Development of the Endosomal Escape Vehicle (EEV™) Platform for Enhanced Delivery of Oligonucleotides to Skeletal and Cardiac Muscle

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6th International Caparica Conference on Splicing

entrada THERAPEUTICS

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DMD, Duchenne muscular dystrophy; **EEV**, endosomal escape vehicle.

OUR MISSION:

To Treat Devastating Diseases With Intracellular Therapeutics

We're proud to share the stories of JJ, Andrew, Max and Franklin – all living with Duchenne muscular dystrophy

EEV™ PLATFORM

ENDOSOMAL ESCAPE VEHICLE (EEV™)-BASED THERAPIES

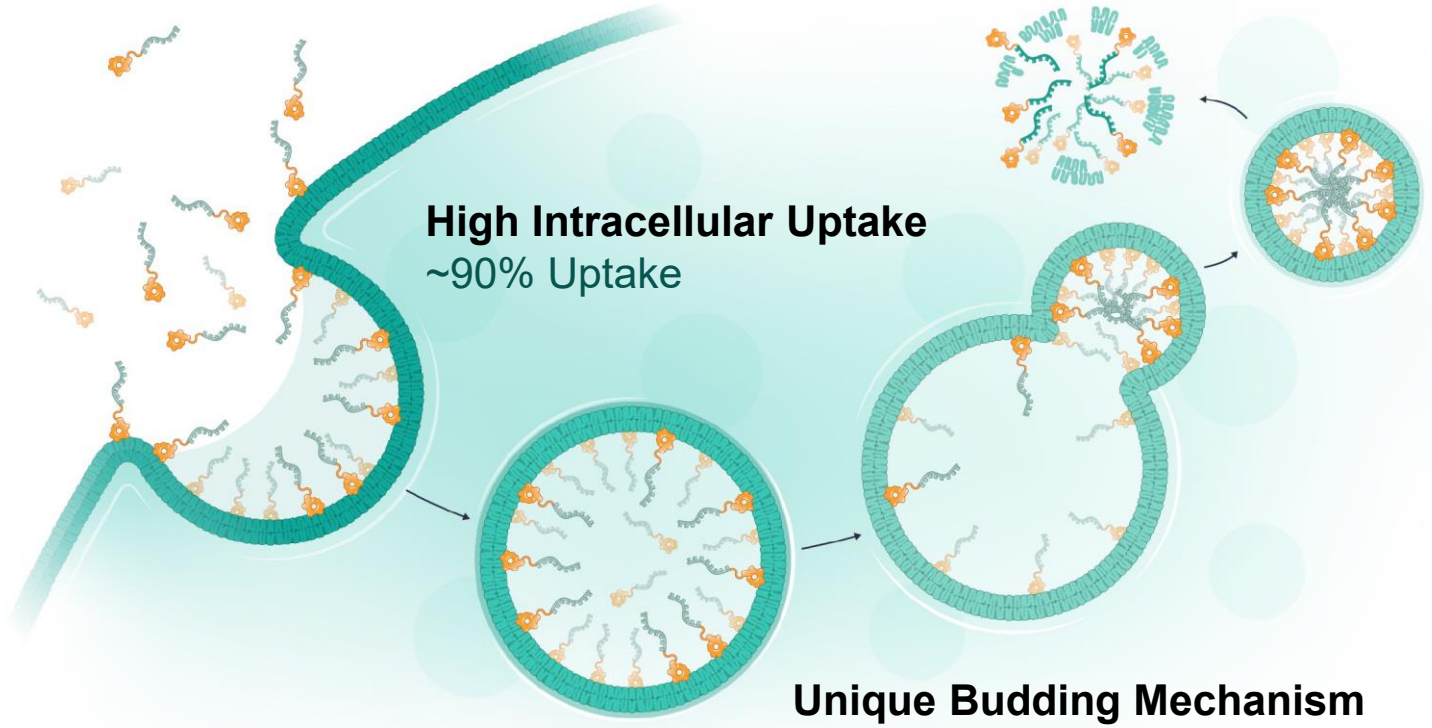
Unique chemistry
Improved uptake and endosomal escape

Cyclic structure
Extended half-life and increased stability

Phospholipid binding
Broad biodistribution to all cells

Consistent and predictable pharmacokinetics
Same EEV used across initial programs

Efficient Endosomal Escape
~50% Escape vs. ~2% Standard



Qian, Z. et al. ACS Chem. Biol. 2013; Qian, Z. et al. Biochemistry 2014; Qian, Z. et al. Biochemistry 2016; Sahni, A. et al. ACS Chem. Biol. 2020; Pei, D. Acc. Chem. Res. 2022.

PIPELINE EXPANSION OPPORTUNITIES

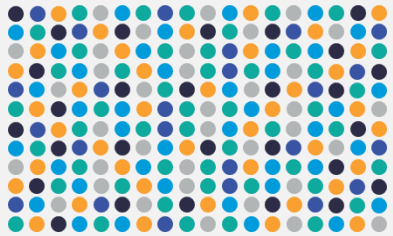
Entrada's flexible approach to intracellular therapeutics enables pipeline expansion by leveraging new moieties and by targeting additional therapeutic areas

TARGET	APPROACH	GOAL
DNA	Gene Editing	Deliver CRISPR enzyme and repair gene function with guide RNA
RNA	RNA Editing	Deliver oligonucleotide therapeutics for RNA editing
	RNA Splicing	Modify RNA via exon/intron splicing to activate protein expression
	RNA Blocking	Block trinucleotide repeats in RNA to inhibit adverse binding
	RNA Silencing	Silence or knockdown RNA to prevent protein expression
PROTEINS	Protein Replacement	Replace proteins and enzymes
	Protein Inhibition	Inhibit protein signaling pathways
	Protein Degradation	Degrade disease-causing proteins

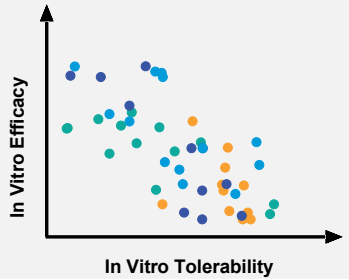
DISCOVERY ENGINE FOR EEV THERAPEUTICS
EEV-OLIGO EXAMPLE

Fit-for-purpose EEVs can be designed for target indications and modalities via iterative optimizations of EEV peptides through medicinal chemistry, *in vitro* and *in vivo* screenings

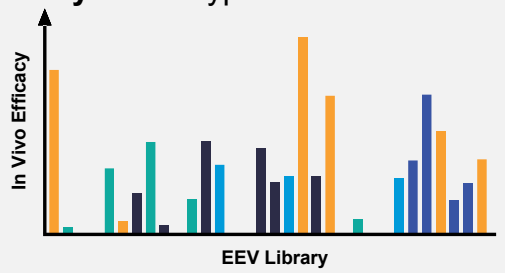
Chemically diverse macrocyclic **EEV library** generated through medicinal and combinatorial chemistry



In vitro **delivery and counter-screening** in relevant cell types with therapeutic payload



In vivo screening to assess **functional delivery and pharmacodynamic activity** in wild-type and disease models

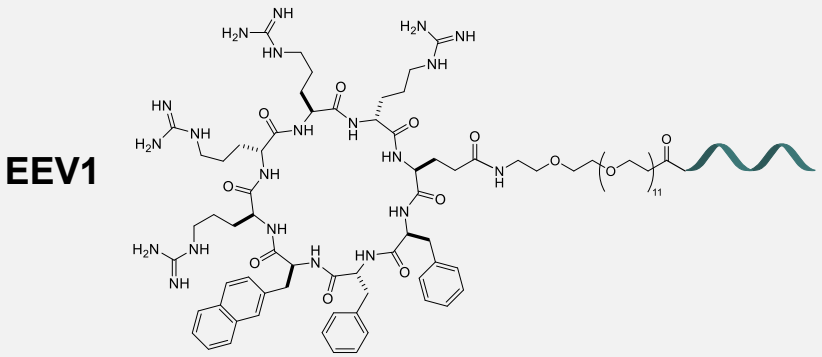


EEV, endosomal escape vehicle.

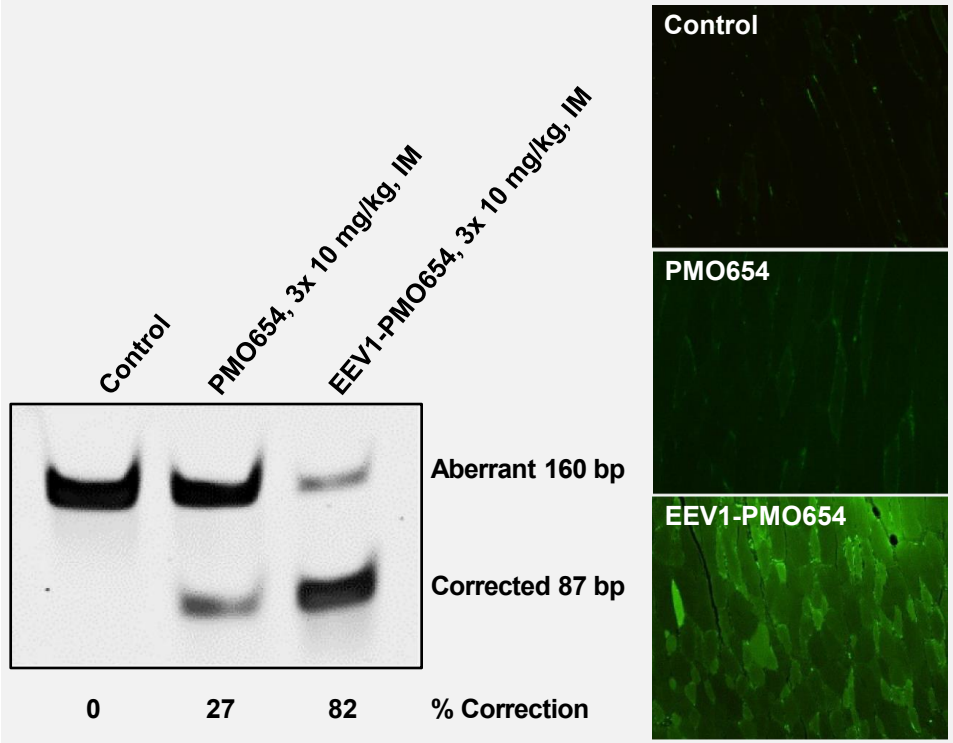
OLIGO DELIVERY WITH FIRST GENERATION EEV
EEV1 EXAMPLE

A first-generation EEV1 peptide-PMO construct enhanced splice correction *in vitro* and after local injection, demonstrated functional delivery of oligonucleotides

Splicing Correction in HeLa EGFP-654 Cells



Three Daily IM Doses of EEV1-PMO654



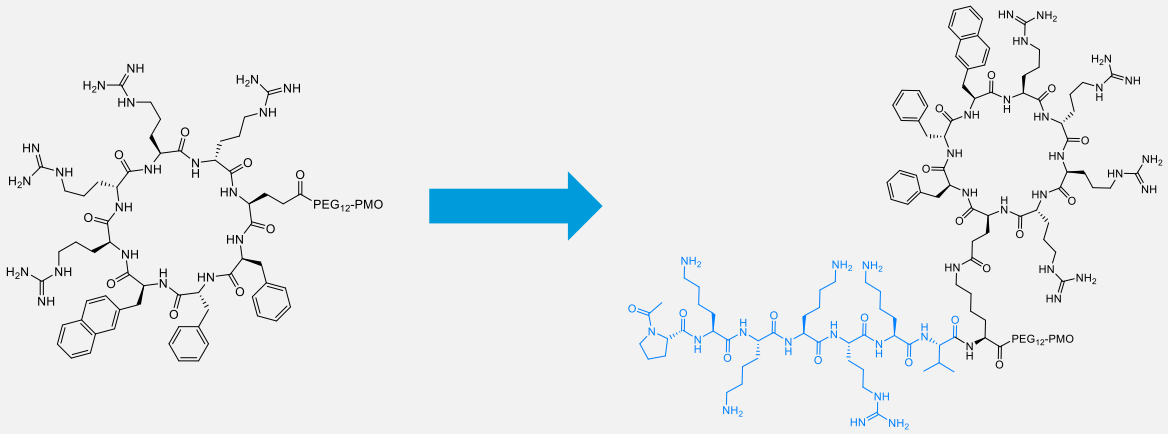
[a]Treatment of HeLa EGFP-654 cells with antisense oligonucleotides, such as PMOs, could switch the splicing and restore expression of EGFP; **EEV**, endosomal escape vehicle; **PMO**, phosphorodiamidate morpholino oligomer; **IM**, intramuscular; Qian, Z. et al. *Biochemistry* 2014, 2016; Li, X. et al. *Mol. Ther. Nucleic Acids* 2023.

