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

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OUR COMMITMENT TO THE DUCHENNE COMMUNITY

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

We appreciate the Duchenne 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 Duchenne franchise from the lab to the clinic, we look forward to learning from the experiences of people and families living with Duchenne and to keeping you informed of our progress

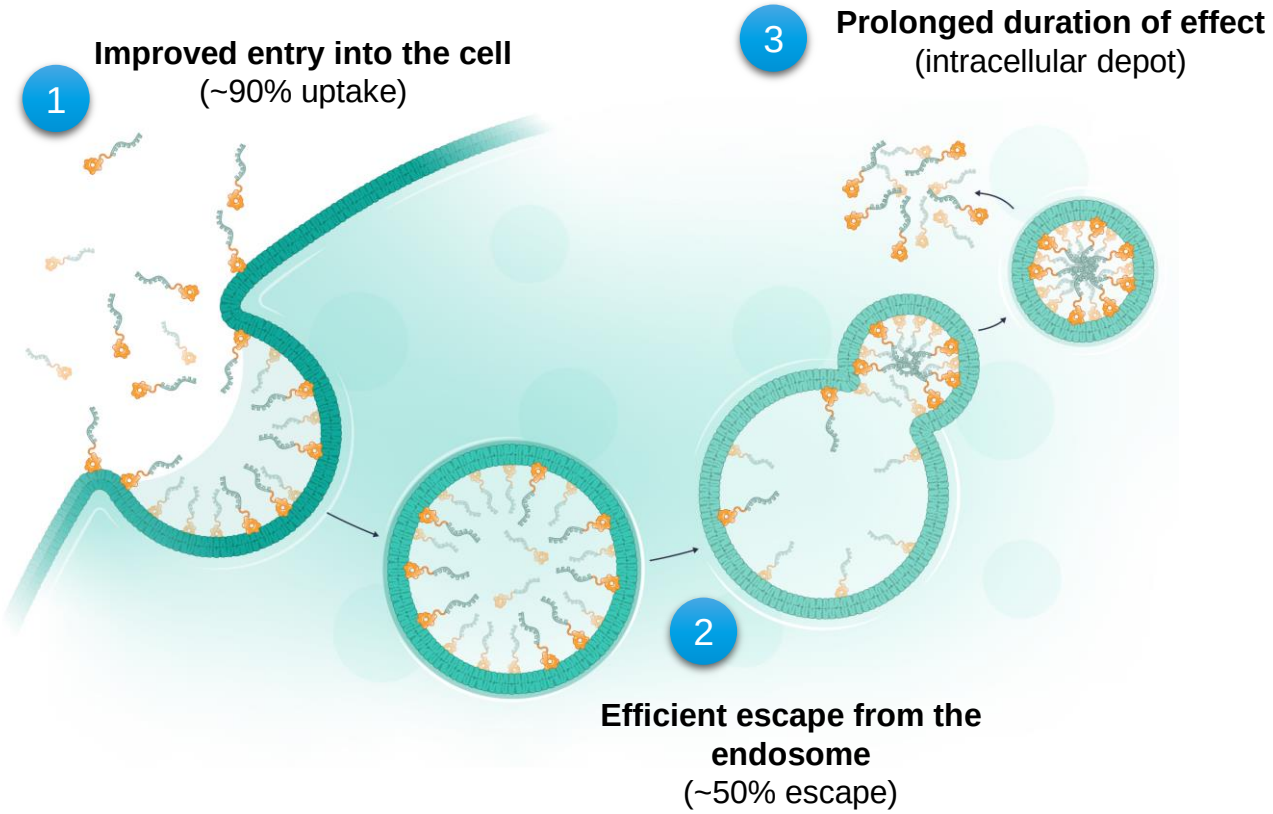
PURSUING TREATMENT OPTIONS FOR PEOPLE LIVING WITH DUCHENNE

- ENTR-601-44 is a potential approach to treating individuals with Duchenne who are **exon 44 skipping amenable**
- Input from the Duchenne community guided our decision to select our first clinical candidate
- ENTR-601-45 is a potential approach to treating individuals with Duchenne who are **exon 45 skipping amenable**
- Discovery efforts underway for individuals with **exon 50 and 51 amenable mutations**

