PP01.53

ELEVATE-44: First-in-patient results from a Phase 1/2 study evaluating ENTR-601-44 in exon 44 skip-amenable DMD

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Background

- Approximately 8% of patients with Duchenne muscular dystrophy (DMD) possess exon 44 skip-amenable dystrophin gene mutations[1,2]; available therapies for DMD face challenges related to limited intracellular delivery to therapeutic targets or unfavorable safety profiles[3,4]
- ENTR-601-44 is an Endosomal Escape Vehicle (EEV™) peptide-phosphorodiamidate morpholino oligomer (PMO) conjugate intended to target dystrophin pre-mRNA and induce exon 44 skipping, thereby restoring expression of near-full-length and functional dystrophin protein
  - The EEV Platform was designed to improve cellular uptake and endosomal escape of PMOs[5,6]
  - EEV-PMOs were shown to be localized to quiescent satellite cells and newly regenerated centrally nucleated fibers in preclinical studies[7]
- In preclinical studies, ENTR-601-44 demonstrated exon 44 skipping and increased dystrophin production in patient-derived and mouse muscle cells with exon 44 skip-amenable dystrophin mutations and exon 44 skipping in nonhuman primates[8]
- In the first-in-human Phase 1 ENTR-601-44-101 study in healthy adult male volunteers, ENTR-601-44 was well tolerated at the highest dose tested (6 mg/kg), with no study drug-related adverse events or clinically relevant changes in biomarkers of renal toxicity, and showed more than dose-proportional increases in urinary excretion of the final metabolite (PMO-44) and statistically significant exon 44 skipping at 6 mg/kg vs placebo[7]
- Here, we present first-in-patient clinical results from the double-blind, placebo-controlled period of the ongoing ELEVATE-44-201 study in participants with exon 44 skip-amenable DMD who received ENTR-601-44 at 6 mg/kg or placebo every 6 weeks

Objective

- To evaluate safety, tolerability, pharmacokinetics (PK), exon skipping, dystrophin production, and measures of function in participants with DMD who received ENTR-601-44 6 mg/kg or placebo in Cohort 1 of the ongoing ELEVATE-44 study

Methods

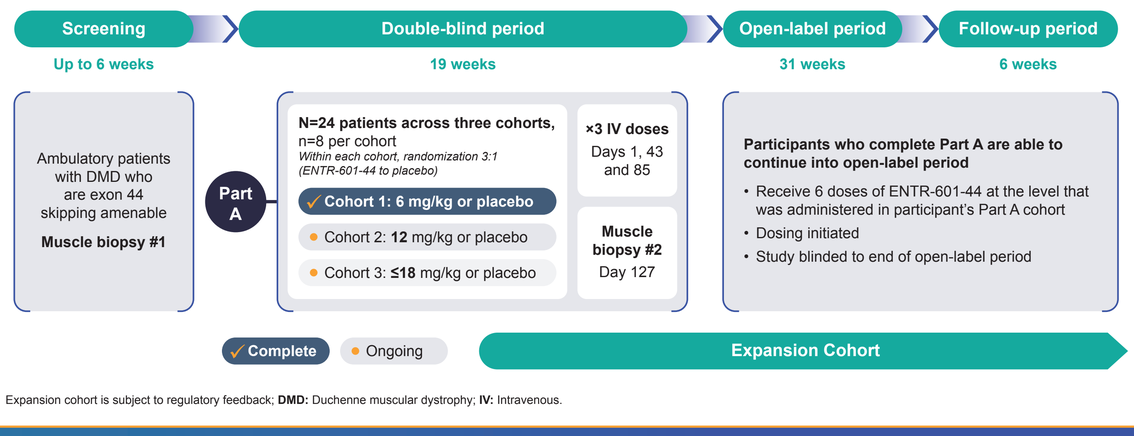
Study design

- ELEVATE-44 (NCT07037862) is an ongoing, global, first-in-patient, Phase 1/2b, two-part study consisting of a 19-week randomized, double-blind, placebo-controlled period (Part A) followed by a 31-week open-label period (**Figure 1**)
- Key eligibility criteria included ambulatory males aged 4–20 years with a confirmed genetic diagnosis of exon 44 skip-amenable DMD with a Performance of the Upper Limb v2.0 entry item A score of at least 3 at screening
- Muscle biopsies were performed at baseline, during screening, and again at the end of the treatment period at Week 19 (6 weeks after the final dose)