ENHANCED OLIGONUCLEOTIDE DELIVERY
EEV2 EXAMPLE

The addition of an exocyclic peptide sequence to a first-generation EEV1 peptide improved exon skipping in skeletal and cardiac muscle of *mdx* mice after intravenous injection

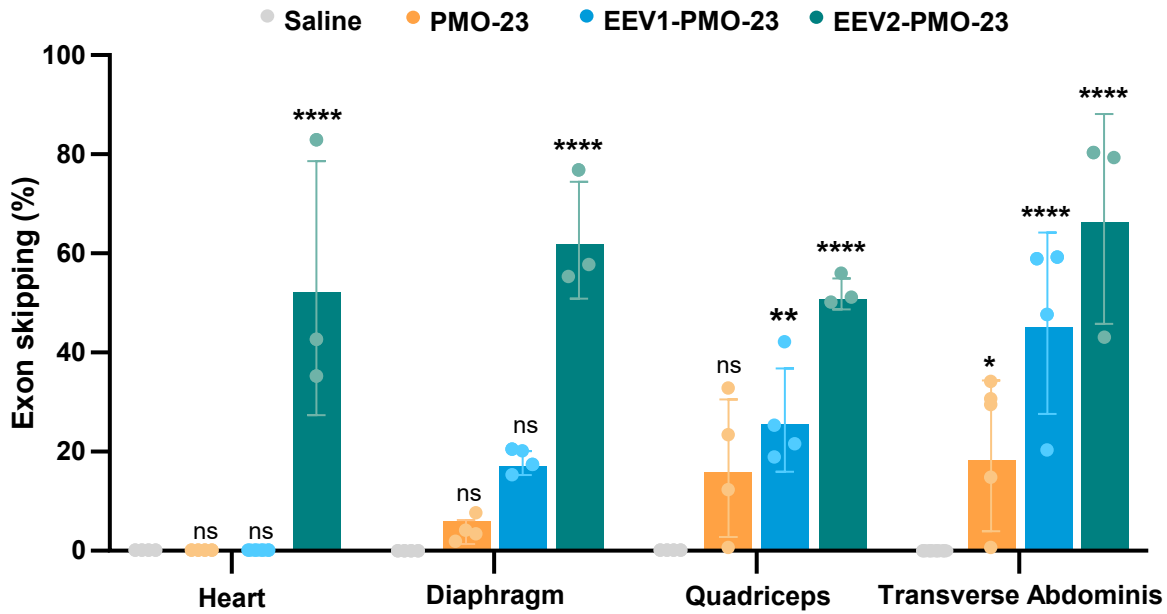
Structure of EEV2 Construct

EEV1 + exocyclic peptide sequence = EEV2



- To create the EEV2 construct, EEV1 was modified to include an exocyclic peptide sequence to improve delivery to the nucleus

Higher In Vivo Exon Skipping with EEV2 vs. EEV1



- *mdx* mice were evaluated for exon skipping (via RT-PCR) 7 days following a single 20-mg/kg IV injection of saline, PMO-23, EEV1-PMO-23, or EEV2-PMO-23

p<0.01, ****p<0.0001 vs. Vehicle. Values are shown as mean ± standard deviation. *mdx* is a DMD mouse model with a nonsense mutation in DMD exon 23; **EEV, endosomal escape vehicle; **IV,** intravenous; **ns**, not significant; **PMO**, phosphorodiamidate morpholino oligomer; **RT-PCR,** reverse transcription polymerase chain reaction; Li, X. et al. *Mol. Ther. Nucleic Acids* 2023.

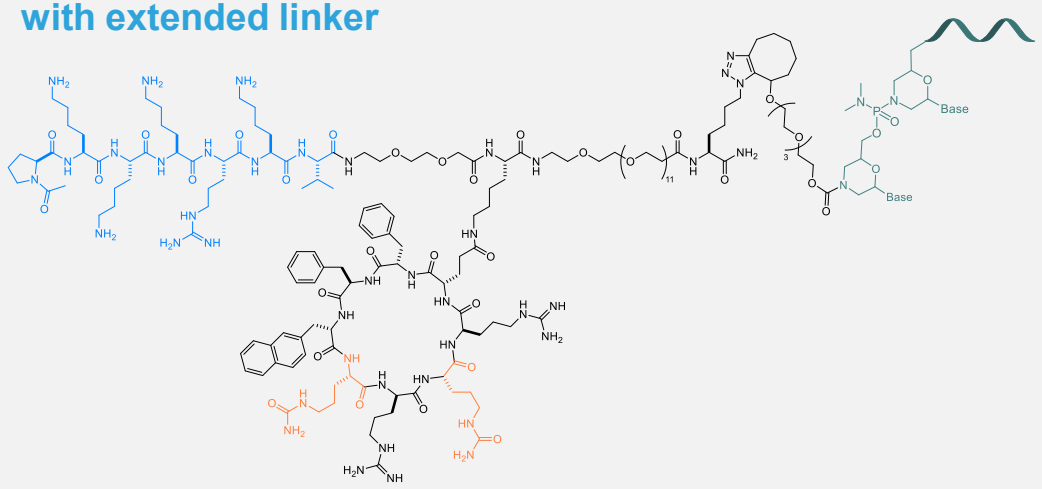
OPTIMIZATION OF EEV FOR MUSCLE DELIVERY
EEV3 Example

Rational substitution of cationic residues with a surrogate results in robust functional delivery to skeletal and cardiac muscle

EEV3-PMO654 Structure and Medicinal Chemistry

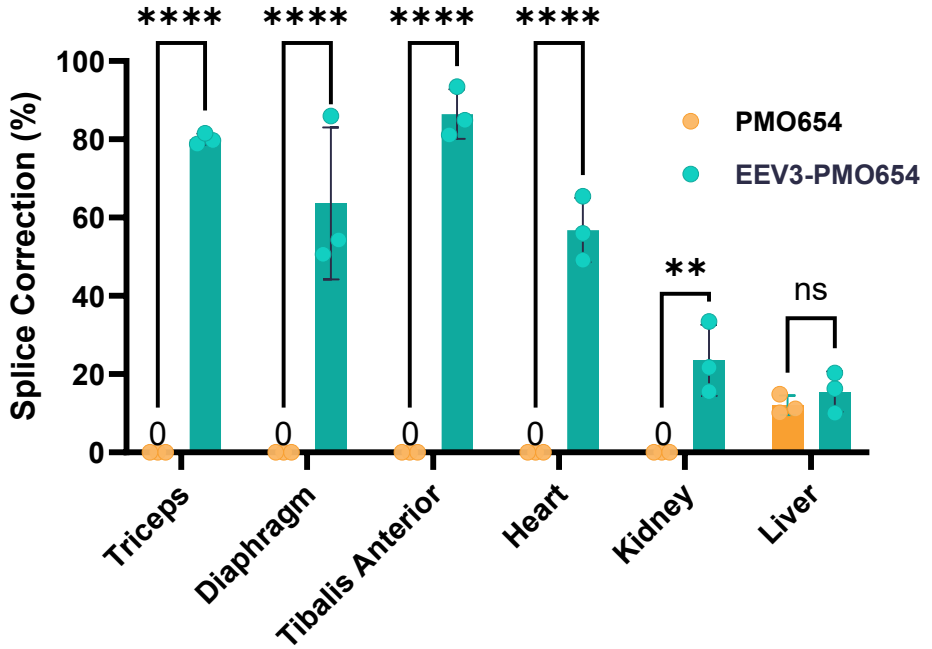
Exocyclic peptide sequence with extended linker

Conjugation with PMO



Substitution of positively charged arginine residues with neutral charged citrullines

Enhanced Functional Delivery to Muscle



- *EGFP654* mice were evaluated for splice correction 7 days following three weekly 10 mg/kg IV injections of PMO654 or EEV3-PMO654

p<0.01, ****p<0.0001; values are shown as mean ± standard deviation. **EEV, endosomal escape vehicle; **IV,** intravenous; **ns**, not significant; **PMO**, phosphorodiamidate morpholino oligomer.

TRANSLATION FROM UPTAKE TO OUTCOMES

Murine Example

EEV-therapeutic candidates have demonstrated favorable pharmacological properties: efficient intracellular delivery, significant uptake in target tissues and potent pharmacodynamic outcomes

Tissue Uptake in Muscle

- ✓ Skeletal muscle
- ✓ Cardiac muscle

+

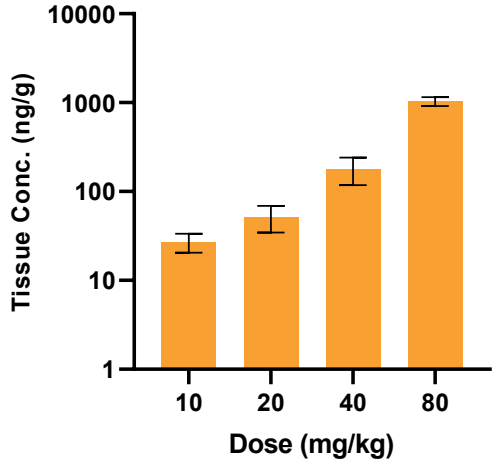
Intracellular Delivery

- ✓ Endosomal escape
- ✓ Nuclear localization

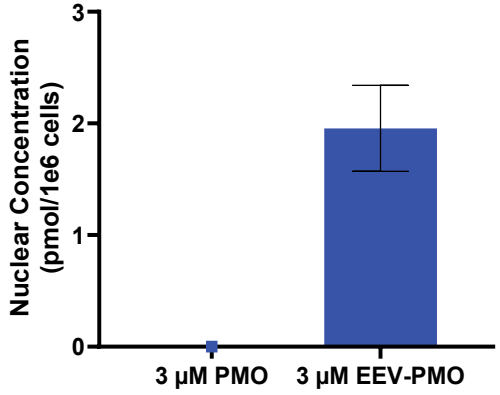
=

Pharmacodynamic Outcome

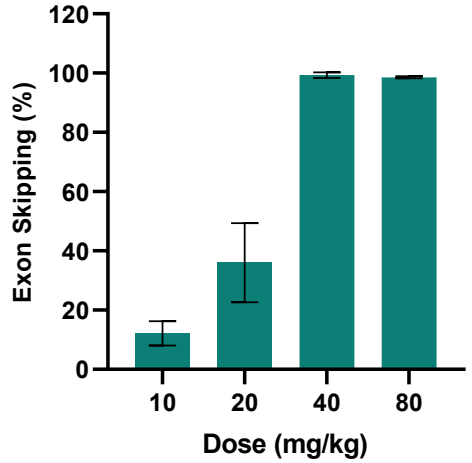
- ✓ Rapid, dose-dependent response
- ✓ Duration of at least 12 weeks



