# Endosomal Escape Vehicle (EEV™) Platform for Delivery of Oligonucleotides in Duchenne Muscular Dystrophy

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# MEET ENTRADA

We are driven to transform the lives of patients by establishing Endosomal Escape Vehicle therapeutics as a new class of medicines and become the world's foremost intracellular therapeutics company

## Our Commitment

- Developing treatments for people living with devastating diseases for which no or insufficient options currently exist.
- Partnering with patient communities to ensure the perspectives of patients and their loved ones inform our research programs

## Our Culture

- We are building a company culture where everyone can belong, contribute and grow.
- Fostering a workplace environment that embraces diversity, equity and inclusion.
- Prioritizing the experiences and perspectives of patients and their loved ones.

## Our Team

- ~120 employees with an experienced leadership team
- Recognized as a Top Place to Work 2021 by *The Boston Globe*
- Later this year, Entrada plans to move our science from the lab to the clinic with our first regulatory filing

# OUR COMMITMENT TO THE DMD COMMUNITY

At the heart of our work to bring innovative therapies to people living with devastating diseases are our partnerships with community leaders and patient advocacy organizations

- We appreciate the Duchenne muscular dystrophy (DMD) community's deep experience participating in clinical trials and the work you have done to create a collaborative environment that is welcoming to novel research
- As we progress our research program from the lab to the clinic, we look forward to learning from the experiences of boys living with DMD and their families, and to keeping you informed of our progress

**PURSUING A TREATMENT OPTION FOR EXON 44 SKIPPING AMENABLE PATIENTS**

- ENTR-601-44 is a potential approach to treating individuals with DMD who have **exon 44 amenable mutations**.
- Input from the DMD community guided our decision to select our first clinical candidate
- Planning **Investigational New Drug (IND) submission in Q4 2022** for ENTR-601-44
- Continue to explore a clinical candidate for individuals with **exon 45 amenable mutations**

# THE FUNDAMENTAL CHALLENGE OF INTRACELLULAR THERAPEUTICS


of all disease-causing targets are located inside cells.[1]

Yet, most are still considered **INACCESSIBLE.**

There are two major challenges to delivering a therapy to a target within the cell:

1. Getting the therapy inside the cell.
2. **Most importantly, avoiding the cell's natural clearing system.**

**At Entrada Therapeutics, we believe we have discovered the solution.**

[1]Verdine GL, Walensky LD. *Clin Cancer Res*. 2007;13(24):7264-70.

# A DISCOVERY ENGINE FOR INTRACELLULAR THERAPEUTICS

- Oligonucleotides offer a therapeutic approach to treat genetic disorders such as DMD. However, they often cannot effectively reach the disease-causing targets inside cells and fail to widely distribute across muscle tissue, including cardiac muscle
- **Exon skipping therapeutics have been approved based on a modest improvement in dystrophin levels ranging from ~1 to 6%**[1-4]
- 40% of people living with DMD[5] have mutations amenable to exon skipping of exons 44, 45, 51 and 53
- There are ~2,300 boys and young men (US and Europe) with mutations amenable to exon 44 skipping, yet there is **currently no approved therapy available**