Assessments

- The primary endpoint is safety and tolerability; assessments include incidence and severity of treatment-emergent adverse events (TEAEs) and changes in clinical laboratory results including serum markers of kidney function (ie, estimated glomerular filtration rate [eGFR], serum cystatin C, serum magnesium, and serum creatinine)
- Secondary endpoints include ENTR-601-44 PK, exon 44 skipping, and dystrophin production
  - Changes from baseline in dystrophin expression, measured by western blot and normalized to myosin heavy chain, and exon 44 skipping, measured by droplet digital polymerase chain reaction (ddPCR), in muscle biopsies were summarized using descriptive statistics
- Measures of function are included as an exploratory endpoint in Part A and a secondary endpoint in the open-label period and include Time to Rise (TTR), among other endpoints
  - In a post hoc analysis, change from baseline to Week 19 of Part A in Time to Rise Velocity (TTRV; defined as 1/TTR) with ENTR-601-44 vs placebo was evaluated for participants in Cohort 1 using a Wilcoxon rank-sum (one-sided) test, and nominal *p* values were generated; the difference between treatment and placebo groups is presented to maintain study blinding to the greatest extent possible
  - Post hoc Spearman correlations were used to evaluate the relationship between the change from baseline to Week 19 in TTRV and the change from baseline to Week 19 in dystrophin levels within the treatment group

Figure 1. ELEVATE-44 study design



Expansion cohort is subject to regulatory feedback; **DMD:** Duchenne muscular dystrophy; **IV:** Intravenous.

Conclusions

- In Cohort 1 of the ongoing ELEVATE-44-201 study, ENTR-601-44 6 mg/kg was well tolerated in participants with exon 44 skip-amenable DMD
- Clinically meaningful improvement in TTRV ~3.5 times above the MCID threshold was observed with ENTR-601-44 6 mg/kg
- Potential early signals of functional benefit were observed with ENTR-601-44; functional endpoints must be interpreted cautiously given the small number of participants and will be further evaluated in the ongoing Cohort 1 open-label period and higher dose cohorts of ELEVATE-44

Results

ELEVATE-44 Cohort 1 participant demographics and baseline characteristics

- Eight males were enrolled into Cohort 1 (ENTR-601-44 6 mg/kg, n=6; placebo, n=2; **Table 1**); all participants completed Part A and are ongoing in the open-label period of the study
- Among all participants, mutations were identified in the dystrophin gene in exons 26–43, 43, 45, and 45–54

Table 1. Cohort 1 demographics and baseline characteristics

Characteristics	Placebo n=2	ENTR-601-44 6 mg/kg n=6
Age, mean, years	13.5	9.3
Body mass index, mean, kg/m²	17.96	20.00
Age at disease onset, mean, years	1.0	2.2
Corticosteroid use, n (%)	2 (100)	6 (100)
Ambulatory, n (%)	2 (100)	6 (100)
Baseline dystrophin, mean, %	4.6	4.0
Baseline TTRV, mean, rises/second	0.191	0.126

Biopsy performed at baseline; Dystrophin measured by western blot and normalized to myosin heavy chain; **TTRV:** Time to Rise Velocity.