IV, hDMD mice, 5-day post injection



24-hour incubation



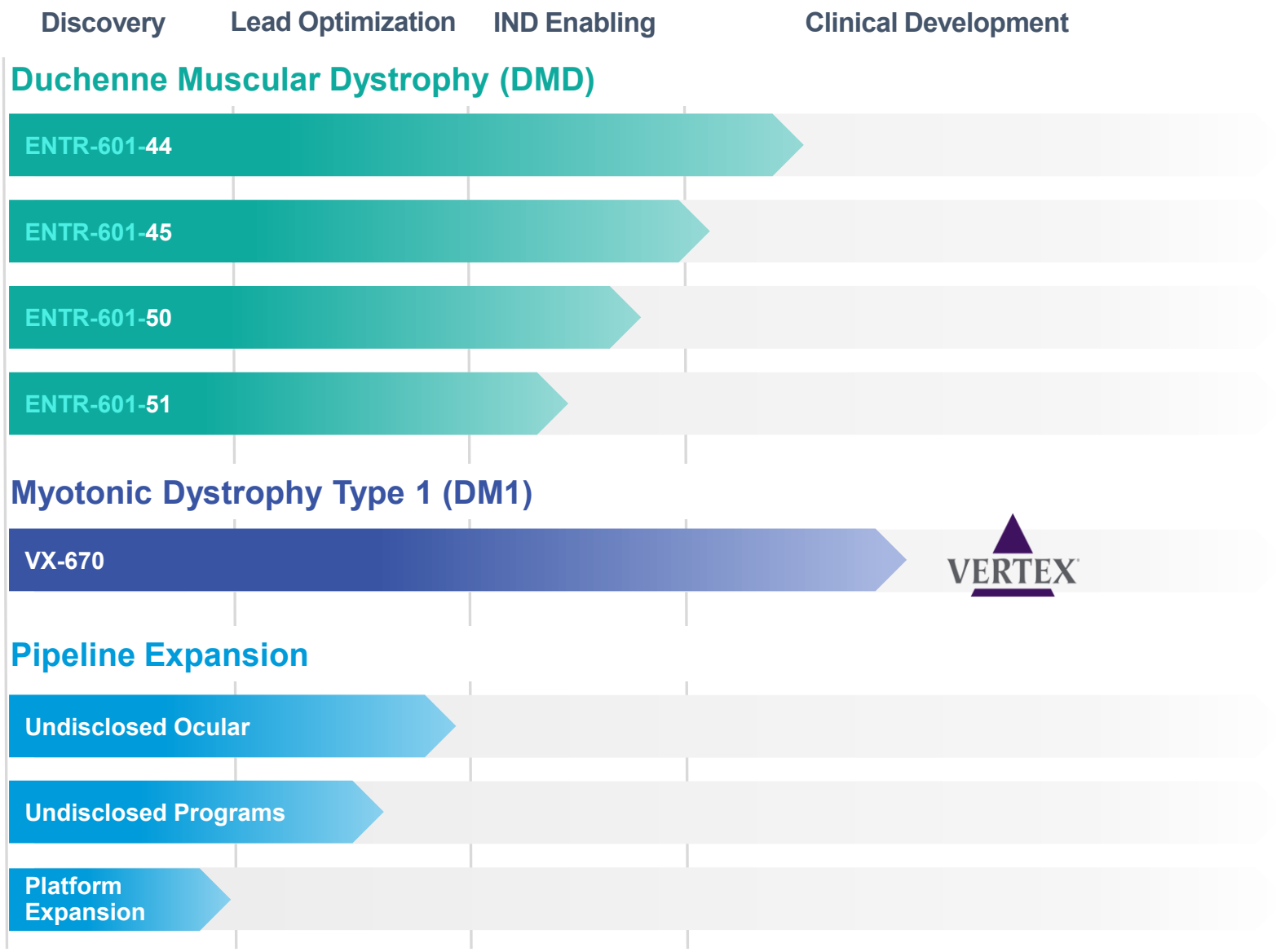
IV, hDMD mice, 5-day post injection

hDMD mice express full-length human dystrophin gene; **IV,** intravenous; **PMO**, phosphorodiamidate morpholino oligomer.

An Expanding Pipeline of Intracellular Therapeutics

Entrada's pipeline includes a diverse array of high potential and high value assets

Each target disease has a substantial patient population with a significant unmet medical need



DUCHENNE MUSCULAR DYSTROPHY

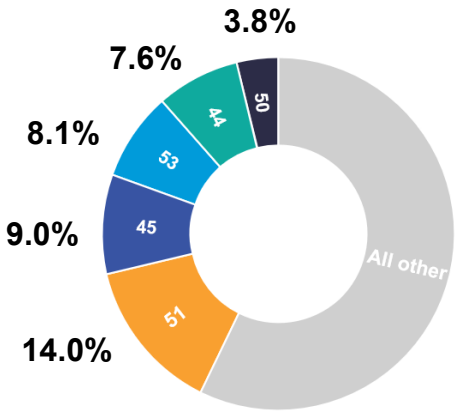
SIGNIFICANT THERAPEUTIC NEED EXISTS WITHIN A VALIDATED DUCHENNE MARKET

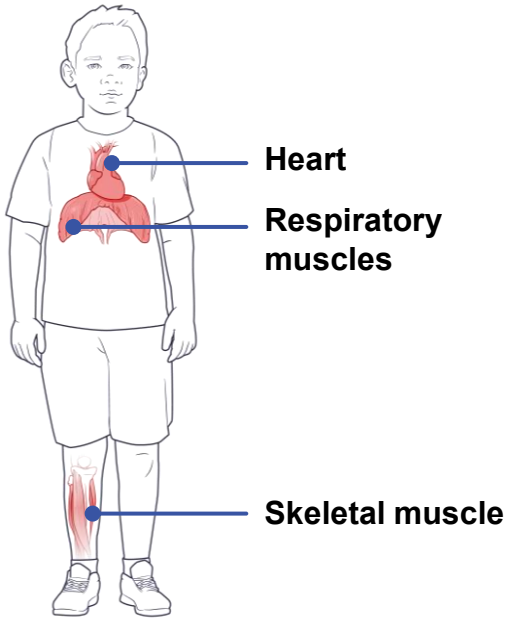
Duchenne is caused by **mutations in the *DMD* gene, which lead to a lack of functional dystrophin**, causing progressive loss of muscle function throughout the body

Exon skipping therapeutics have been approved based on **modest improvement in dystrophin levels ranging from ~1% to 6%**[4-7]

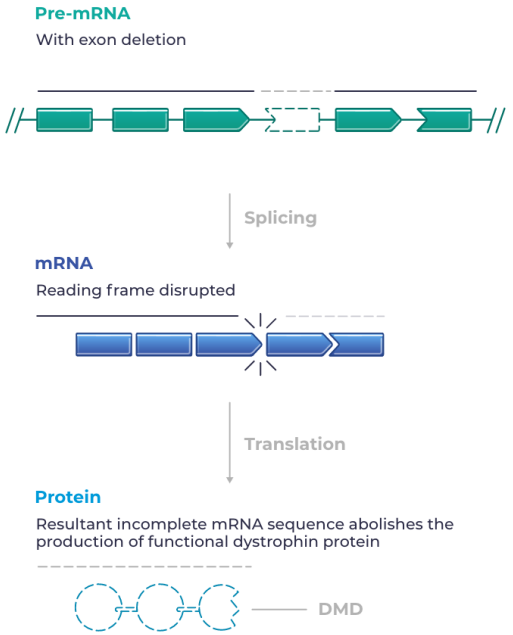
Approximately **41,000** people in the **U.S.**[1] **and Europe**[2] have Duchenne

>40% of patients with Duchenne[3] have mutations amenable to exon skipping of exons 44, 45, 50, 51 and 53