**We are harnessing our EEV Platform to address these historical limitations**

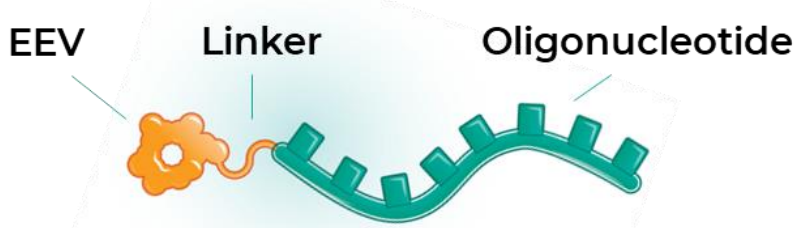




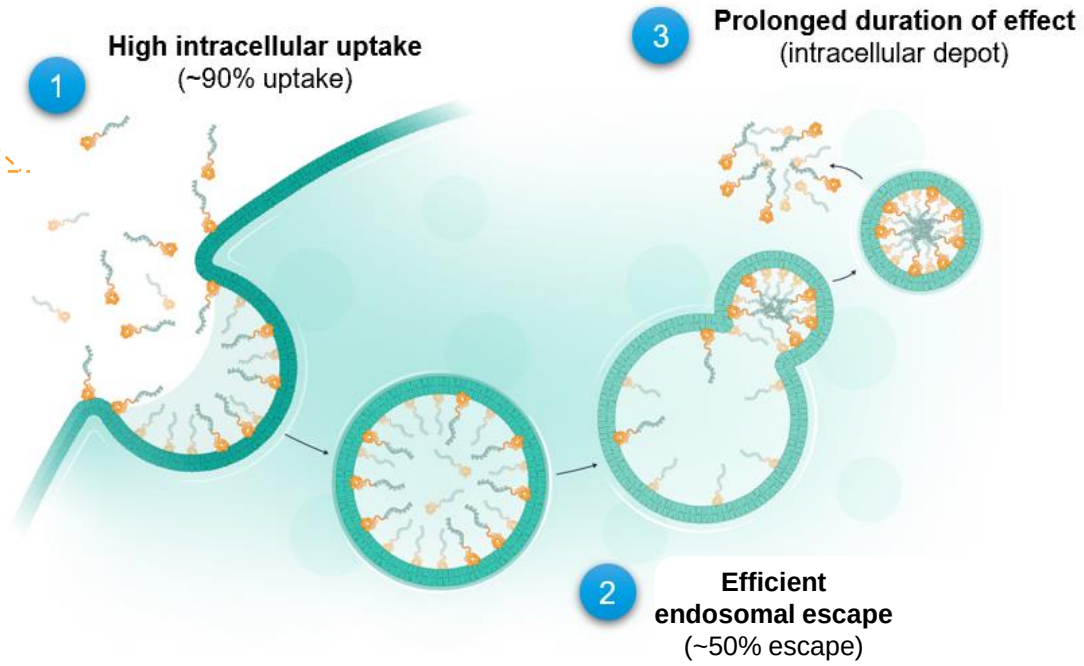
[1]EXONDYS 51® Prescribing Information; [2]VYONDYS 53® Prescribing Information; [3]AMONDYS 45® Prescribing Information; [4]VILTEPSO® Prescribing Information; [5]https://www.parentprojectmd.org/about-duchenne/what-is-duchenne/types-of-mutations/mutation-specific-therapies

# ENDOSOMAL ESCAPE VEHICLE (EEV™) PLATFORM

## We are developing EEV-oligonucleotide conjugates for the treatment of individuals with DMD




- **Entrada's EEV™ platform** consists of a library of proprietary cyclic peptides with unique chemistry that **enable improved uptake into the cell and escape from the endosome**
- In preclinical studies, we have observed that our EEV-Oligonucleotide approach has **promoted enhanced exon skipping and dystrophin production**







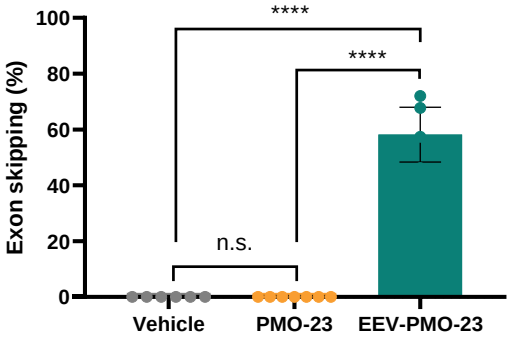

Qian, Z. et al. *ACS Chem. Biol.* 2013; Qian, Z. et al. *Biochemistry* 2014; Qian, Z. et al. *Biochemistry* 2016; Sahni, A. et al. *ACS Chem. Biol.* 2020; Pei, D. *Acc. Chem. Res.* 2022.

