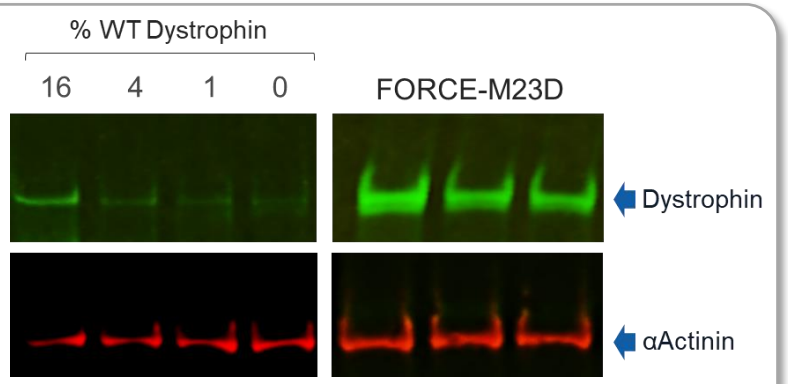
51% of wild-type dystrophin

Diaphragm

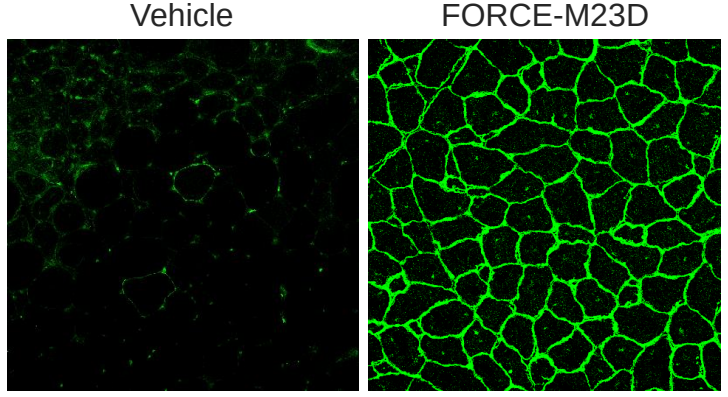


90% of wild-type dystrophin

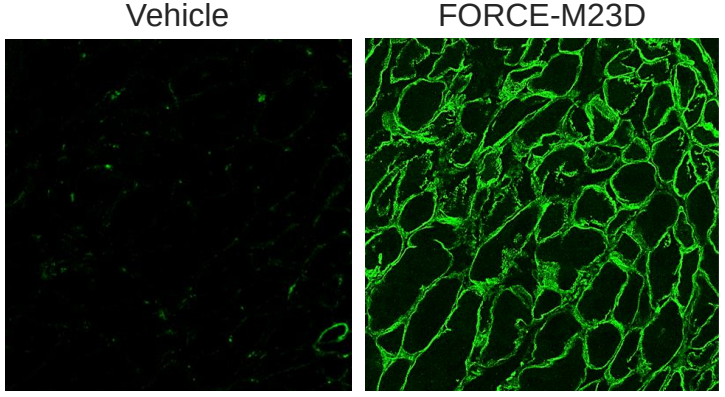
Heart



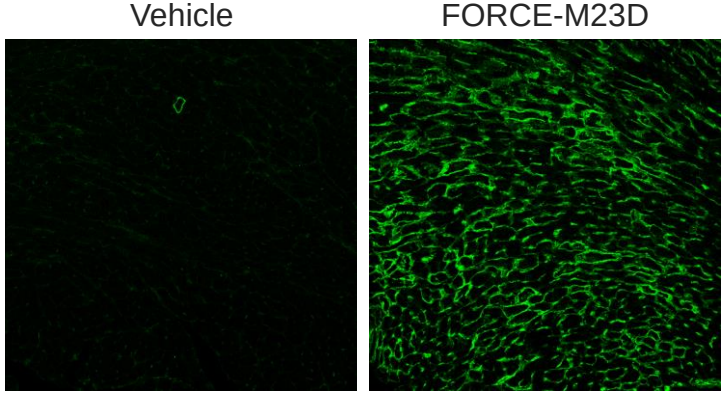
77% of wild-type dystrophin



68% dystrophin-positive fibers



~80% dystrophin-positive fibers

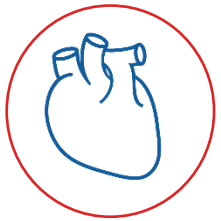


~80% dystrophin-positive fibers

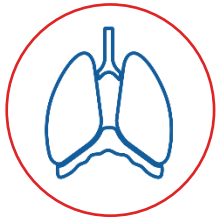
Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0; analysis on week 4 for all muscles. N= 3 - 5 per cohort.