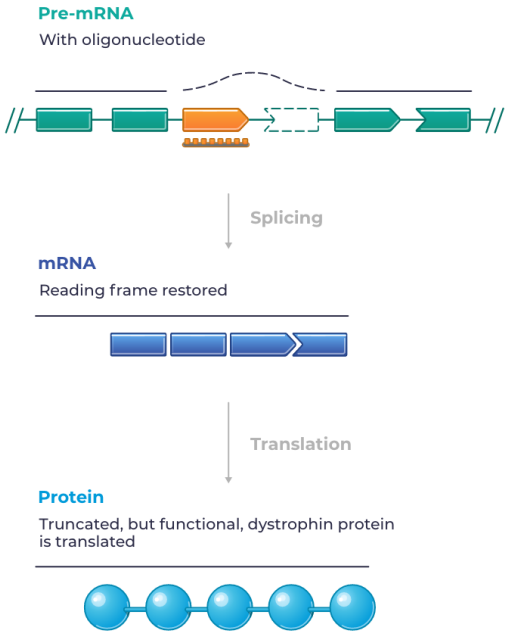




Patients with Duchenne



EEV-Oligonucleotide Approach

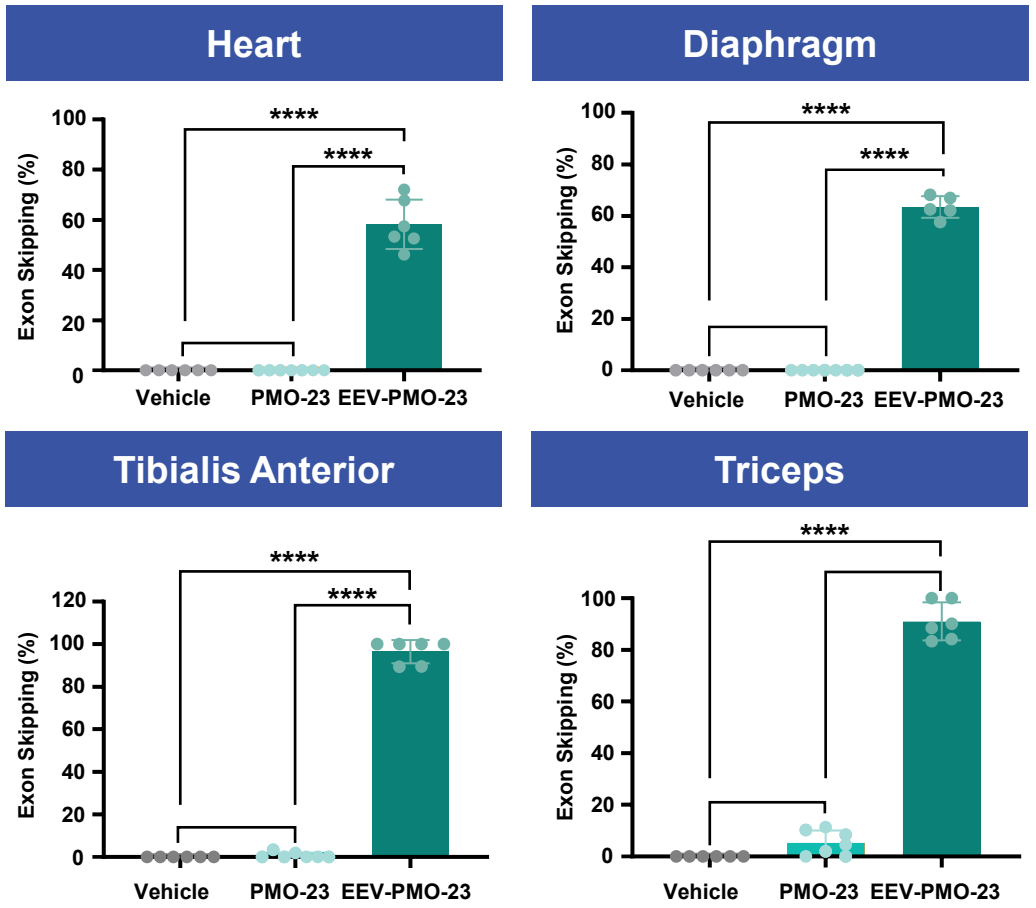


TIDES USA

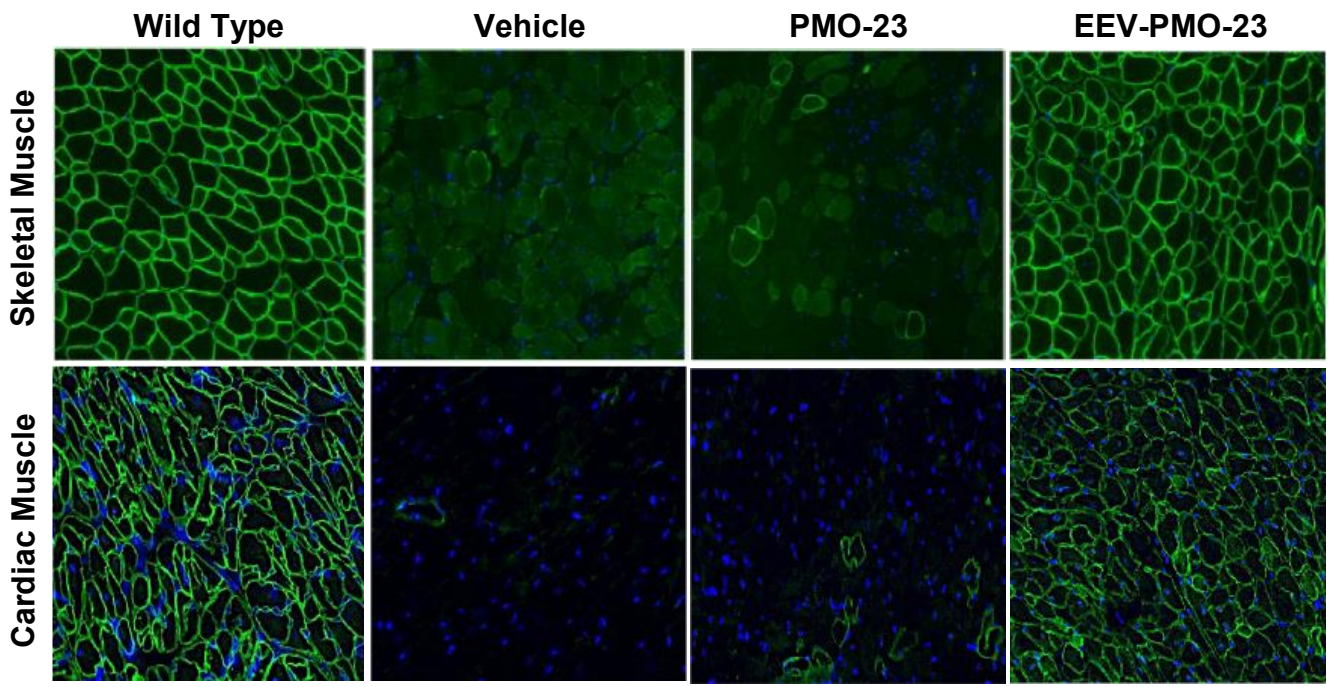
1. Parent Project Muscular Dystrophy. https://www.parentprojectmd.org/about-duchenne/. Accessed August 18, 2023. **2.** Europeans Medicines Agency. https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3202375. Accessed August 18, 2023. **3.** Bladen, C.L. et al. *Hum Mutat*. 2015. **4.** AMONDYS 45 PI. **5.** VILTEPSO PI. **6.** VYONDYS 53 PI. **7.** EXONDYS 51 PI. **DMD**, Duchenne muscular dystrophy; **EEV**, endosomal escape vehicle

REPEAT EEV-PMO-23 TREATMENT IN D2-*mdx* MICE

Robust exon 23 skipping after 4 monthly IV doses of EEV-PMO-23 in D2-*mdx* mice



Broad dystrophin expression and restoration of muscle integrity after four monthly IV doses of EEV-PMO-23 in D2-*mdx* mice



- D2-*mdx* mice (male, n=6-7) were treated with 4 monthly doses of either vehicle, 20 mg/kg unconjugated PMO-23 or 20 mg/kg PMO-23 equivalent of EEV-PMO-23, and the data were collected ~4 weeks after the last dose.

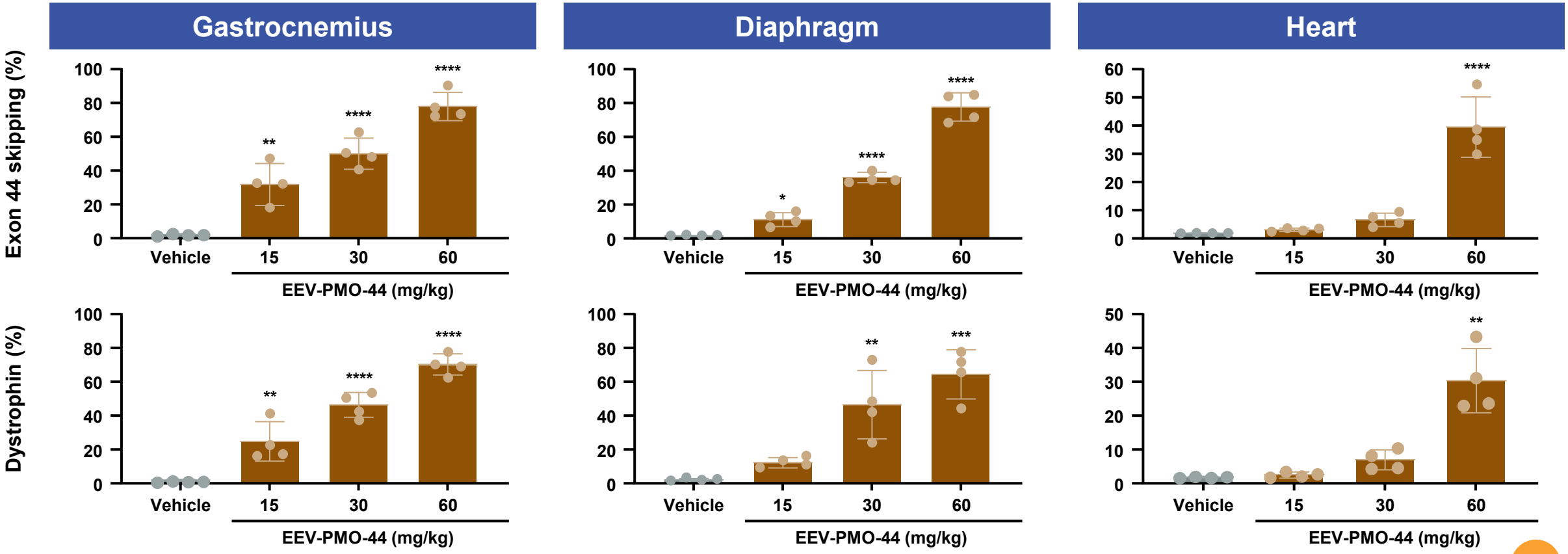
****p<0.0001. Values are shown as mean ± standard deviation. **D2-*mdx*** is a DMD mouse model with a nonsense mutation in *DMD* exon 23 (Coley, W.D. et al. *Hum. Mol. Genet.* 2016). Li, X. et al. *Mol. Ther. Nucleic Acids* 2023. **EEV**, endosomal escape vehicle; **DMD**, Duchenne muscular dystrophy; **IV,** intravenous; **ns**, not significant; **PMO**, phosphorodiamidate morpholino oligomer; **PMO-23**, mouse *DMD* exon 23 skipping phosphorodiamidate morpholino oligomer.

ENTR-601-44 PRECLINICAL STUDIES

EEV-PMO-44 EFFICACY IN del45hDMD.*mdx* MICE

A single dose of EEV-PMO-44 produced robust human *DMD* exon 44 skipping and dystrophin production 2 weeks post-dose in mice amenable to exon 44 skipping

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$ vs. Vehicle

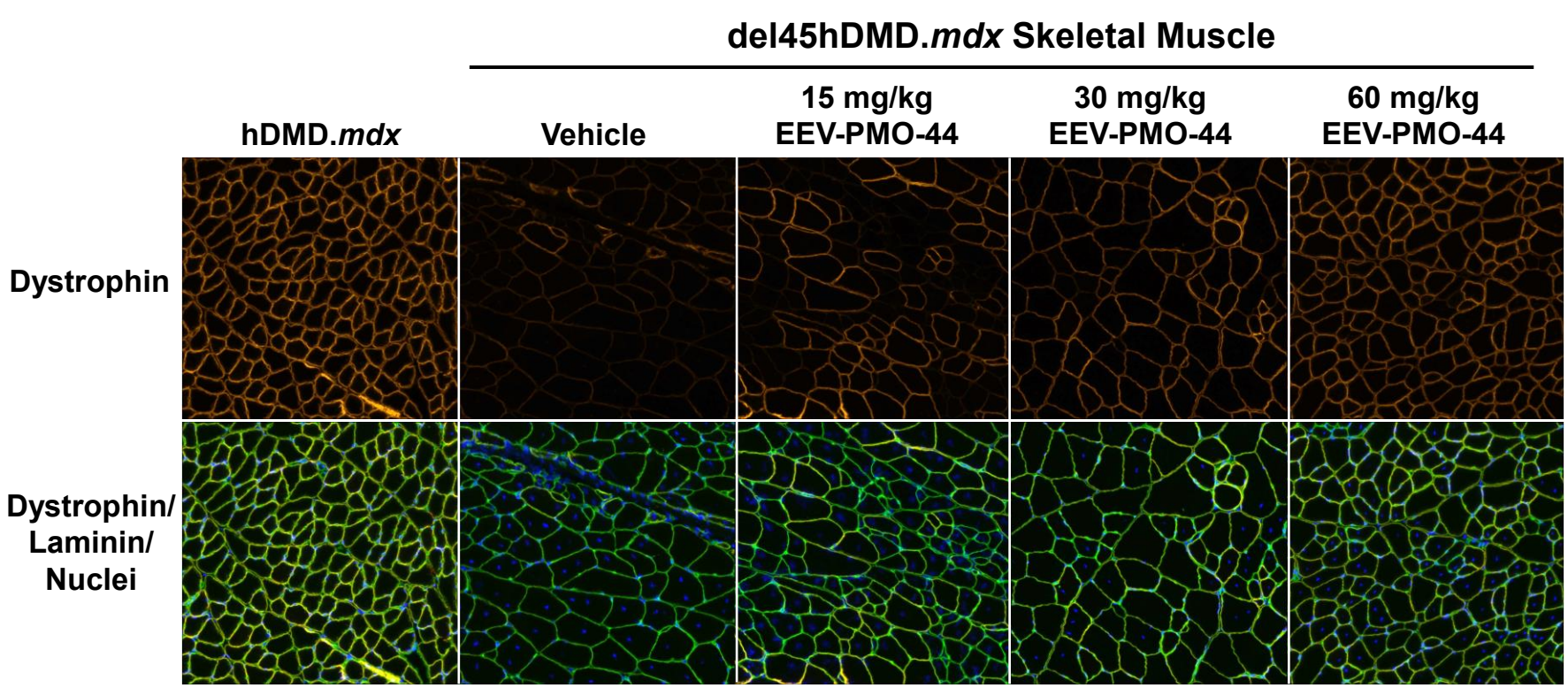


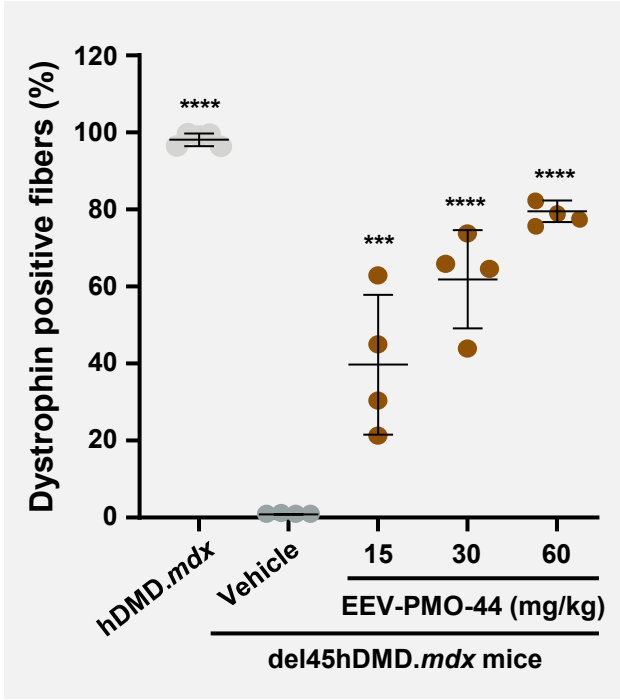
del45hDMD.*mdx* mice were treated with a single IV injection of EEV-PMO-44 (*DMD* exon 44 skipping EEV-oligonucleotide construct) or vehicle. Human *DMD* exon 44 skipping (top) and dystrophin protein expression (bottom) were analyzed in the gastrocnemius, diaphragm, and heart 2 weeks after the final dose. Percent dystrophin protein restoration is normalized to total protein and normalized to hDMD.*mdx* controls. Data shown as mean ± standard deviation. One-way ANOVA was used for statistical comparison; **ANOVA**, analysis of variance; **hDMD**, human dystrophin transgene; **IV**, intravenous.

