Del-zota (*delpacibart zotadirsen*) produced statistically significant increases in exon skipping and dystrophin levels in EXPLORE44®, a Phase 1/2 study in individuals with DMD44

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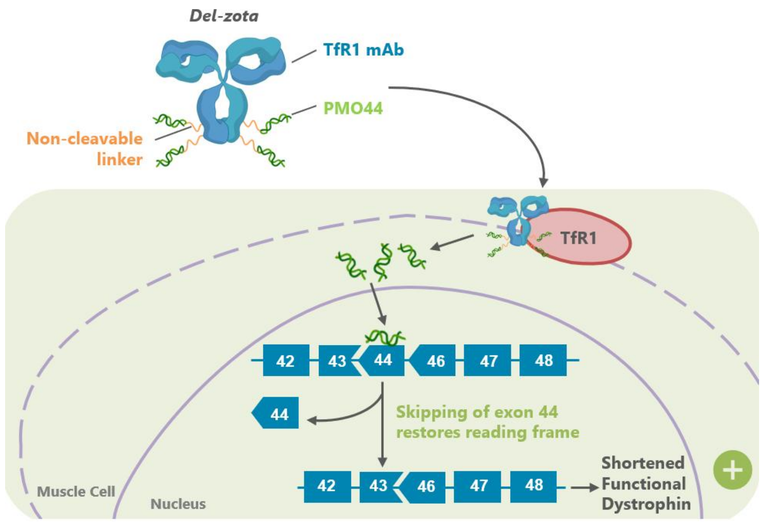
Introduction

- **Duchenne muscular dystrophy** (DMD) is a **monogenic, X-linked muscular disease** caused by **mutations in the *DMD* gene** that prevent the expression of a functional dystrophin protein, resulting in muscle cell death and progressive loss of muscle function.[1]
- Progressive muscle degeneration, wasting, and paralysis generally lead to **death via respiratory and/or cardiac failure** in the third to fourth decade of life.[1]
- Dystrophin protein expression can often be restored through **oligonucleotide-mediated skipping** of individual *DMD* exons to restore the reading frame.[2]
  - Of DMD skip-amenable individuals, **~7%** have mutations amenable to exon 44 skipping (**DMD44**).[3]
  - There are ~900 people with DMD44 in the United States (ultra rare).[3]
- There are currently **no approved exon skipping therapies** for individuals with DMD44.
- Avidity's **antibody-oligonucleotide conjugate** (AOC™) technology is designed to optimize the delivery of oligonucleotides to muscle tissue.
- *Del-zota* is comprised of a humanized anti-transferrin receptor 1 (TfR1) antibody conjugated to multiple copies of a phosphorodiamidate morpholino oligomer (PMO) designed to **restore the dystrophin reading frame** and produce **functional, internally truncated dystrophin protein** in individuals with DMD44 (Figure 1).

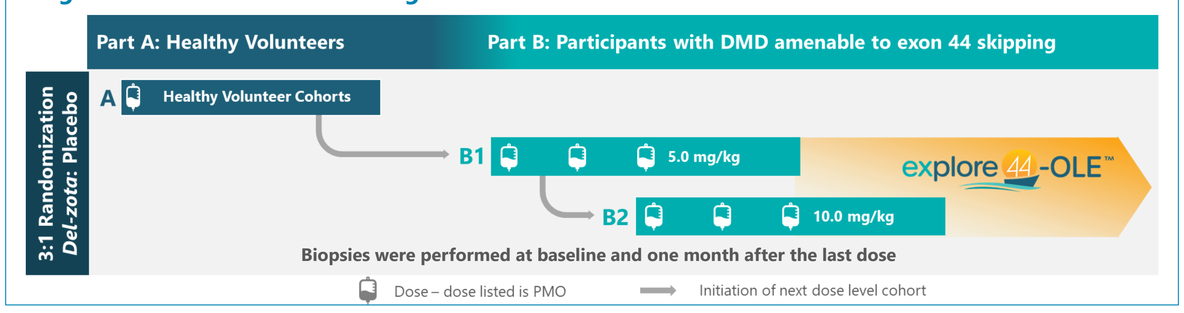
Figure 1. *Del-zota*, an exon-skipping AOC targeting *DMD* exon 44.[4]



Study Design

- **EXPLORE44®** (NCT05670730) is a randomized, placebo-controlled, double-blind **Phase 1/2 trial** (Figure 2).[5]
  - **Part A** assessed the effects of *del-zota* in single-dose cohorts of **healthy volunteers**, who were monitored for 3 months (Part A healthy volunteer data has been previously reported).
  - **Part B** assessed the safety, tolerability, pharmacokinetics, and exon skipping efficacy of multiple-ascending doses of *del-zota*.
    - EXPLORE44® enrolled **26 ambulatory and non-ambulatory individuals** aged 7–27 years with DMD44.
- This poster reports data from **Part B of the EXPLORE44® trial**.