DYNE-251 Demonstrated Robust Exon Skipping & Favorable Safety Profile in NHPs

High Level of Exon 51 Skipping Achieved in Key Muscles at 2 Months[1]



43% in heart



52% in diaphragm

18% in quadriceps

GLP Toxicology Studies: 5-Week & 13-Week[2]

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

Notes: 1. Based on 5 weekly doses (Week 0 – Week 4) with tissue analysis at 8 weeks. 2. Based on conclusions of report from third-party CRO.
NOAEL: No-observed-adverse-effect level

DELIVER Trial Informed by Input from Multiple Stakeholders

Global, Multi-disciplinary KOL & Regulatory Input

- Overall design for the MAD portion in patients with DMD amenable to exon 51 skipping
- Patient population, biomarker and functional endpoints, and key safety considerations
- Natural history data to contextualize clinical trial data for patients and families, clinicians, payers, regulators

Global Advocacy Leaders, Patient and Caregiver Input

- Considerations for trial selection
- Clinical trial protocol and visit schedule
- Minimizing patient burden during trial conduct
- Ensuring support and education to patients and families

Phase 1/2 Clinical Trial to Evaluate DYNE-251 in Patients with DMD

Population

- Patients with DMD with mutations amenable to exon 51 skipping therapy
- Ages 4 to 16 years
- ~46 male participants
- Ambulant and non-ambulant

Primary Endpoints

- Safety and tolerability
- Change from baseline in dystrophin protein levels by Western Blot

Key Secondary Endpoints

- Pharmacokinetics
- Change from baseline of:
  - Exon 51 skipping levels
  - Muscle tissue PDPF
  - Multiple assessments of muscle function, including NSAA score and certain timed functional tests

Stages of DELIVER

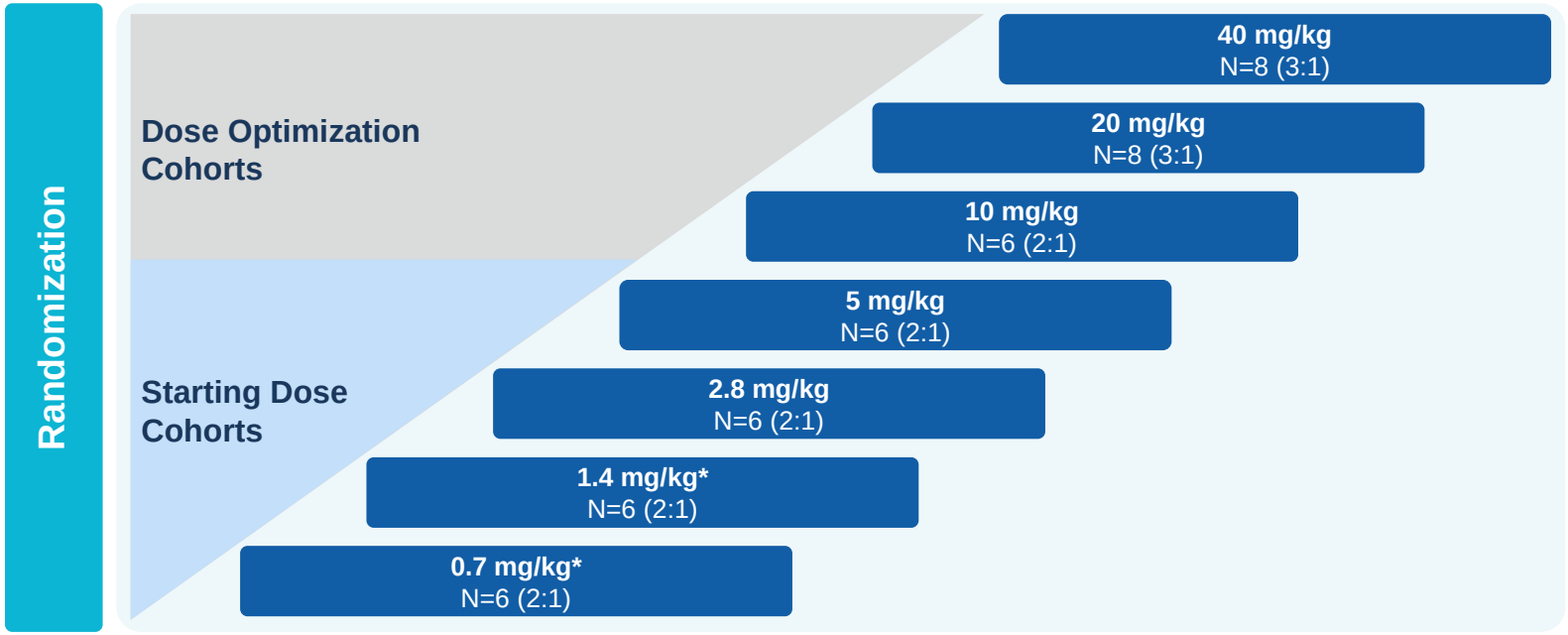
- Multiple Ascending Dose (MAD): 24 weeks
- Open-Label Extension (OLE): 24 weeks
- Long-Term Extension (LTE): 96 weeks