DYSTROPHIN LOCALIZATION WITH EEV-PMO-44 IN del45hDMD.*mdx* Mice

EEV-PMO-44 produced dose-dependent increases in dystrophin-positive muscle fibers localized to the sarcolemma of del45hDMD.*mdx* mice 2 weeks post-dose

***$p \leq 0.001$, ****$p \leq 0.0001$ vs. Vehicle





- del45hDMD.*mdx* mice were treated with a single IV dose of EEV-PMO-44 or vehicle. Dystrophin protein distribution and cellular localization were analyzed by immunofluorescence in the gastrocnemius 2 weeks post-dose.

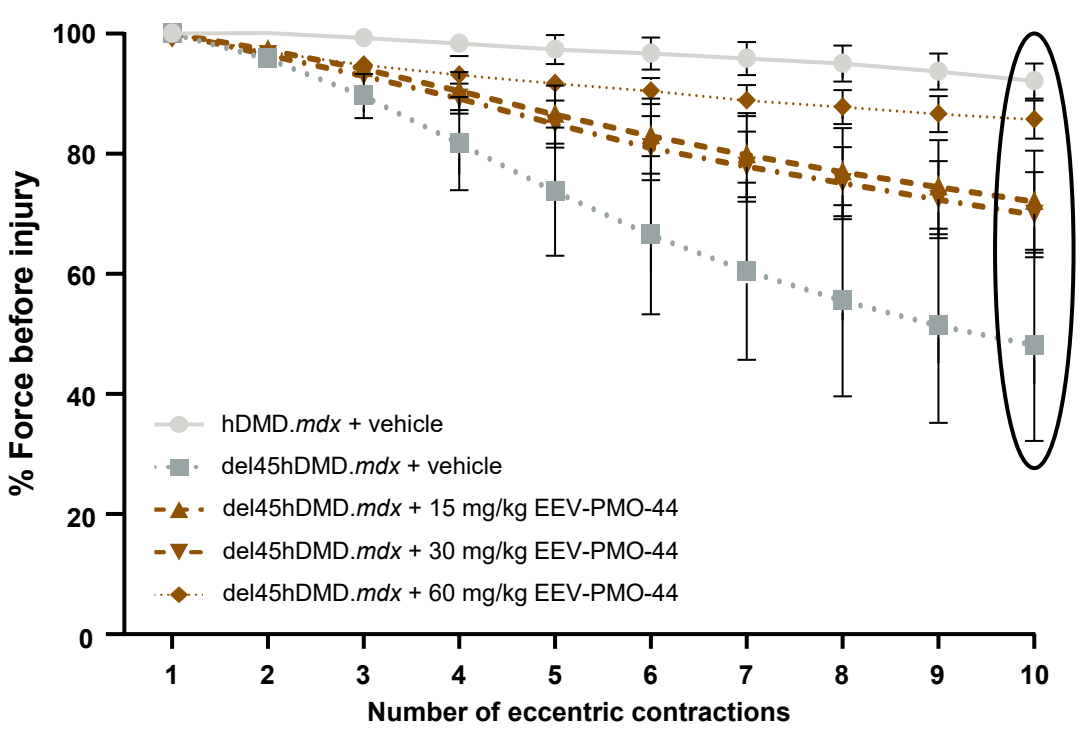
Quantification via Halo Image Analysis Software is shown as the percentage of dystrophin-positive muscle fibers relative to the total number of muscle fibers as determined by laminin staining (green) and dystrophin staining (red); co-localization to the sarcolemma appears yellow and nuclei appear blue. Data shown as mean ± standard deviation. One-way ANOVA was used for statistical comparison; **ANOVA**, analysis of variance; **hDMD**, human dystrophin transgene; **IV**, intravenous.

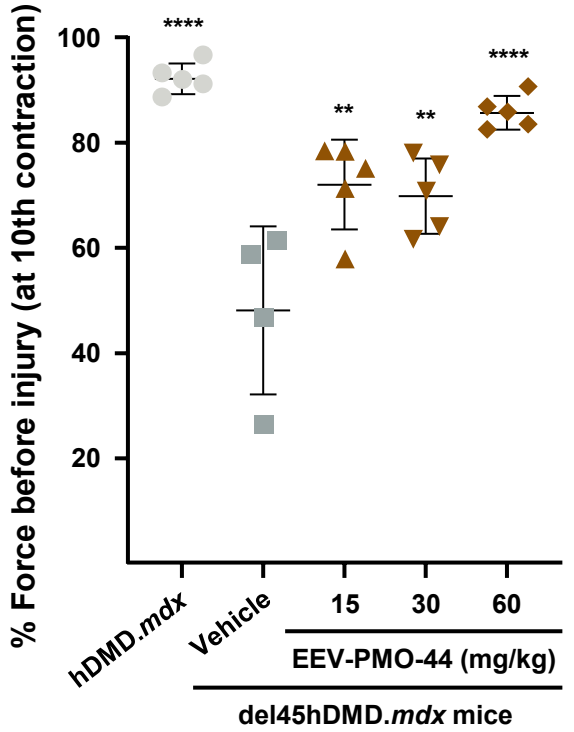
EEV-PMO-44 IMPROVES MUSCLE FUNCTION IN del45hDMD.*mdx* Mice

A dose-dependent increase in resistance to membrane damage was observed following the tenth contraction, as well as an increase in tetanic force 2 weeks post-dose of EEV-PMO-44

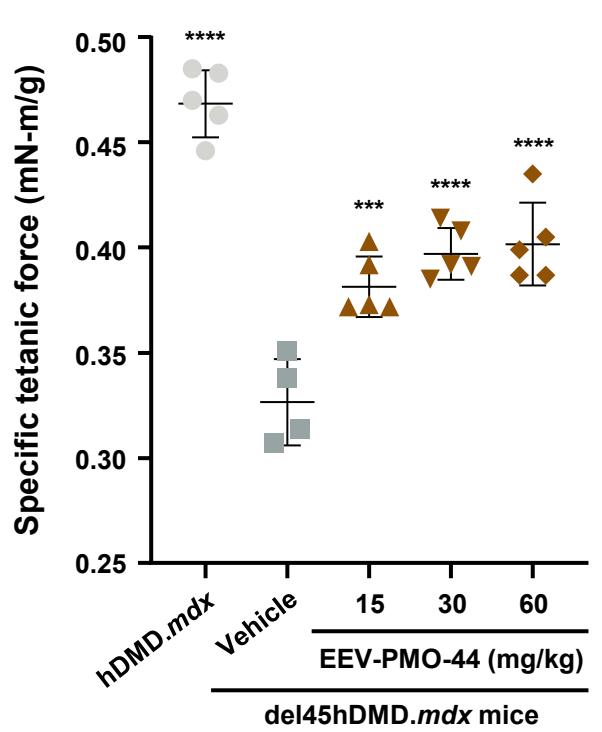
$^{**}p<0.01$, $^{***}p<0.001$, $^{****}p<0.0001$ vs. Vehicle

