ELEVATE-44-201, a Phase 1/2b Study to Assess the Safety and Efficacy of ENTR-601-44 in Patients With DMD Amenable to Exon 44 Skipping

666P

Laurent Servais[1,2], Dania Porco[3], Terrance A. Stadheim[3], Ridhi Parasrampuria[3], Natarajan Sethuraman[3]

[1]Department of Paediatrics, MDUK Oxford Neuromuscular Centre & NIHR Oxford Biomedical Research, University of Oxford, Oxford, UK; [2]Department of Paediatrics, Neuromuscular Reference Centre, University Hospital of Liège, Liège, Belgium; [3]Entrada Therapeutics, Boston, MA, USA

BACKGROUND AND RATIONALE

- Currently approved antisense phosphorodiamidate morpholino oligomer (PMO)–mediated exon-skipping therapies for Duchenne muscular dystrophy (DMD) produce only a very modest amount of dystrophin in skeletal muscle, likely due to poor cell entry and limited endosomal escape in muscle cells.[1-4]
- The Endosomal Escape Vehicle (EEV™) platform is a family of proprietary cyclic cell-penetrating peptides that were designed to enhance PMO delivery to muscles[5,6] (**Figure 1**).
- ENTR-601-44 is a *DMD* exon 44–skipping PMO conjugated to the EEV platform and is currently being investigated for the treatment of patients with DMD amenable to exon 44 skipping.
  - ENTR-601-44 has demonstrated exon skipping and dystrophin restoration in skeletal muscle cells derived from patients with DMD who have a *DMD* exon 44 skip-amenable mutation, as well as robust exon 44 skipping in cardiac and skeletal muscle of human dystrophin-expressing mice and nonhuman primates.[7]
  - Furthermore, a phase 1 study in healthy male human volunteers showed that a single intravenous (IV) dose of ENTR-601-44 produced significant exon 44 skipping compared with placebo, with no treatment-related adverse events at the highest dose evaluated (6 mg/kg).[8]
  - Together, these preclinical and clinical findings support further study in patients with exon 44 skip-amenable DMD for which there is currently no approved exon-skipping therapy.

Figure 1. EEV-PMO Construct Structure and Mechanism of Action

(A) Structure of EEV-PMO construct consisting of a cyclic cell-penetrating peptide-based EEV construct and exon-skipping PMO. **(B)** Mechanism of EEV construct-mediated delivery of PMOs. EEV, Endosomal Escape Vehicle; PMO, phosphorodiamidate morpholino oligomer.

STUDY OBJECTIVE

- ELEVATE-44-201 is a global, multiple ascending dose, phase 1/2b study that will evaluate the safety, dose response, and efficacy of ENTR-601-44 in patients with DMD amenable to exon 44 skipping.

STUDY ELIGIBILITY

Part A: Key Study Eligibility

- Must be assigned male at birth (aged 4–20 years, inclusive) with a confirmed genetic diagnosis of exon 44 skip-amenable DMD.
- Must be ambulatory with a Performance of the Upper Limb v2.0 (PUL 2.0) entry item A of at least 3 at screening.
- If on glucocorticoid therapy, participant must be on a stable dose and regimen for at least 3 months before dosing.
- No treatment with any exon-skipping therapy or gene therapy at any time.

Part B: Key Study Eligibility

- Participants from Part A of this study are not eligible for Part B.
- Must be assigned male at birth with a confirmed genetic diagnosis of exon 44 skip-amenable DMD.
- Can be either ambulatory or non-ambulatory, with a PUL 2.0 entry item A of at least 3 at screening.
- If on glucocorticoid therapy, participant must be on a stable dose and regimen before dosing.
- No treatment with any exon-skipping therapy or gene therapy at any time.

STUDY DESIGN AND ASSESSMENTS

- This is a 2-part study:
  - Part A will evaluate the safety, pharmacokinetics (PK), and pharmacodynamics of three IV doses of ENTR-601-44 administered every 6 weeks (Q6W) (**Figure 2**).
  - Part B will further evaluate safety and PK, as well as dystrophin expression, functional change, and quality of life (QoL) following ENTR-601-44 treatment.