OUR ENDOSOMAL ESCAPE VEHICLE (EEV™) PLATFORM

We are developing EEV-oligonucleotide conjugates for the treatment of Duchenne

- EEV-oligonucleotide conjugates are cyclic peptides attached to oligonucleotides
- This unique chemistry results in **improved uptake into the cell and escape from the endosome** (part of the cell's natural clearing system)
- The cyclic structure of the peptide is designed to **extend half-life and increase stability**
- In animal studies, we have observed that our EEV-oligonucleotide approach has **promoted enhanced exon skipping and dystrophin production**

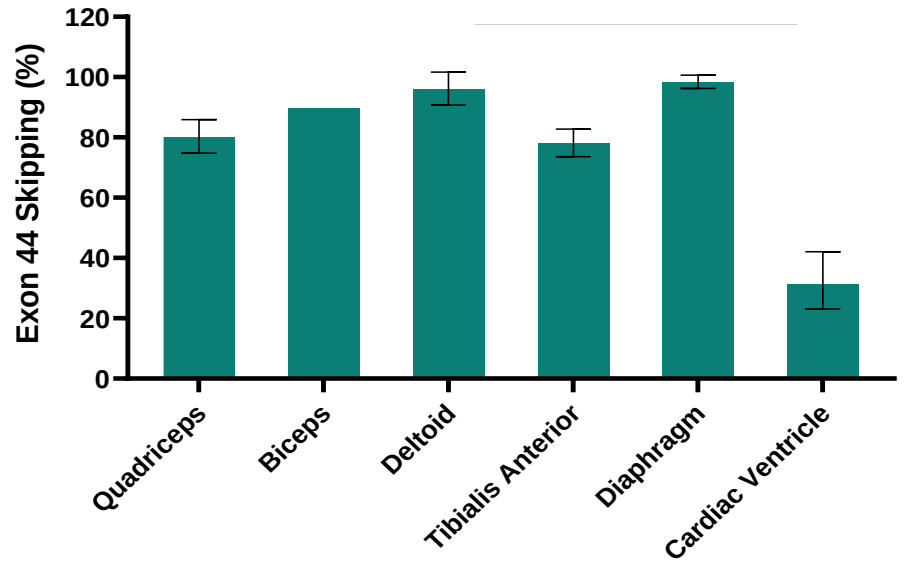


Qian, Z. et al. *ACS Chem. Biol.* 2013; Qian, Z. et al. *Biochemistry* 2014; Qian, Z. et al. *Biochemistry* 2016; Sahni, A. et al. *ACS Chem. Biol.* 2020; Pei, D. *Acc. Chem. Res.* 2022.

ENTR-601-44 IS OUR EXON 44 SKIPPING CLINICAL CANDIDATE

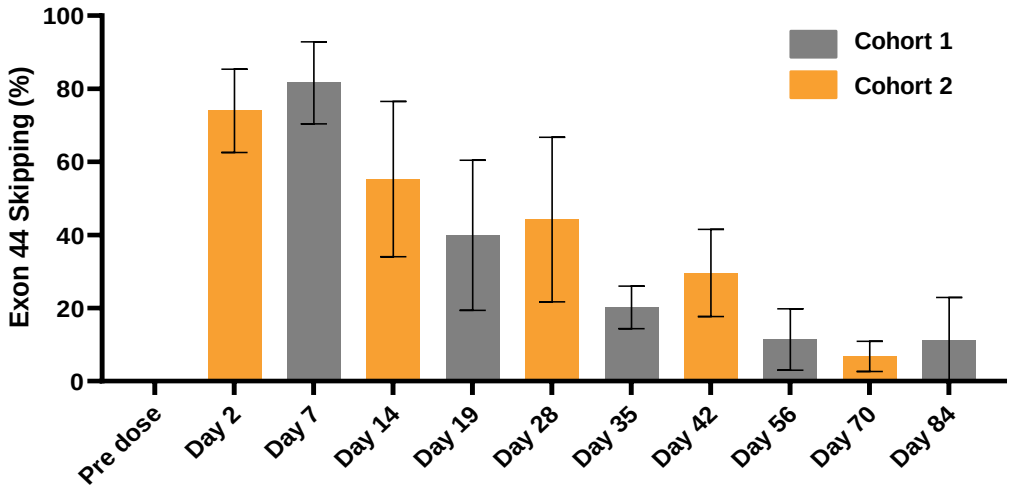
A single IV dose of ENTR-601-44 resulted in robust exon skipping in both skeletal and cardiac muscles in non-human primates (NHP), as well as prolonged duration of effect for at least 12 weeks