ENTR-601-44 was well tolerated at the initial 6 mg/kg dose in Cohort 1, with a safety profile consistent with prior study

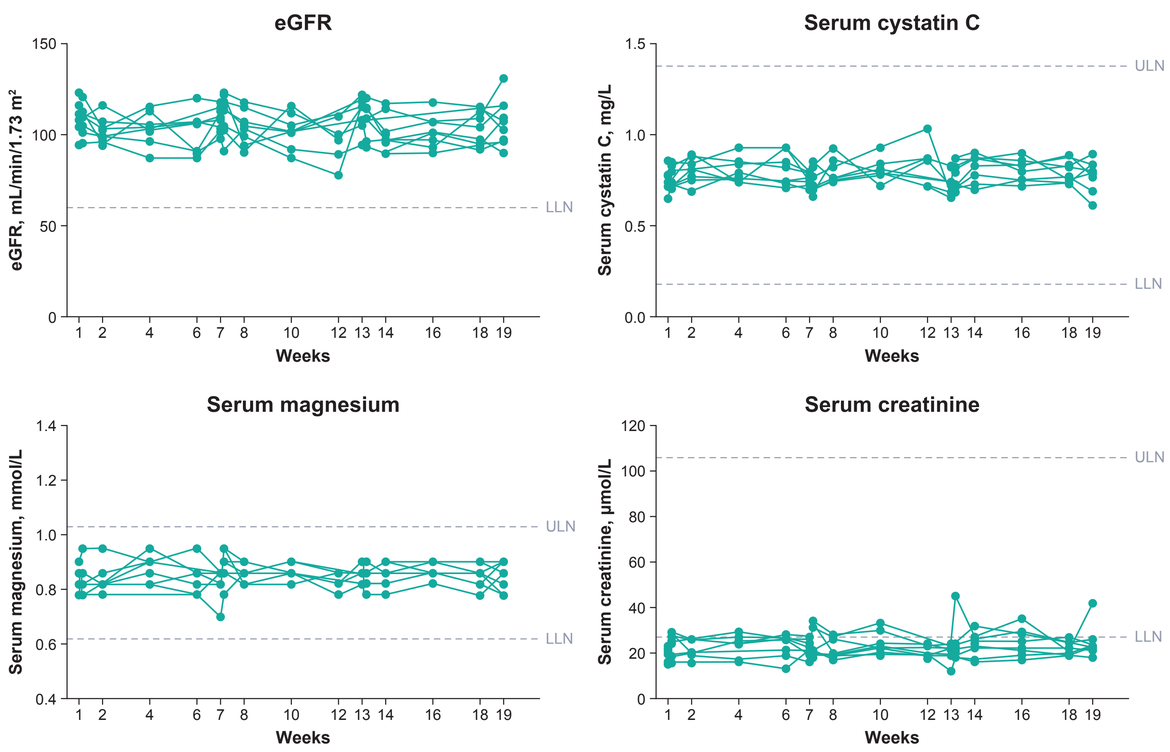
- All TEAEs in Cohort 1 were mild to moderate in severity; there were no serious TEAEs and no TEAEs leading to study discontinuation (**Table 2**)
- The most common TEAE related to study drug was headache (ENTR-601-44, n=3; placebo, n=1); all events resolved
- No hypomagnesemia or renal safety concerns were noted, and serum levels of markers of kidney function were generally within normal ranges (**Figure 2**)

Table 2. Safety summary for Cohort 1

Participants with ≥1 TEAE, n (%)	Placebo n=2	ENTR-601-44 6 mg/kg n=6
Any TEAE	2 (100)	6 (100)
TEAEs related to study drug	1 (50)	5 (83)
Serious TEAEs	0	0
TEAEs leading to study discontinuation	0	0
TEAEs leading to death	0	0

TEAE: Treatment-emergent adverse event.

Figure 2. Serum markers of kidney function in participants (n=8) receiving ENTR-601-44 6 mg/kg or placebo