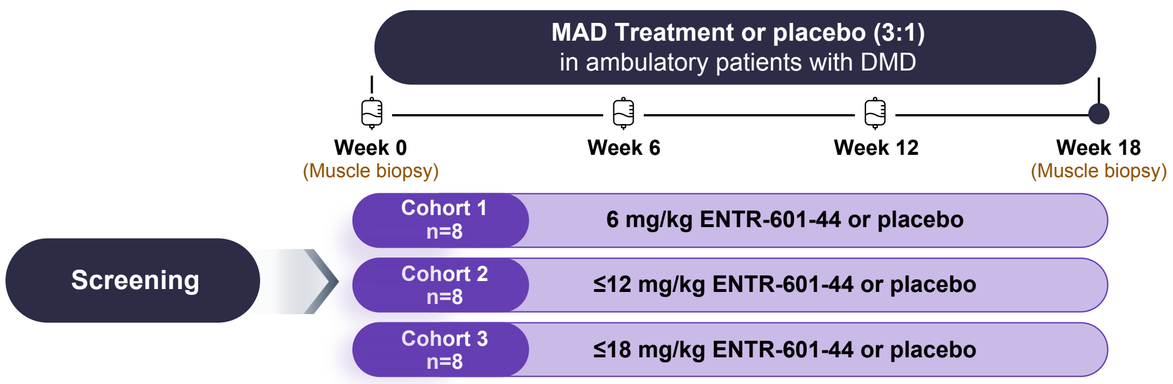
Part A: Placebo-Controlled, Multiple Ascending Dose Study

- Participants will be randomized (3:1) into 3 cohorts (n=8 each) to receive 3 Q6W IV doses of ENTR-601-44 (6, ≤12, or ≤18 mg/kg) or placebo.
- All confirmed, eligible participants will undergo a baseline muscle biopsy during the screening period, before the first dose of treatment (Week 0), and then again at the end of the treatment period at Week 18 (6 weeks after the final dose).
- The primary assessment for Part A will be to evaluate the safety and tolerability of ENTR-601-44, which will be monitored throughout the study.
- Change in dystrophin, exon 44 skipping, and PK of ENTR-601-44 will be key secondary assessments (**Table 1**).
- All participants who complete Part A may be eligible to continue or begin (for those randomized to placebo) ENTR-601-44 treatment in an open-label extension.

Part B: Placebo-Controlled, Single-Dose Cohort Study

- Part B will further evaluate the efficacy of ENTR-601-44 (at the optimal dose level selected following data review of Part A) compared to placebo.
- The primary assessment for Part B will be to evaluate the change in dystrophin from baseline to end of study.
- As with part A, all participants who complete Part B may be eligible to continue or begin (for those randomized to placebo) ENTR-601-44 in an open-label extension.

Figure 2. ELEVATE-44-201 Study Schematic for Part A



ELEVATE-201-44 is a 2-part, placebo-controlled study. Part A will include 3 dose cohorts of ENTR-601-44 (or placebo). Muscle biopsies will be taken before initial treatment and 6 weeks after the final dose in both parts of the study. Participants from Part A and Part B will be eligible to participate in an open-label extension. DMD, Duchenne muscular dystrophy; MAD, multiple ascending dose.

Table 1. Study Assessments for Part A

	Part A (Multiple Ascending Dose)
Primary Assessments	• Safety and tolerability of ENTR-601-44
Secondary Assessments	• Change in dystrophin from BL to EOS • Change in exon 44 skipping from BL to EOS • PK of ENTR-601-44 • Immune response to ENTR-601-44

BL, baseline; EOS, end of study; PK, pharmacokinetics; QoL, quality of life.

ACKNOWLEDGMENTS

The current study design may change based on regulatory feedback, feasibility assessments, and evolving scientific insights. Conflicts of Interest: LS is a paid consultant for Biomarin, Dyne, Entrada, Italfarmaco, Pfizer, Regenxbio, Santhera, Solid, and Wave; and DP, TAS, RP, and NS are employees of Entrada Therapeutics, Inc. ELEVATE-201-44 (EU CT 2024-517584-23, UK IRAS 1010846) is funded by Entrada Therapeutics, Inc (Boston, MA). The authors would like to thank Aji Nair for assistance with poster development (Entrada Therapeutics, Inc). Editorial and studio support for this poster were provided by Ashfield MedComms (US), an Inizio company, and were funded by Entrada Therapeutics, Inc. References: 1. EXONDYS 51® Prescribing Information. 2. VILTEPSO® Prescribing Information. 3. Qian Z. *Biochemistry*. 2016. 4. Sahni A. *ACS Chem Biol*. 2020. 5. Qian Z, et al. *ACS Chem*. 2013. 6. Li X, et al. *Mol Ther Nucleic Acids*. 2023. 7. Kumar A, et al. MDA 2022. Poster 126. 8. Sethuraman N. MDA 2025. Poster 95.