Figure 2. EXPLORE44® trial design.



Results

Table 1. EXPLORE44® demographics and baseline characteristics.

	Placebo (N=7)	5 mg/kg (N=9)	10 mg/kg (N=10)
Age (yrs)	13.6 (3.5)	16.0 (4.7)	10.8 (2.7)
Body Mass Index (kg/m^2)	26.4 (8.4)	24.2 (5.6)	19.2 (2.5)
Age of Symptom Onset (yrs)	3.8 (2.4)	3.5 (2.3)	3.3 (2.0)
Creatine Kinase (U/L)	9,564 (7787)	5,033 (3246)	10,150 (7857)
Corticosteroid Use	100%	100%	70%
Ambulatory	71%	44%	100%
Genotype: 45Del / Other*	86% / 14%	67% / 33%	40% / 60%

Data are presented as mean (SD) unless otherwise indicated. *Represents 7 additional genotypes.

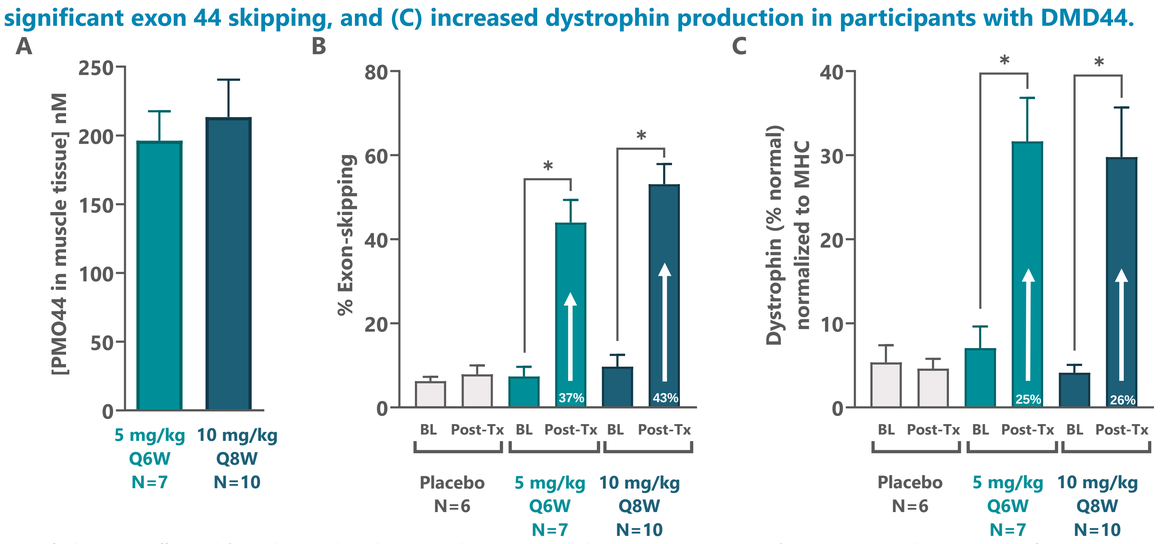
Results (Continued)

Table 2. Safety and tolerability summary of *del-zota* in participants with DMD44.

Treatment Emergent Adverse Events (TEAEs)	Placebo N=7	5 mg/kg N=9	10 mg/kg N=10	OLE* N=38
Any adverse event (AE)	6 (86%)	8 (89%)	8 (80%)	19 (50%)
Related to study drug	0	2 (22%)	4 (40%)	3 (7.9%)
Serious AE	0	1 (11%)	0	0
AE leading to treatment discontinuation	0	2 (22%)	0	0
AE leading to death	0	0	0	0