Exon Skipping in Muscles at Day 7



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

Duration of Effect in Biceps for at Least 12 Weeks



- After an intravenous (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.

PRECLINICAL DATA SUPPORT ADVANCEMENT OF ENTR-601-44 TO THE CLINIC

Results show:

Effective exon skipping seen in skeletal, diaphragm and heart muscles in animal models

Robust dystrophin production observed in skeletal muscle cells from patients living with Duchenne

Prolonged duration of effect, which may translate to administration of drug up to every 6 weeks

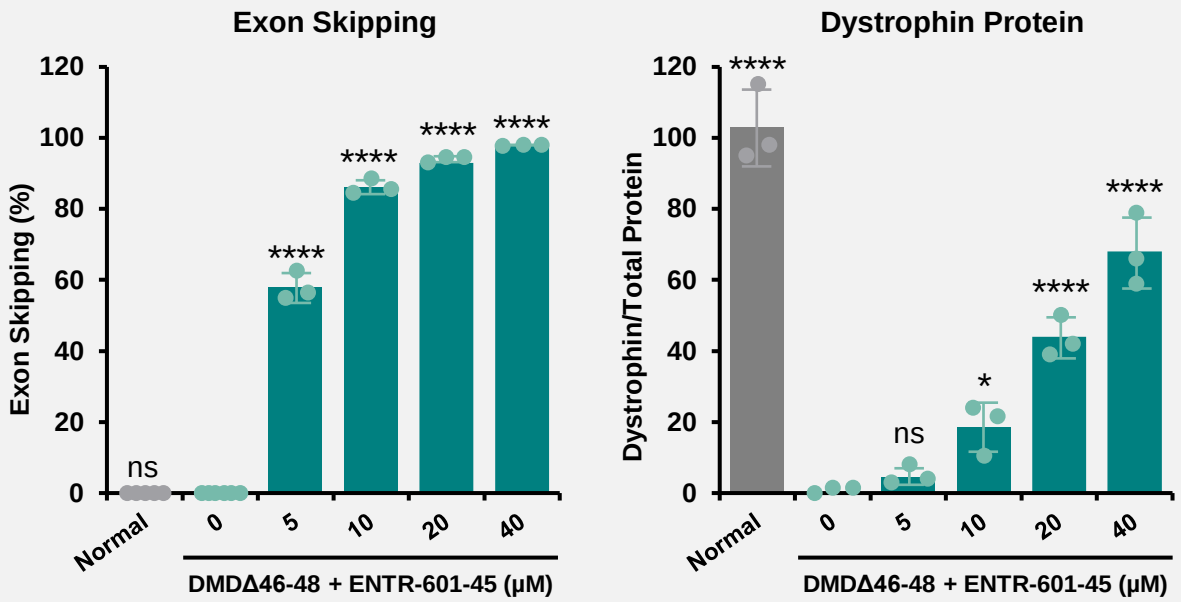
We are developing **ENTR-601-44** for the potential treatment of the roughly 7.5% of individuals with Duchenne who are **exon 44 skipping amenable**

*Following regulatory feedback and potential IND clearance.