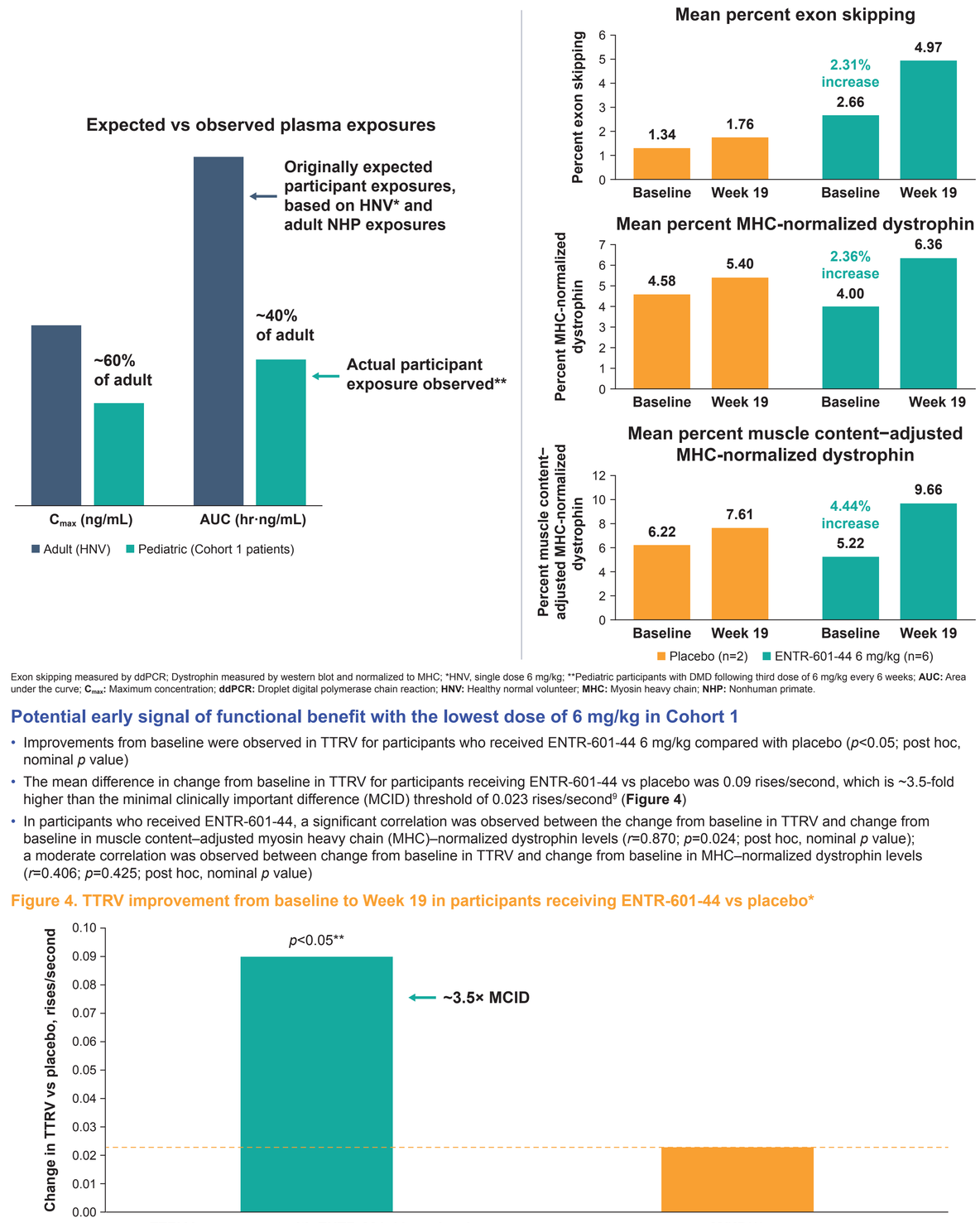


Serum creatinine reference range shown is 27–106 µmol/L and depends on age of the participant enrolled in Cohort 1; Serum creatinine is below the reference range in participants with DMD due to reduced muscle mass; **DMD:** Duchenne muscular dystrophy; **eGFR:** Estimated glomerular filtration rate; **LLN:** Lower limit of normal; **ULN:** Upper limit of normal.

