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Delpacibart Zotadirsen (*Del-zota*) Increased Dystrophin and Improved Muscle Integrity Markers Regardless of Ambulatory Status in Individuals with DMD44

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INTRODUCTION

- DMD is a severe, progressive neuromuscular disorder caused by mutations in the dystrophin gene, leading to muscle degeneration and early mortality[1-4]
- Approximately 6–7% of individuals with DMD have mutations amenable to exon 44 skipping (DMD44), yet there are currently no exon skipping therapies available for DMD44[5, 6]
- As such, there is a high unmet need for exon skipping therapies to treat DMD44, particularly those that can benefit a broad range of disease severities[7]
- *Del-zota* (*delpacibart zotadirsen*; AOC 1044) is an antibody-oligonucleotide conjugate (AOC™) designed to deliver a phosphorodiamidate morpholino oligonucleotide targeting dystrophin's exon 44 (PMO44) to muscle cells
  - *Del-zota* induces exon 44 skipping and restores the dystrophin reading frame, enabling the production of a near full-length dystrophin that is expected to restore muscle cell integrity and protect against damage
- The completed Phase 1/2 EXPLORE44® trial (NCT05670730) is the first clinical study to evaluate *del-zota*
  - Participants had the opportunity to enroll into a long-term open-label extension (OLE; EXPLORE44-OLE™, NCT06244082) to assess *del-zota*'s long-term safety and efficacy

OBJECTIVES

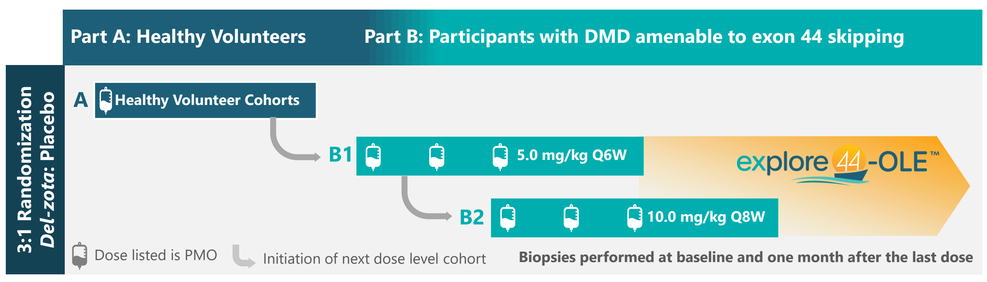
- Evaluate the safety, tolerability, pharmacokinetics, exon skipping, dystrophin expression, and exploratory efficacy of multiple ascending doses of *del-zota* in individuals with DMD44
  - This subgroup analysis examines the effect of *del-zota* on levels of dystrophin and muscle integrity markers by ambulatory status

METHODS

Study Design

- EXPLORE44® was a randomized, placebo-controlled, double-blind, multiple ascending dose study in males aged 7–27 years with a confirmed diagnosis of DMD44, which included both ambulatory (n=19) and non-ambulatory (n=7) individuals (Part B; **Figure 1**)
  - Participants received three intravenous (IV) infusions of *del-zota* at either 5 mg/kg or 10 mg/kg or placebo (dosing was informed by Part A)
  - Data from Part B through Months 4/5 (4 weeks post-3rd dose) are presented herein

Figure 1. EXPLORE44® Study Design



Part A included a placebo-controlled single ascending dose Phase 1 study conducted at a single US center with healthy adult men randomized (3:1; *del-zota*:placebo) into 5 single dose cohorts. Part B included participants with DMD44 randomized (3:1) to receive either *del-zota* or placebo in two multiple ascending doses cohorts: B1 (5 mg/kg) and B2 (10 mg/kg). Muscle biopsies were performed at baseline and one month after the last dose (Month 4 for 5 mg/kg and Month 5 for 10 mg/kg). DMD, Duchenne muscular dystrophy; PMO, phosphorodiamidate morpholino oligomer; Q6W, every 6 weeks; Q8W, every 8 weeks.

Safety

- Participants were monitored throughout the study through regular assessments including laboratory tests, ECGs, vital signs, and physical examinations

Pharmacodynamics

- Exon 44 skipping in muscle was measured via digital droplet polymerase chain reaction and dystrophin protein quantification was analyzed by western blot and immunofluorescence (IF)
- Biopsies were performed at baseline and post-treatment (Month 4 or 5 depending on dosing schedule)

Biomarkers

- The following serum biomarkers of muscle integrity were evaluated longitudinally to assess treatment-related change: creatine kinase (CK), myoglobin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)

RESULTS

Safety

- *Del-zota* demonstrated acceptable safety and tolerability (**Table 1**)

Table 1. Safety and Tolerability Summary of *Del-zota* in Participants with DMD44