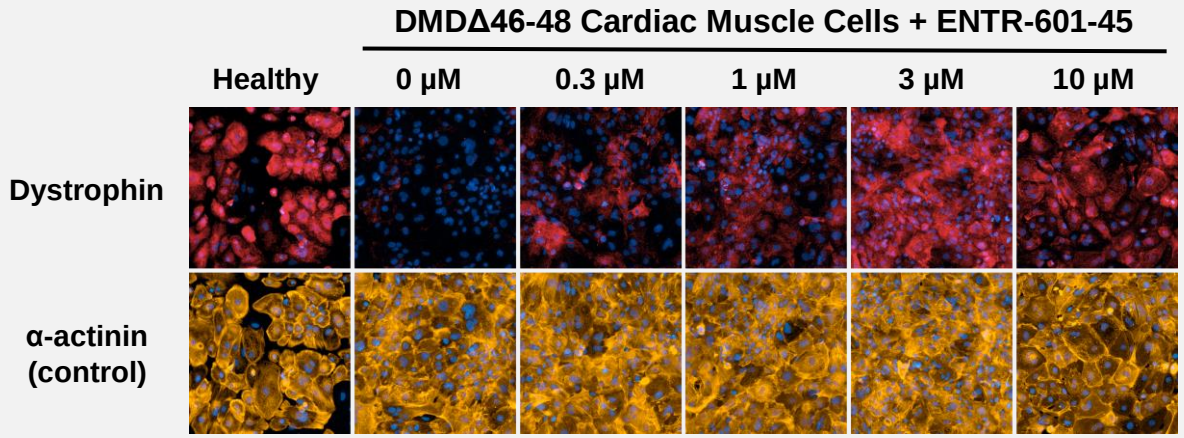
ENTR-601-45 EFFECTIVE IN SKELETAL AND CARDIAC MUSCLE CELLS

ENTR-601-45 showed robust exon skipping and dystrophin production in skeletal and cardiac muscle cells from patients living with Duchenne who are amenable to exon 45 skipping

ENTR-601-45 in Skeletal Muscle Cells



ENTR-601-45 in Cardiac Muscle Cells



- Skeletal muscle cells from patients living with Duchenne who are amenable to exon 45 skipping were treated with ENTR-601-45 for 24 hours and analyzed 5 days later

- Cardiac muscle cells from patients living with Duchenne who are amenable to exon 45 skipping were treated with ENTR-601-45 for 24 hours and analyzed 48 hours later

DMDΔ46-48 iPSC-derived skeletal and cardiac muscle cells from an exon 45 skip amenable DMD patient harboring an exon 46-48 deletion mutation. Data are shown as mean ± SD (n = 3 skeletal muscle; n = 4 cardiac muscle); one-way ANOVA; *p<0.05, ****p<0.0001; relative to untreated DMDΔ46-48 cells.

IN SUMMARY

Entrada lead programs are advancing new therapeutic options for people living with exon 44 and exon 45 skip amenable Duchenne

- **ENTR-601-44 produced robust exon skipping and dystrophin production in cell and animal models of Duchenne**
  - We observed robust exon skipping over 12+ weeks from a single injection of ENTR-601-44 in non-human primates
  - Entrada received a clinical hold notice from the FDA regarding our investigational new drug (IND) application for ENTR-601-44 in December 2022
  - We are pursuing global opportunities to initiate a healthy volunteer clinical trial while simultaneously working to address FDA's feedback; we remain very confident in achieving our goal of initiating a trial in 2023
- **ENTR-601-45 showed robust exon skipping and dystrophin production in cardiac and skeletal muscle cells from people living with Duchenne**
  - High levels of exon skipping were measured in hDMD mouse heart and skeletal muscle
  - An IND regulatory filing for a direct to patient, multiple ascending dose (MAD) trial is planned in late 2024
- **Discovery efforts are underway for individuals with exon 50 and 51 amenable mutations**

THANK YOU FROM OUR WHOLE TEAM

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For questions, contact:
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