# OUR TECHNOLOGY PRODUCES EXON SKIPPING AND DYSTROPHIN PRODUCTION IN A DMD MOUSE MODEL

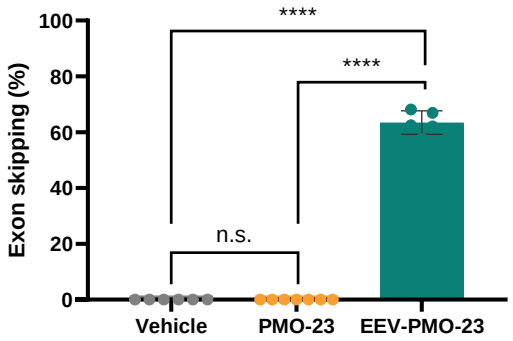
entrada THERAPEUTICS

## Robust exon 23 skipping was observed after four monthly IV doses of our proprietary EEV-PMO-23 in D2-*mdx* mice

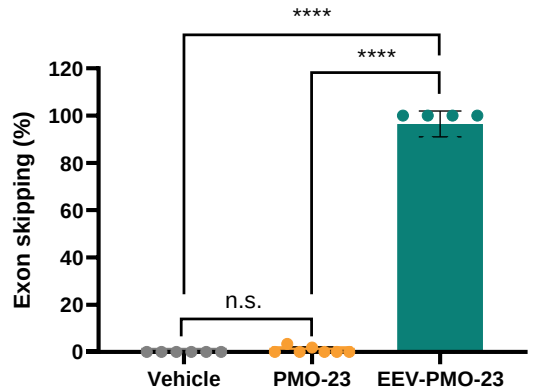
**Heart**




**Diaphragm**

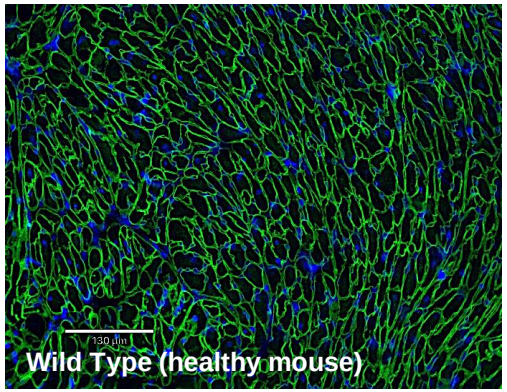


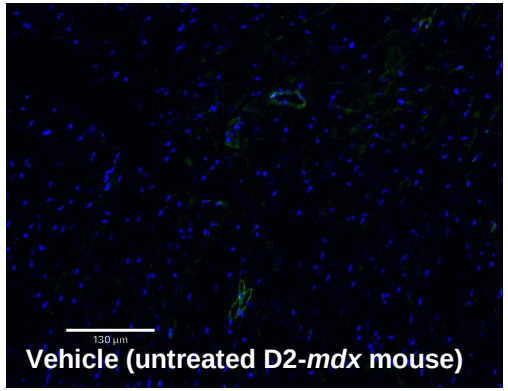

**Tibialis Anterior**

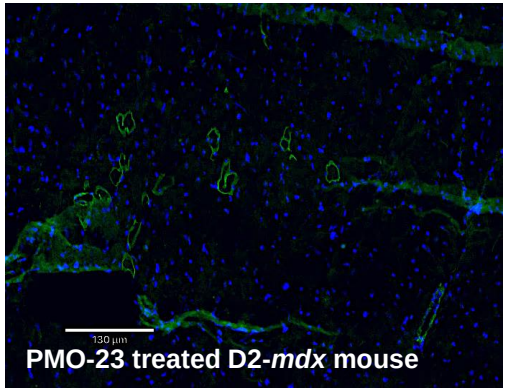


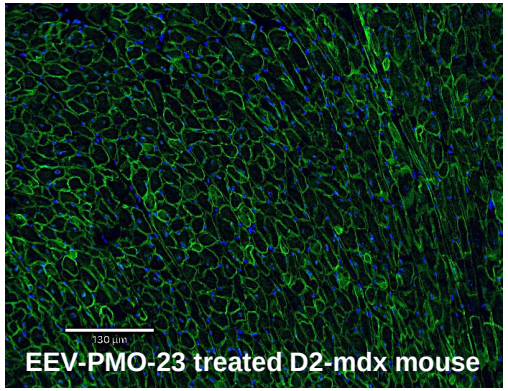

****p<0.0001; **n.s.**, not significant; Data shown as mean ± standard deviation

## Treatment with Entrada's EEV-PMO-23 corrected dystrophin expression in the heart of D2-*mdx* mice




Dystrophin; Cell Nuclei