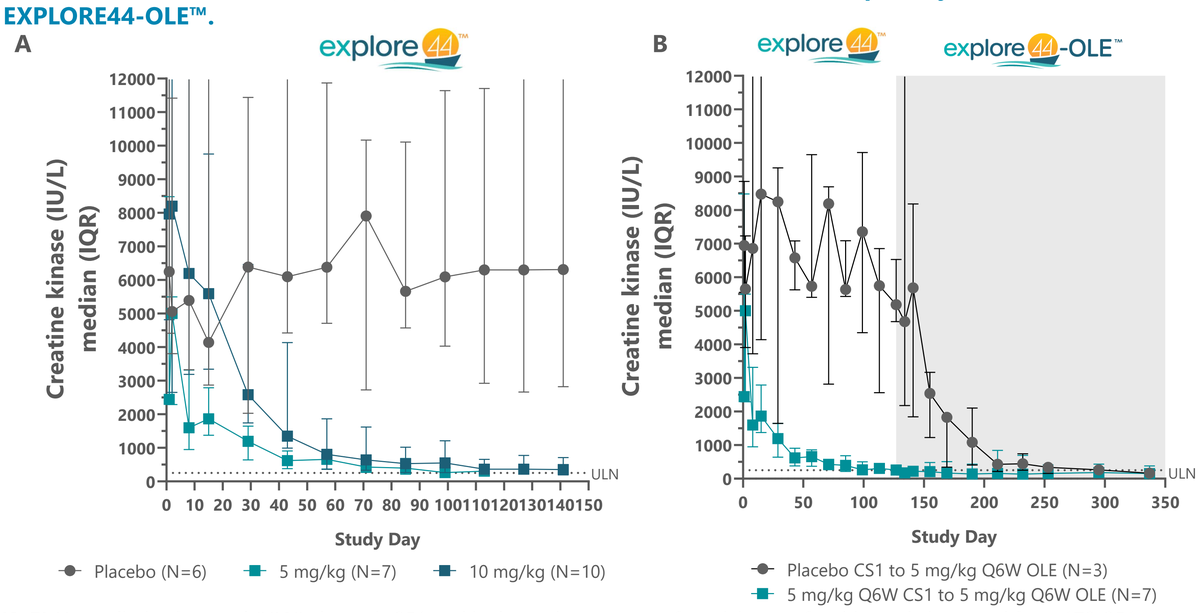
Data are presented as the number of participants (%) with ≥ 1 TEAE unless indicated otherwise. The data cut occurred on January 22, 2025 for EXPLORE44-OLE™ (interim cut). *OLE safety data represents a variety of doses and includes participants who enrolled into EXPLORE44-OLE™ *de novo* and those who rolled over from EXPLORE44®.

Figure 3. Treatment with *del-zota* resulted in (A) consistent and high PMO muscle concentrations, (B) significant exon 44 skipping, and (C) increased dystrophin production in participants with DMD44.



Muscle biopsy collected from biceps brachii at 28 days post 3rd dose (Day 113 or 141 for 5 or 10 mg/kg, respectively). (**A**) PMO44 muscle tissue concentrations were determined utilizing high performance liquid chromatography. (**B**) Exon 44 skipping determined using droplet digital polymerase chain reaction. Mean +/- standard error of mean (SEM). Doses expressed as PMO component. *p<0.05 by Wilcoxon test. (**C**) Dystrophin protein determined in biceps brachii muscle biopsy by western blot. Data normalized to myosin heavy chain. Mean +/- SEM. Dose expressed as PMO component. *p<0.05 by Wilcoxon test. BL, baseline; Q6W, every 6 weeks; Q8W, every 8 weeks; Tx, treatment.

Figure 4. *Del-zota* (A) consistently decreased creatine kinase levels to near normal in participants with DMD44 in the EXPLORE44® trial. (B) These reductions were sustained for up to 1 year in the EXPLORE44-OLE™.



(A-B) Upper limit of normal (ULN) shown is 251 and is dependent on age of participant – for this study it ranged from 178-251. IQR, interquartile range.

Conclusions

- The EXPLORE44® trial represents the **first-in-patient** experience using Avidity's proprietary AOC™ technology to deliver PMOs to muscle.
- **Favorable safety and tolerability** was observed following *del-zota* treatment.
  - Most TEAEs were mild to moderate.
- *Del-zota* achieved **robust, dose-dependent delivery of PMO to skeletal muscle**, resulting in a consistent and significant **increase in exon 44 skipping** – up to 67% in participants with DMD44 – compared to placebo.
- **Substantial increases in dystrophin production** – an average increase of 25% and up to 58% of normal levels – were observed in both cohorts, alongside a **sustained reduction in creatine kinase levels** by more than 80% to near-normal levels following *del-zota* treatment.
- These data highlight *del-zota's* **potential to improve the lives of individuals with DMD44** and support the continued evaluation of *del-zota* in the Phase 2 EXPLORE44-OLE™ trial (NCT06244082).

Disclosures, Acknowledgements, and References

- Authors **MM**, **YT**, **TC**, **PK**, **JH**, **SH**, **YZ**, and **EJA** are employees of Avidity Biosciences and have stock or stock options.
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1. Duan D, et al. Nat Rev Dis Primers. 2021;7(1):13. **2.** Arechavala-Gomeza V, et al. Curr Gene Ther. 2012;12(3):152-60. **3.** Bladen CL, et al. Hum Mutat. 2015;36(4):395-402. **4.** Aartsma-Rus A, et al. BMC Medical Genetics. 2007;8(43);2. **5.** Clinicaltrials.gov.NCT05670730 [EXPLORE44]. https://clinicaltrials.gov/ct2/show/NCT05670730. Accessed March 2025.

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