Safety, Tolerability & Dystrophin Data Expected in H2 2023

Multiple Ascending Dose Stage of DELIVER

DELIVER

Global, Randomized, Placebo-Controlled Stage Evaluating Once Monthly Administration of DYNE-251 in ~46 Ambulant and Non-Ambulant Male DMD Patients with Mutations Amenable to Exon 51 Skipping Therapy



MAD Study Details

- IV administration of DYNE-251 or placebo every 4 weeks
- Muscle biopsies: Baseline and 24 weeks in 2.8 mg/kg and higher cohorts
- Patients in MAD study escalated to highest tolerable dose in OLE and LTE

Global Trial Designed to be Registrational and Enable Rapid Achievement of Predicted Pharmacologically Active Dose Levels

Dyne THERAPEUTICS

Patient cohorts will be dosed from 0.7 mg/kg to 40 mg/kg in the U.S. Outside the U.S., starting doses and number of cohorts will vary by region. Doses provided refer to PMO component of DYNE-251. Muscle biopsies taken at baseline and 24 weeks in 2.8 mg/kg and higher cohorts; biopsies not taken in 0.7 mg/kg and 1.4 mg/kg cohorts.

Driving Toward Meaningful Clinical Data in DM1 & DMD in H2 2023

ACHIEVE | DELIVER

Global, Randomized Placebo-Controlled Trials Designed to Be Registrational

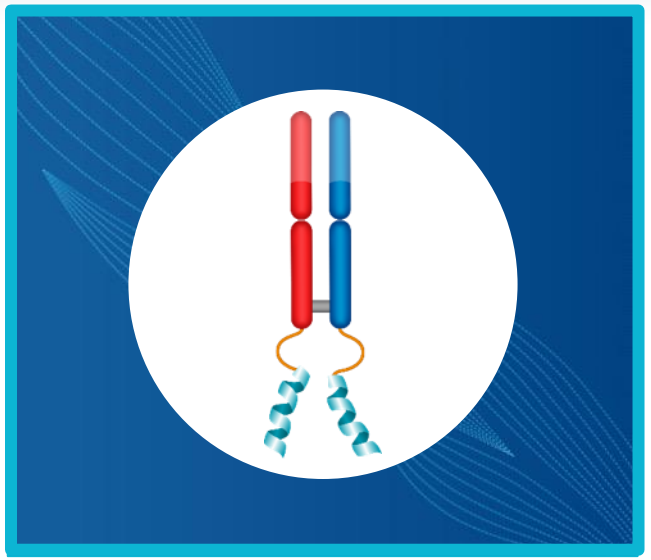
Dosing Patients at Predicted Pharmacologically Active Doses

Significant Unmet Patient Need Provides Confidence in Ability to Enroll Rapidly

ACHIEVE	DELIVER
Safety, Tolerability & Splicing Data Expected in H2 2023	**Safety, Tolerability & Dystrophin Data Expected in H2 2023**

Building the World's Leading Muscle Disease Company

Win in DM1, DMD, FSHD



Own Muscle Delivery

Dynamo Culture