**D2-*mdx*** is a DMD mouse model with a nonsense mutation in *Dmd* exon 23 (Coley et al. *Hum. Mol. Genet.* 2016); D2-*mdx* mice were treated with 4 monthly doses of either vehicle, 20 mg/kg PMO or 20 mg/kg PMO equivalent of EEV-PMO, and the data were collected ~4 weeks after the last dose

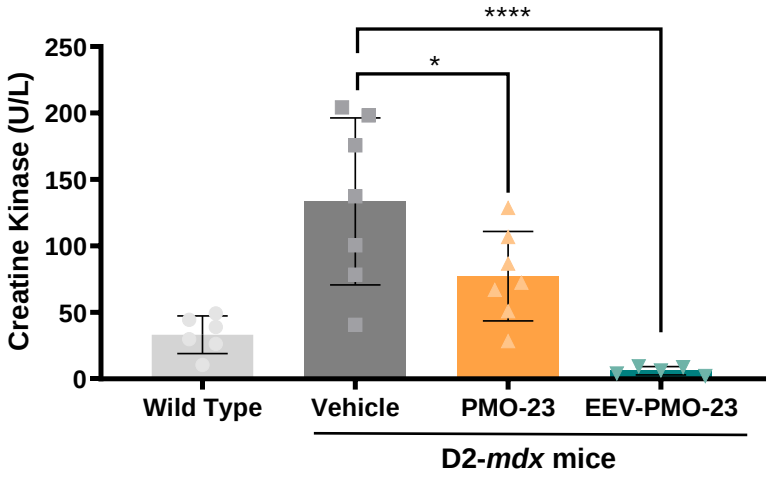
# KEY TAKEAWAY

Our approach to treating DMD
in mice has shown effective exon skipping
and dystrophin production in skeletal,
diaphragm and heart muscles.

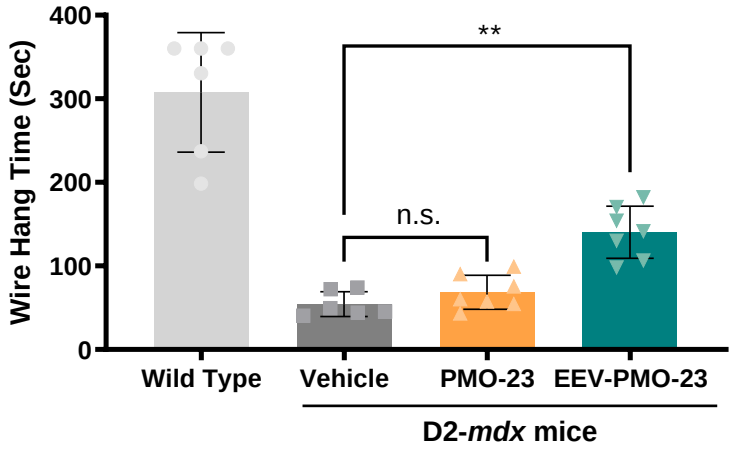
# TREATMENT OF MICE WITH EEV-PMO REVERSES MUSCLE DAMAGE AND IMPROVES MUSCLE FUNCTION

D2-*mdx* mice treated with our EEV-PMO-23 showed reduced muscle damage (lower CK levels) and significant improvements in muscle function when compared to unconjugated PMO-23