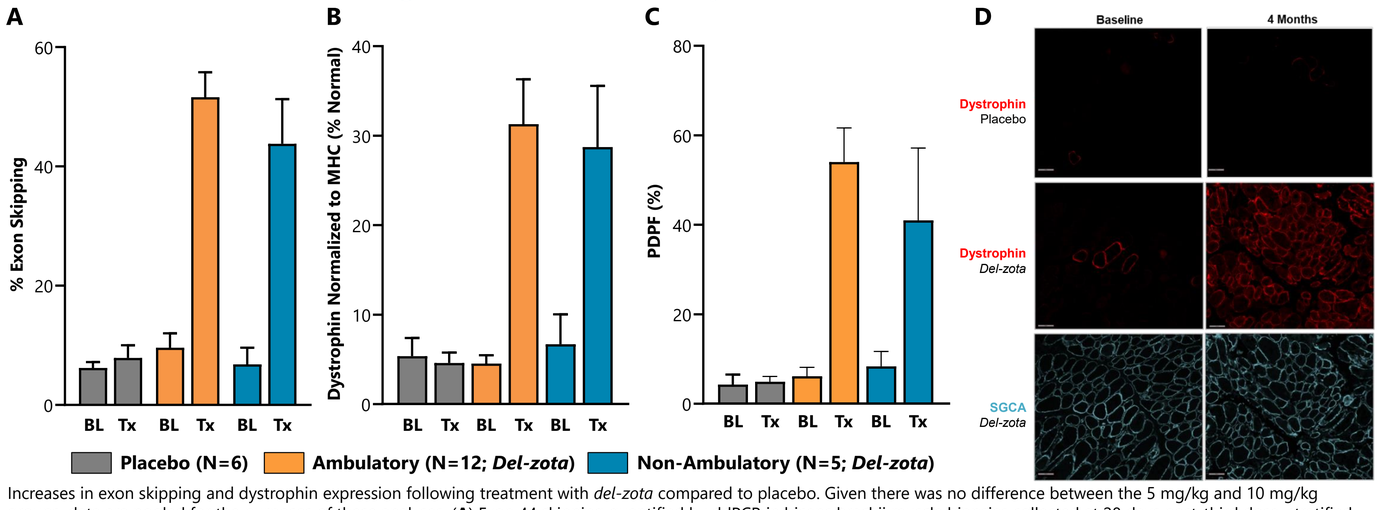
	EXPLORE44®		EXPLORE44-OLE™
AEs	Placebo (N=7)	*Del-zota* (N=19)	*Del-zota* (N=39)
Any AE	6 (86%)	16 (84%)	33 (85%)
Related to study drug	0	6 (32%)	10 (26%)
Serious AE	0	1 (5%)	3 (8%)
Serious AE related to study drug	0	1 (5%)	1 (3%)
AE leading to discontinuation	0	2 (11%)	1 (3%)
AE leading to death	0	0	0

AE, adverse event; IRR, infusion-related reaction; OLE, open-label extension. Data are presented as the number of participants (%) with ≥ 1 AE unless indicated otherwise. The data cut occurred in June 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®. †1 EXPLORE44® participant discontinued due to serious AE of anaphylaxis and another participant discontinued due to moderate IRRs. In the OLE, one SAE of hypersensitivity was considered related to study drug and resulted in discontinuation.

Pharmacodynamics

- *Del-zota* treatment resulted in increased exon 44 skipping from baseline to Month 4/5 in both ambulatory (~42% skipping) and non-ambulatory (~37% skipping) participants (**Figure 2A**)
- Treatment with *del-zota* led to a meaningful increase in dystrophin protein levels and percent dystrophin positive fibers (PDPF) from baseline to Month 4/5 in both ambulatory and non-ambulatory participants:
  - There was a statistically significant mean increase of ~25% of normal dystrophin from baseline across *del-zota*-treated participants compared to placebo, with a ~27% increase in ambulatory participants and a ~22% increase in non-ambulatory participants, as measured by western blot (**Figure 2B**)
  - An increase compared to baseline was also observed in PDPF, with mean increases from baseline of ~48% in ambulatory participants and ~33% in non-ambulatory participants, as measured by IF (**Figure 2C-D**)

Figure 2. Treatment with *Del-zota* Increased Exon 44 Skipping and Dystrophin Expression in Participants with DMD44 Regardless of Ambulatory Status