Skeletal Muscle Membrane Stability





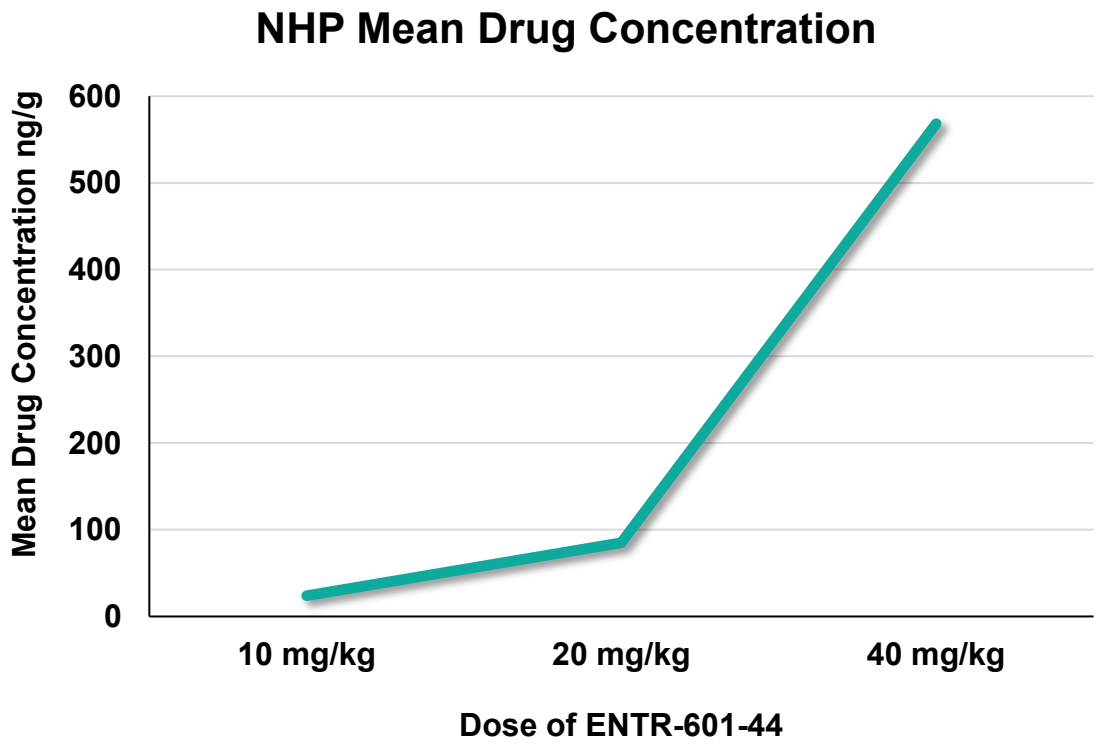
Specific Tetanic Force

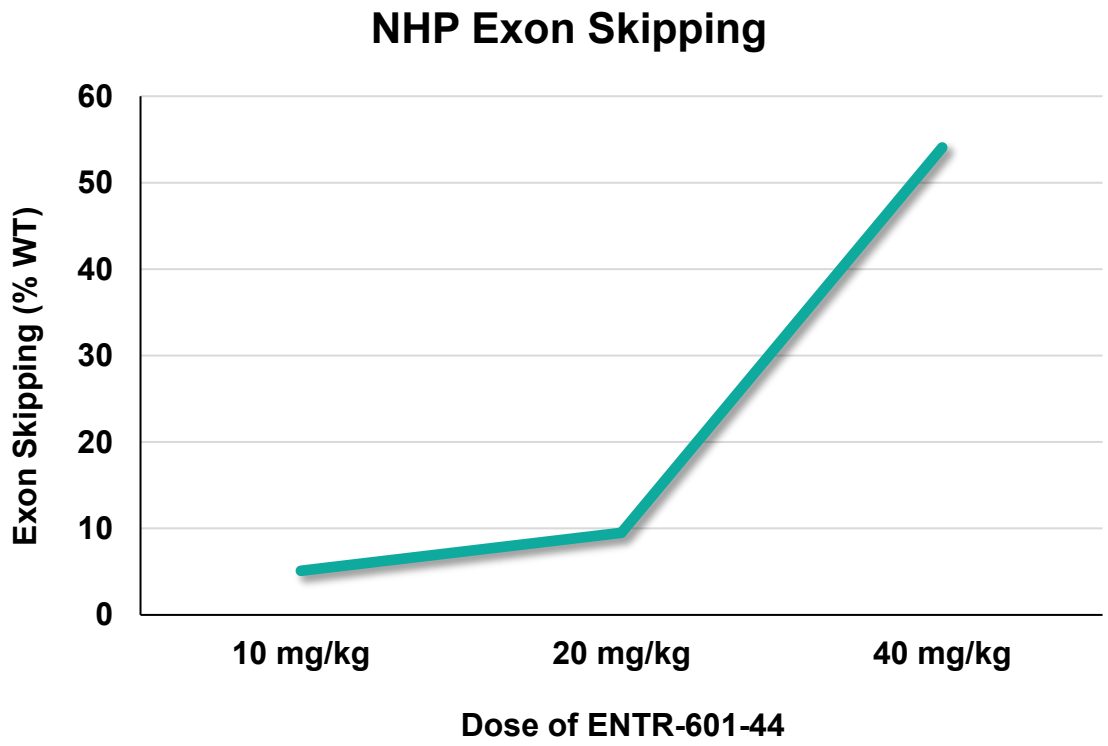


del45hDMD.*mdx* mice were treated with a single IV injection of EEV-PMO-44 or vehicle. ECC-induced muscle force loss generated by repeated ECC contraction and tetanic force of the gastrocnemius muscle was assessed 2 weeks post-dose. Data (mean ± standard deviation) shown across 10 ECC contractions normalized into a percentage of the initial force before any ECC contractions and as the percentage of force retained after the 10th contraction. Vehicle-treated hDMD.*mdx* mice were used as a control group for normal muscle function. One-way ANOVA was used for statistical comparison to vehicle-treated del44hDMD.*mdx* mice. **ECC**, eccentric force; **hDMD**, human dystrophin transgene; **IV**, intravenous.

DOSE-DEPENDENT PK/PD WITH ENTR-601-44 IN NHP

NHP data demonstrated exponential increases in exon skipping at higher doses;
A close correlation between drug concentration and exon skipping was observed



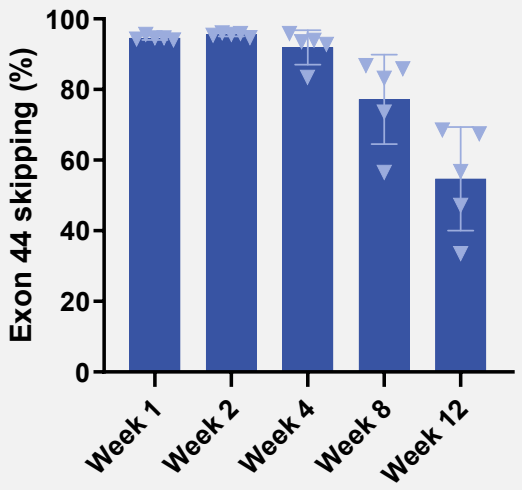


Non-human primates were administered a single intravenous dose of ENTR-601-44. Bicep biopsy was taken at 48 hours post-infusion; *R^2=0.9996; **PK**: pharmacokinetics; **PD**: pharmacodynamics; **ENTR-601-44** is a *DMD* exon 44 skipping EEV-oligonucleotide construct; **NHP,** Non-human primates.

CONSISTENT AND DURABLE EFFICACY OF EEV-PMO WAS DEMONSTRATED ACROSS SPECIES

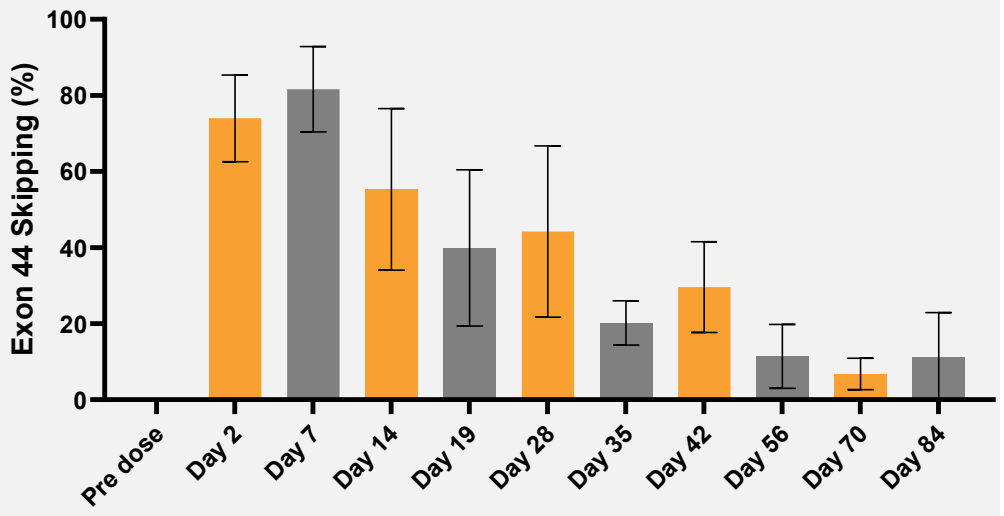
Significant patient benefit is implied by data in the mouse and the monkey at clinically relevant levels; *in vitro* data suggests much higher target engagement in patient cells

Exon 44 Skipping in hDMD Mouse



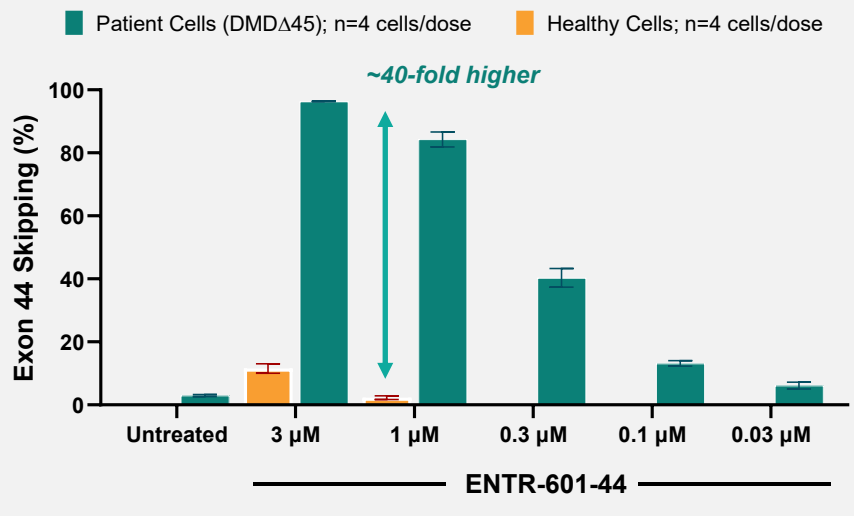
- Single IV 80 mg/kg dose of ENTR-601-44
- Tibialis Anterior

Exon 44 Skipping in Monkey



- Post IV infusion of single 45 mg/kg dose of ENTR-601-44, robust exon 44 skipping observed in biceps of treated monkeys (n=3 per cohort) for at least 12 weeks

Exon 44 Skipping in Healthy and Patient-Derived Muscle Cells



- Robust dose-dependent exon 44 skipping was observed in DMD patient-derived muscle cells harboring an exon 44 skip-amenable mutation

hDMD transgenic mice (left) express full-length human dystrophin gene ('t Hoen, A.C. et al. *J. Biol. Chem.* 2008). **DMDΔ45** (right) are immortalized myoblasts from DMD patients harboring an out-of-frame exon 45 deletion and further differentiated into myotubes. Values are shown as mean ± standard deviation. **ENTR-601-44** is a *DMD* exon 44 skipping EEV-oligonucleotide construct. **DMD**, Duchenne muscular dystrophy; **hDMD,** human Duchenne muscular dystrophy; **IV,** intravenous.

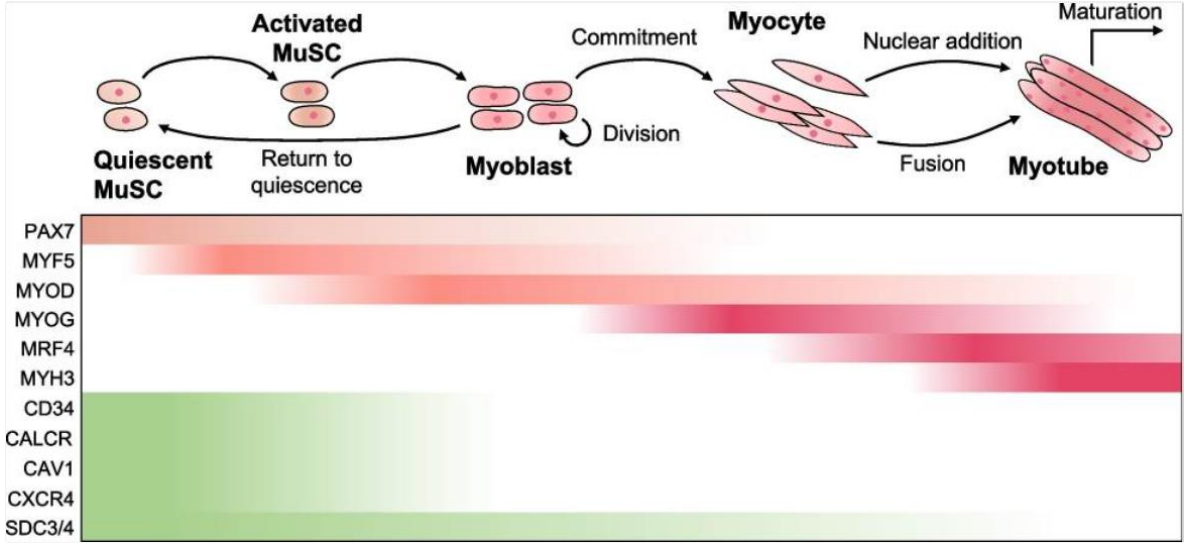
DELIVERY OF PMO TO SATELLITE CELLS

MUSCLE SATELLITE CELLS

Muscle satellite cells as a new therapeutic target with potential in several neuromuscular disorders

- **Satellite cells are muscle stem cells responsible for generating myoblasts for early muscle growth**
  - Mitotically quiescent in mature muscle, satellite cells maintain their own population by self renewal
  - In post-mitotic muscles, they can be activated to generate myoblast for homeostasis, repair, and hypertrophy
- **Quiescent satellite cells are historically challenging to access by therapeutic modalities**
- **EEV-mediated delivery to access quiescent satellite cells could enable early disease intervention**
  - Ability to deliver to myonuclei of muscle fibers and to quiescent satellite cells holds potential in several neuromuscular disorders
- **The ability to access satellite cells provides an opportunity to treat several satellite cell-opathies, including DMD**