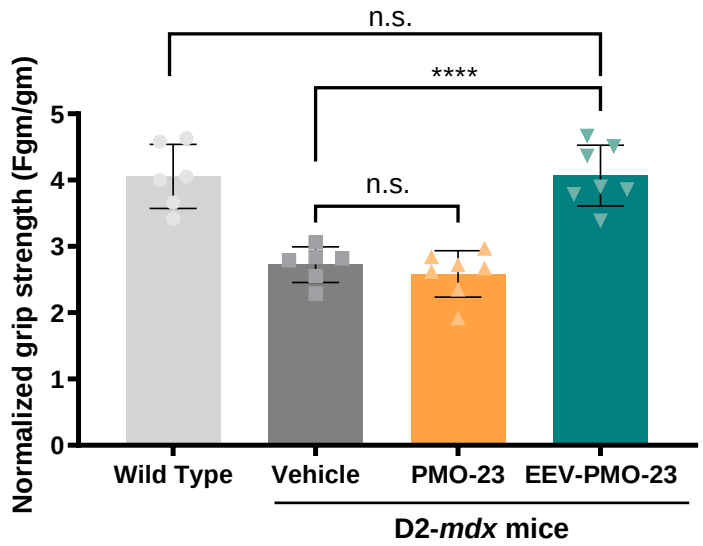
## Serum CK (Muscle Damage)




## Wire Hang Time




## Grip Strength




- **Wild type** (healthy mouse)
- **Vehicle** (untreated DMD-affected mouse)
- **PMO-23** (DMD-affected mouse treated with PMO without an EEV)
- **EEV-PMO-23** (DMD-affected mouse treated with PMO conjugated to an EEV)



**CK**, creatine kinase; *p<0.05, **p<0.01, ****p<0.0001; **n.s.**, not significant; Data shown as mean ± standard deviation. D2-*mdx* mice (male, n=6-7) were treated with 4 monthly doses of either vehicle, 20 mg/kg PMO-23 or 20 mg/kg PMO-23 equivalent of EEV-PMO-23, and the data were collected ~2 weeks after the last dose

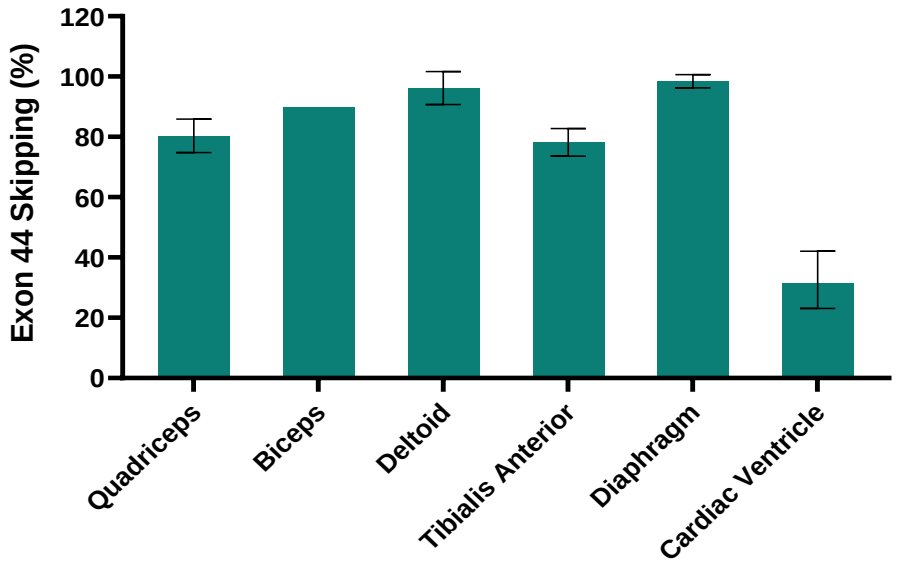
# KEY TAKEAWAY

The data show that mice treated with Entrada's technology (EEV+PMO) experienced improved muscle function and reduced muscle damage when compared current approach (PMO alone).