Target engagement and dystrophin production observed with initial plasma exposures in Cohort 1

- Lower ENTR-601-44 plasma exposures were observed in the pediatric participants enrolled in Cohort 1 when compared with previously observed levels in healthy adults and adult nonhuman primates (**Figure 3**)
  - Measurable concentrations of PMO in muscle were observed 6 weeks after the last dose (data not shown)
- ENTR-601-44 induced exon 44 skipping and dystrophin protein production in Cohort 1 (**Figure 3**)

Figure 3. Expected vs observed plasma exposures, exon skipping, and dystrophin protein production in Cohort 1



Exon skipping measured by ddPCR; Dystrophin measured by western blot and normalized to MHC; *HNV, single dose 6 mg/kg; **Pediatric participants with DMD following third dose of 6 mg/kg every 6 weeks; **AUC:** Area under the curve; **C_{max}:** Maximum concentration; **ddPCR:** Droplet digital polymerase chain reaction; **HNV:** Healthy normal volunteer; **MHC:** Myosin heavy chain; **NHP:** Nonhuman primate.

Potential early signal of functional benefit with the lowest dose of 6 mg/kg in Cohort 1

- Improvements from baseline were observed in TTRV for participants who received ENTR-601-44 6 mg/kg compared with placebo ($p<0.05$; post hoc, nominal *p* value)
- The mean difference in change from baseline in TTRV for participants receiving ENTR-601-44 vs placebo was 0.09 rises/second, which is ~3.5-fold higher than the minimal clinically important difference (MCID) threshold of 0.023 rises/second[9] (**Figure 4**)
- In participants who received ENTR-601-44, a significant correlation was observed between the change from baseline in TTRV and change from baseline in muscle content–adjusted myosin heavy chain (MHC)–normalized dystrophin levels ($r=0.870$; $p=0.024$; post hoc, nominal *p* value); a moderate correlation was observed between change from baseline in TTRV and change from baseline in MHC–normalized dystrophin levels ($r=0.406$; $p=0.425$; post hoc, nominal *p* value)

Figure 4. TTRV improvement from baseline to Week 19 in participants receiving ENTR-601-44 vs placebo*

*All participants were on stable, individually optimized corticosteroid regimens for ≥6 months prior to and throughout the study; **Analysis of TTRV shown vs placebo to maintain study blinding, Wilcoxon rank-sum (one-sided) test, nominal *p* value, post hoc analysis; ***12-month MCID; **MCID:** Minimal clinically important difference; **TTRV:** Time to Rise velocity.

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Author Disclosures

LS: Paid consultant for BioMarin, Dyne, Entrada, Italfarmaco, Pfizer, Regenxbio, Santhera, Solid, and Wave. **ND:** Speaker and/or consultancy fees from Dyne, Entrada, Italfarmaco, Santhera, Sarepta, and Wave; Clinical trial activities for BioMarin, Dyne, Entrada, FibroGen, Généthon, GlaxoSmithKline, Italfarmaco, Lilly, Pfizer, Prosensa, ReveraGen, Santhera, Sarepta, and Wave. **LDW:** Speaker and/or consultancy fees from Dyne, Entrada, Italfarmaco, Pfizer, Santhera, and Wave; Clinical trial activities for BioMarin, Dyne, Entrada, FibroGen, Généthon, GlaxoSmithKline, Italfarmaco, Lilly, Pfizer, Prosensa, PTC Therapeutics, ReveraGen, Santhera, Sarepta, and Wave. **DG-A:** Speaker and/or consultancy fees from Alexion, Astellas Gene Therapies, Biogen, Entrada, Italfarmaco, Novartis, Pfizer, PTC Therapeutics, Roche, Santhera, and Sarepta; Travel support from Biogen, Italfarmaco, Pfizer, and Roche; Participated in clinical trials and other studies sponsored by Biogen, Dyne, Entrada, FibroGen, Novartis, Pfizer, Quince, Roche, Santhera, and UCB Pharma; Stocks or stock options in Aura Robotics and UCB Pharma; Research support from Astellas Gene Therapies and Roche. **KD, JL, NLi, NLo, MM, RP, KP, DMDP, DR, MR,** and **NS**: Employees of Entrada Therapeutics, Inc.

Acknowledgments

We thank all the study participants, their families, and the investigators and their study teams. This study is sponsored by Entrada Therapeutics, Inc. (Boston, MA). Medical writing and editorial assistance were provided by Sarah Ludwig, BS, of Peloton Advantage, LLC, an OPEN Health company, and funded by Entrada Therapeutics, Inc.

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