Developmental Stages of Muscle Satellite Cells



- **The developmental stages of muscle satellite cells can be delineated by various myogenic factors**
  - Pax7, a canonical myogenic marker essential for orchestrating proper muscle regeneration, is mainly expressed in **quiescent** state, and at a lower level in activated state
  - Stage-specific expression of myogenic factors provides tools for studying EEV-PMO uptake at different developmental stages of satellite cells

Image from Byun et al., Inflamm Regen, 2024

DELIVERY OF PMO TO SATELLITE CELLS PROVIDES A BASIS FOR THE RAPID AND DURABLE EFFICACY IN DMD

EEV-PMO shows co-localization with quiescent satellite cells (Pax7 positive) at 48 hours and 1-week post-dose by both RNA-ISH and IHC

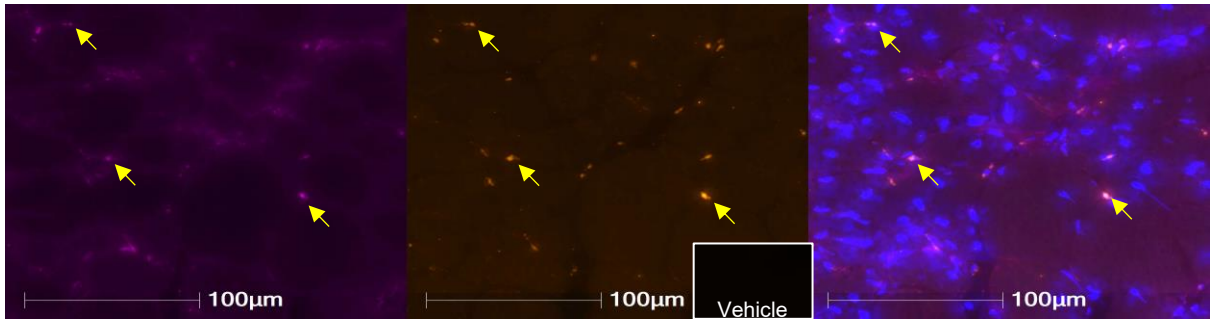
- **Two independent molecular techniques were utilized to determine EEV-PMO distribution within specific cell lineages across muscle tissue**
  - RNA-ISH: Highly selective and sensitive technique to assess specific cell lineages across muscle tissue
  - Immunohistochemistry Assessment
- **Quantification analysis of RNA-ISH data confirms that EEV-PMO is co-localized in 100% of satellite cells at 48 hours**
  - Quantitative assessment confirms qualitative data (data not shown)
- **Qualitative assessment of IHC data demonstrates co-localization of satellite cells in hDMD mice with EEV-PMO at 7 days**

PMO Distribution (48 hours, RNA-ISH Quantitation)

Treatment Group (D2-*mdx* mice)	% Pax7 Positive Cells	% Pax7 + PMO Positive Cells
Saline	1-10%	0%
EEV-PMO Treated	1-10%	1-10%

PMO Distribution in hDMD Mice (Day 7, IHC)

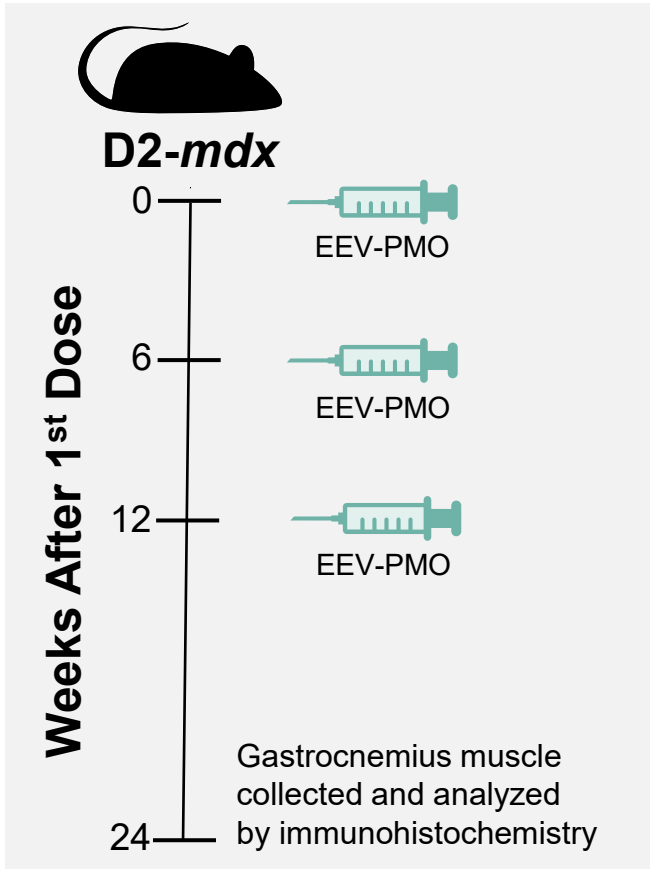
Pax7 (Satellite Cells) **PMO** **Pax7 / PMO / Nuclei**

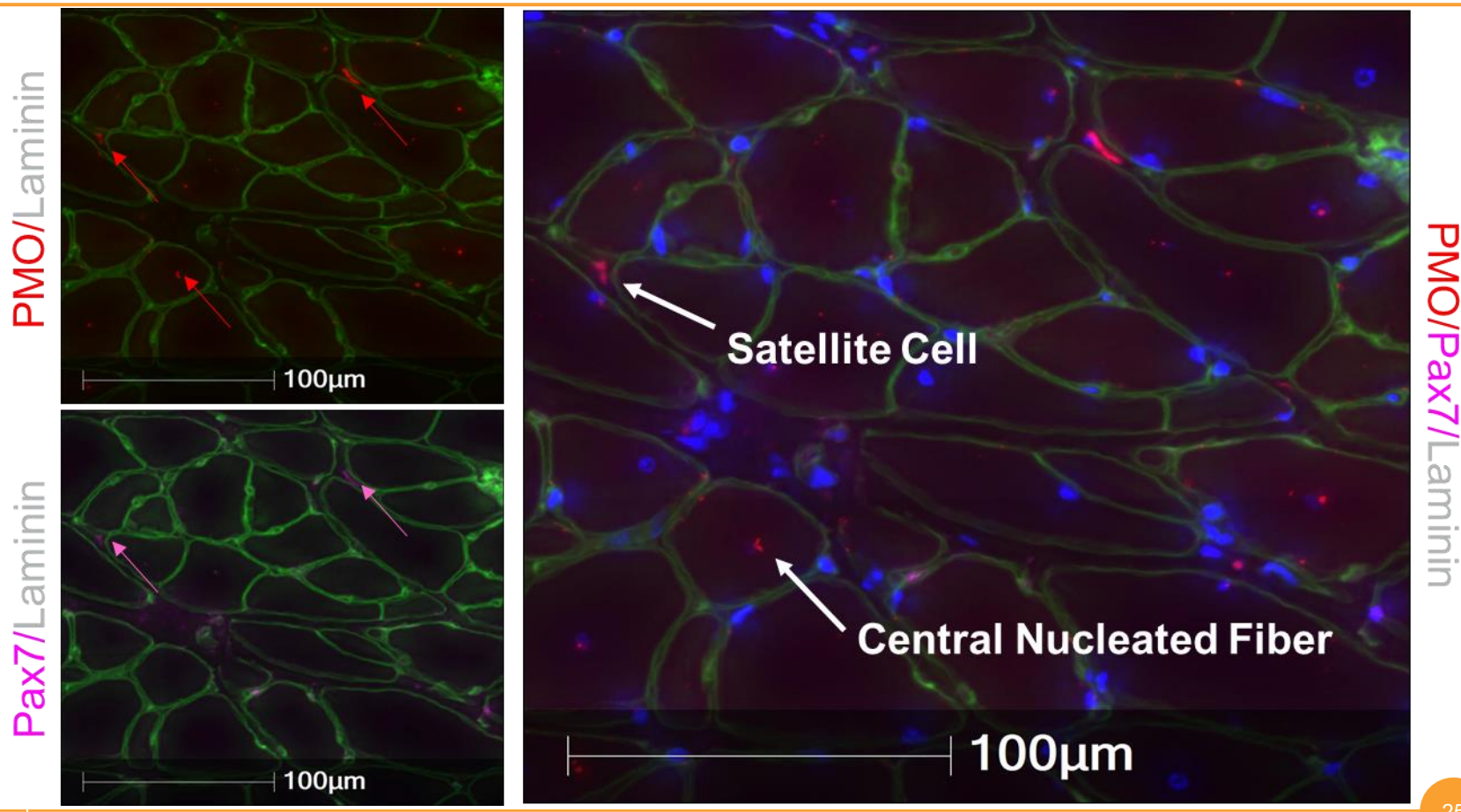


(Top right) D2-*mdx* mice were treated with a single IV dose of EEV-PMO; Gastrocnemius was collected at 48 hours and analyzed by RNA-ISH. (Bottom right) hDMD mice were treated with a single IV dose of EEV-PMO; Gastrocnemius was collected at 7 days and tissues analyzed by IHC. Pax7 is a satellite cell marker (Seale, P. et al *Cell* 2000). **hDMD,** human Duchenne muscular dystrophy; **IV,** intravenous; **RNA-ISH**: RNA *in situ* Hybridization image analysis; **IHC**: immunohistochemistry.

EEV-PMO PERSISTS IN SATELLITE CELLS 12 WEEKS AFTER FINAL DOSE

PMO co-localizes with satellite cells and newly regenerated centrally nucleated fibers 12 weeks post washout after 3 Q6W doses

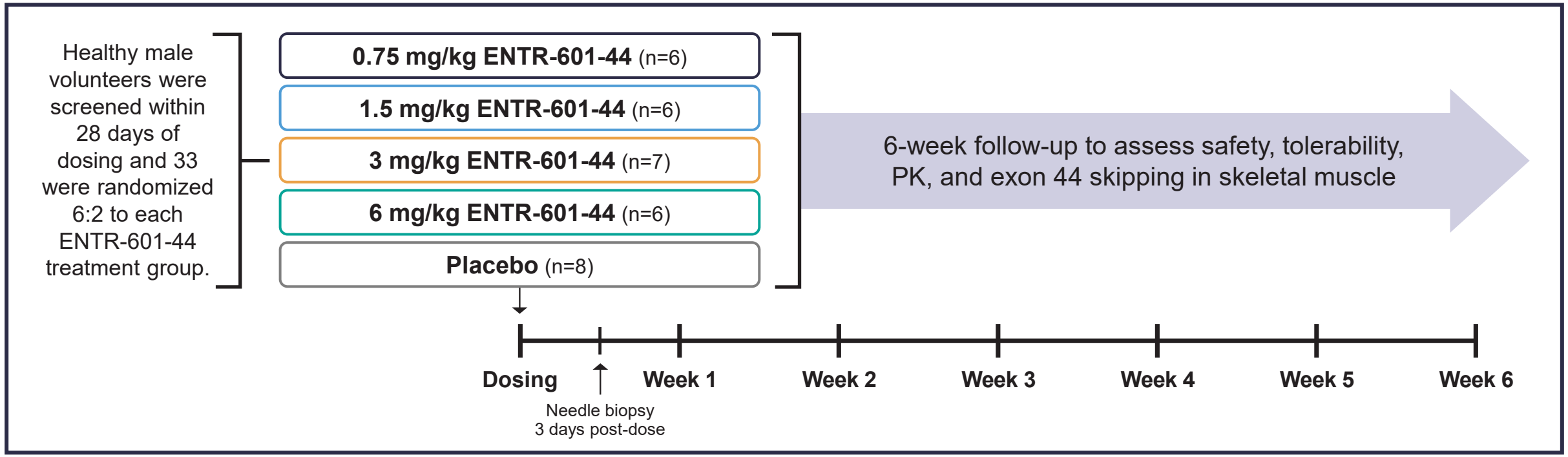




D2-*mdx* mice were treated with 3 IV doses of EEV-PMO administered every six weeks; Gastrocnemius was collected 12 weeks after the 3rd dose and analyzed by immunohistochemistry. **Q6W**: every six weeks.