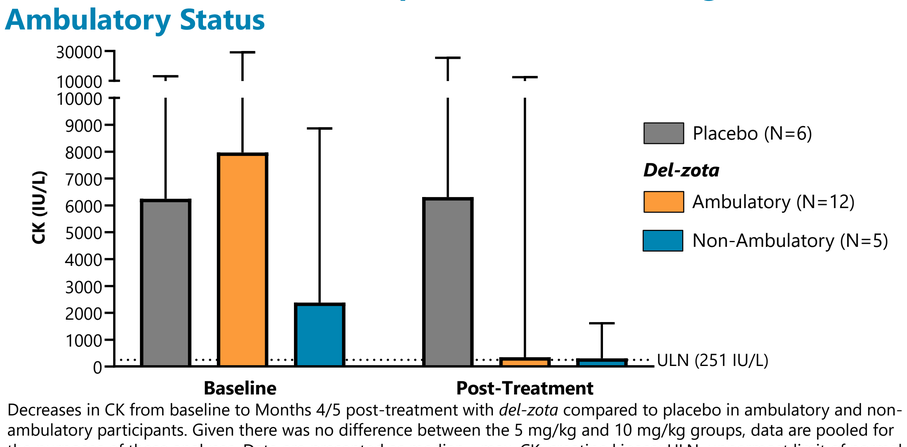


Increases in exon skipping and dystrophin expression following treatment with *del-zota* compared to placebo. Given there was no difference between the 5 mg/kg and 10 mg/kg groups, data are pooled for the purposes of these analyses. (**A**) Exon 44 skipping quantified by ddPCR in biceps brachii muscle biopsies collected at 28 days post-third dose, stratified by ambulatory status. Data are presented as mean ± SEM. (**B**) Dystrophin expression normalized to MHC, measured by western blot, stratified by ambulatory status. Data are presented as mean ± SEM. (**C**) Quantification of PDPF measured by immunofluorescence, stratified by ambulatory status. Data are presented as mean ± SEM. (**D**) Representative immunofluorescence images (5 mg/kg). BL, baseline; ddPCR, droplet digital polymerase chain reaction; MHC, myosin heavy chain; PDPF, percent positive dystrophin fiber; SGCA, sarcoglycan alpha; tx, post-treatment.

Biomarkers

- *Del-zota* treatment reduced serum biomarkers of muscle damage to near normal levels from baseline to Month 4/5 in both ambulatory and non-ambulatory participants:
  - CK levels decreased by ~88% in ambulatory participants and by ~73% in non-ambulatory participants (**Figure 3**)
  - Additional biomarkers of muscle damage, including myoglobin, AST, and ALT similarly decreased in both ambulatory and non-ambulatory participants (data not shown)

Figure 3. Treatment with *Del-zota* Reduced Levels of Circulating CK to Near Normal in Participants with DMD44 Regardless of Ambulatory Status



Decreases in CK from baseline to Months 4/5 post-treatment with *del-zota* compared to placebo in ambulatory and non-ambulatory participants. Given there was no difference between the 5 mg/kg and 10 mg/kg groups, data are pooled for the purposes of these analyses. Data are presented as median +max. CK, creatine kinase; ULN, uppermost limit of normal.

CONCLUSIONS

- Treatment with *del-zota* is continually associated with acceptable safety and tolerability
- *Del-zota* targets the root cause of DMD44 by leading to unprecedented increases in dystrophin as measured by both western blot and PDPF immunofluorescence
- Rapid and sustained reductions in CK to near normal were observed in both ambulatory and non-ambulatory participants, indicating improved muscle integrity and supporting the broad potential therapeutic impact of *del-zota*

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DISCLOSURES

AV has a consultancy/advisory role with AMO Pharma, AveXis, Biogen, Edgewise Therapeutics, FibroGen, Novartis, Pfizer, PTC Therapeutics, Sarepta Therapeutics, UCB Pharma, Catalyst and Scholar Rock; has received research funding from AMO Pharma, Capricor Therapeutics, Edgewise Therapeutics, FibroGen, the Muscular Dystrophy Association, Novartis, Parent Project Muscular Dystrophy, Pfizer, RegenxBio and Sarepta Therapeutics; and has other relationship(s) with MedLink Neurology for editorial services. **KF** has received clinical trial support from Sarepta, Dyne, Avidity, Ultragenyx, and Solid; received support for serving on advisory boards to Armatus, Encoded, Insmed, Dyne, and Solid; and has received past Royalties from Astellas. **HP** serves as PI for Applied Therapeutics, Sarepta, Dyne, Stealth, Biogen, Ultragenyx, Avidity, Edgewise, Biohaven, Pepgen, NS Pharma, Italofarmaco, NMD Pharma, Takeda, Tyra, and Zynerba. She also has served as consultant for BridgeBio, and Tyra. **ES** declares contracts (as principal investigator) from Avidity Biosciences, Edgewise Therapeutics, and Capricor Therapeutics; consulting and speaking fees from Avidity Biosciences, Catalyst Pharmaceuticals, Italfarmaco, Quince Therapeutics and Sardocor. CTR reports consulting fees- last 12 months (Novartis, Sarepta Therapeutics, Inc., Italpharmaco, RegenxBio, Catalyst and Precision Biosciences) and is a site investigator for clinical trials: Novartis, Biogen, Sanofi, PTC Therapeutics, Roche, Sarepta Therapeutics, Inc., Scholar Rock, Avidity and Janssen. **BW** has participated in advisory committee meetings for Prosensa and Biomarin and has received compensation for consultancy services for Gilead Sciences, Pfizer, GSK, RegenXBio, PepGen and Somite.AI. **MM, YT, TC, PK, JH, SH, YZ, and EJA** are employee[s] of and may own stock/stock options in Avidity Biosciences, Inc
Note: *Del-zota* is in clinical development for treatment of DMD44 and currently has not been authorized for this indication, and its safety and efficacy for such use has not been established.

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