# ENTR-601-44 IS OUR CLINICAL CANDIDATE FOR INDIVIDUALS AMENABLE TO EXON 44 SKIPPING

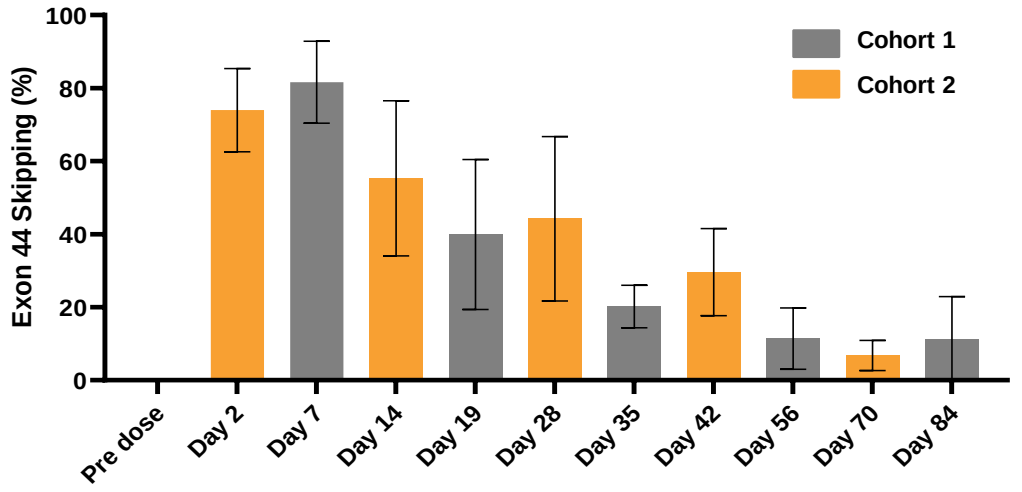
A single IV dose of ENTR-601-44 resulted in robust exon skipping in both skeletal and cardiac muscles in non-human primates (NHP), as well as prolonged duration of effect for at least 12 weeks

## Exon Skipping in Muscles at Day 7




- At 7 days post IV infusion of 30 mg/kg (PMO equivalent), robust exon 44 skipping across different muscle groups isolated from the ENTR-601-44 treated NHP

## Duration of Effect in Biceps for at Least 12 Weeks




- Post IV infusion of 35 mg/kg (PMO equivalent), robust exon 44 skipping observed in biceps in the ENTR-601-44 treated NHP (n=3 per cohort) for at least 12 weeks

**NHP**, non-human primates; Data shown as mean ± standard deviation.

# KEY TAKEAWAY

Our data in non-human primates show prolonged duration of effect, which may translate to administration of drug with a dosing interval of every 6 weeks or potentially longer.

# ENTR-601-44: CURRENT CLINICAL DEVELOPMENT PLAN FOR INDIVIDUALS AMENABLE TO EXON 44 SKIPPING

## First-in-Human Trial

**Single Ascending Dose Study***
in Adult Healthy
Normal Volunteers


### OUTCOME MEASURES

- Safety and tolerability
- Evaluation of PK and PD
- Target engagement – exon skipping

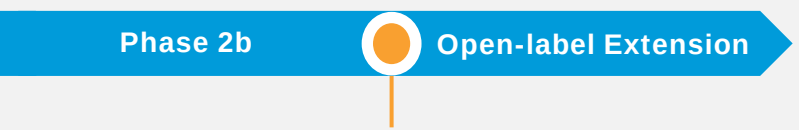
## Multiple Ascending Dose/Phase 2b

**Multiple Ascending Dose Study***
in Exon 44 Skipping Amenable Patients


### OUTCOME MEASURES

- Safety and tolerability
- Evaluation of PK and PD
- Evaluation of exon skipping and dystrophin production (skeletal muscle)

**Phase 2b Study**
in Exon 44 Skipping Amenable Patients




File for accelerated approval

***Target product profile:***

- *Double digit dystrophin improvement from baseline*
- *Dosing interval ≥ every 6 weeks*

### PRIMARY EFFICACY MEASURES

- Change in dystrophin level (skeletal muscle)

### SECONDARY/EXPLORATORY EFFICACY MEASURES

- NSAA (North Star Ambulatory Assessment)
- Other timed function tests
- Other parameters may include cardiac MRI, FVC, QoL

*Number of dose cohorts TBD; **MTD**, Maximum Tolerated Dose

# THANK YOU FROM TEAM ENTRADA!

## Come Visit Us at the Resource Fair!


Hello from Boston!

We look forward to working with you!