ENTR-601-44-101 PHASE 1 STUDY

ENTR-601-44-101: STUDY DESIGN



Key Inclusion Criteria

- Healthy males aged 18–55 years, inclusive.
- Body mass index (BMI) of 18.0 to 32.0 kg/m², inclusive, and a minimum weight of 50 kg at screening.

Key Exclusion Criteria

- No current or prior history of clinically significant illness, organ transplant, cardiac disease, hypertension, long QT syndrome, hepatitis B, or diabetes.

Volunteers were required to stay overnight between dosing and Week 1, as well as 1 day at Weeks 2, 3, and 4 study visits. Volunteers underwent a needle biopsy on the biceps brachii 3 days after dosing. Safety, tolerability, and PK parameters were assessed at each study visit. **IV**, intravenous; **PK**, pharmacokinetics. **BMI**, body mass index; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **QoL**, quality of life.

ENTR-601-44-101: SAFETY AND TOLERABILITY

A single IV dose of ENTR-601-44 was well-tolerated in healthy human volunteers up to a dose of 6 mg/kg. No treatment-related adverse events were reported in the study.

- No AEs related to study drug
- Most common AE was headache (n=7; 5 mild and 2 moderate)
- No clinically significant findings with lab values, ECG or vital signs
- No adverse findings or clinically relevant changes to biomarkers of renal toxicity at highest dose of 6 mg/kg

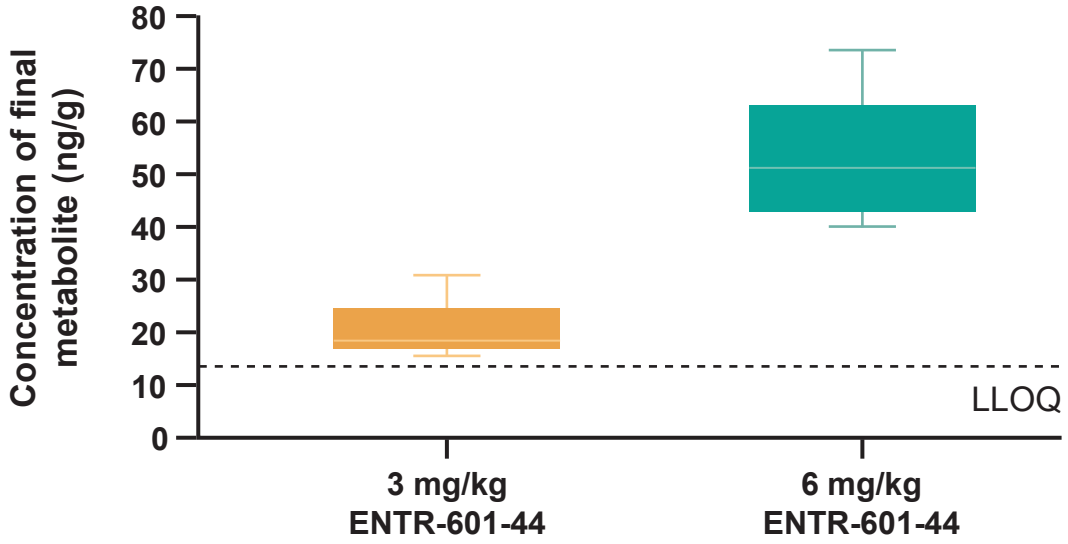
n (%)	Pooled placebo (N=8)	ENTR-601-44				
		0.75 mg/kg (n=6)	1.5 mg/kg (n=6)	3.0 mg/kg (n=7)	6.0 mg/kg (n=6)	Total (N=25)
Randomized	8 (100)	6 (100)	6 (100)	7 (100)	6 (100)	25 (100)
Dosed	8 (100)	6 (100)	6 (100)	6 (85.7)	6 (100)	24 (96)
Completed study	8 (100)	6 (100)	6 (100)	6 (85.7)	6 (100)	24 (96)
Any TEAE	1 (12.5)	5 (83.3)	2 (33.3)	3 (50)	3 (50)	13 (54)
Treatment-related TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe AEs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Safety and tolerability were assessed at each study visit following a single IV dose of ENTR-601-44 or placebo. One participant enrolled and randomized into Cohort 3 was removed prior to dosing. Renal biomarkers assessed using FNIH and the C-Path. Kidney Safety CM Biomarker User's Guide v1.1, 2019. **AE**, adverse event; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event.

ENTR-601-44-101: MUSCLE CONCENTRATION AND EXON SKIPPING

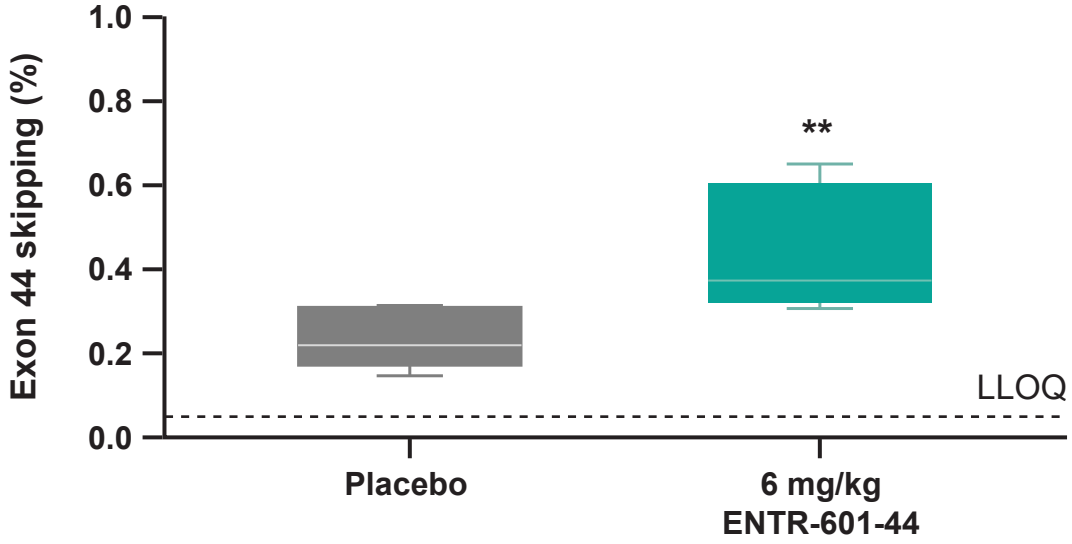
Dose-dependent increases in muscle concentration and *DMD* exon 44 skipping were observed 72 hours following a single IV dose of ENTR-601-44

Skeletal Muscle Concentration



- All six volunteers in the 6 mg/kg dose group had detectable levels of PMO-44 metabolite in skeletal muscle (mean 52.4 ng/g, range 40.0–73.5 ng/g)
- Concentrations of PMO-44 metabolite were below LLOQ in 3 of 6 volunteers in the 3 mg/kg dose group and all volunteers in the 0.75 and 1.5 mg/kg dose groups

DMD Exon 44 Skipping

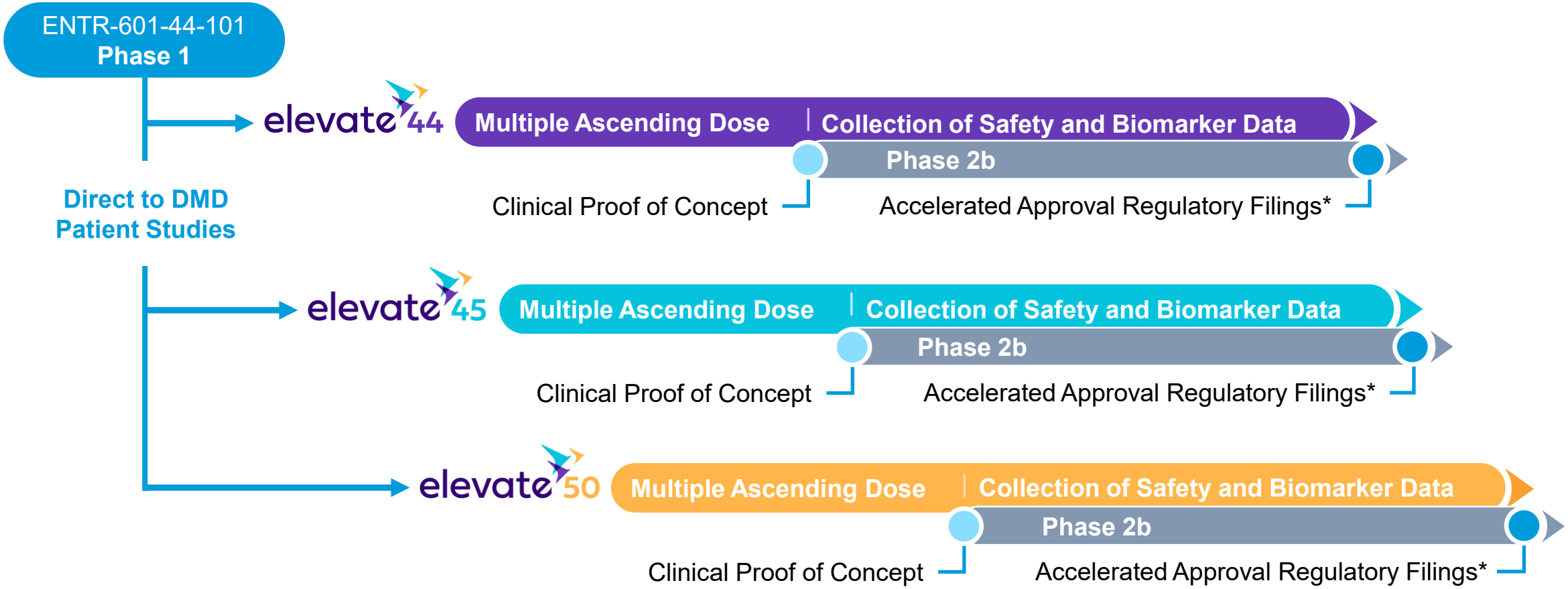


- Statistically significant *DMD* exon 44 skipping was observed with 6 mg/kg ENTR-601-44 (mean 0.44%, range 0.30%–0.65%) in comparison with placebo (mean 0.22%, range 0.14%–0.31%)
- No other ENTR-601-44 dose group was statistically significant in comparison with placebo.

Muscle concentrations and exon skipping were assessed using a needle muscle biopsy taken from biceps brachii 72 hours (±4 hours) post-dose of ENTR-601-44. Box and whisker plot illustration (right): the boxes represent the IQR and median. Whiskers show the smallest and largest values within 1.5 times the IQR. ** $p<0.005$ vs. placebo using Mann-Whitney U test. **IQR**, interquartile range; **LLOQ**, lower level of quantification; **PMO**, phosphorodiamidate morpholino oligomer.

CLINICAL STRATEGY IS DESIGNED FOR EFFICIENT REGULATORY PATH

All ENTR-601-series programs will follow a similar clinical and regulatory approach



Protocols pending regulatory feedback; *Potential for Accelerated Approval in the US, followed by confirmatory Phase 3 studies to obtain Full Approval in the US and ex-US countries.

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Scan the QR code for access to our recent publications and conference presentations.

Meet Franklin and his family, living with Duchenne muscular dystrophy