Delpacibart zotadirsen (Del-zota) Showed Trends for Functional Improvement in the Phase 1/2 EXPLORE44® Study with Continued Trends After 1-Year of Treatment Compared to DMD44 Natural History

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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 (PMO44) targeting dystrophin's exon 44 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*

OBJECTIVES

- To evaluate the effect of *del-zota* on clinical outcomes in individuals with DMD44 versus placebo in EXPLORE44® and effect of up to 1 year of treatment in EXPLORE44-OLE™ versus DMD44 natural history

METHODS

Study Design

- EXPLORE44® (NCT05670730) was a randomized, placebo-controlled, double-blind Phase 1/2 trial which assessed the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of *del-zota* in individuals with DMD44
  - Part A assessed the effects of *del-zota* in single-dose cohorts of healthy volunteers
  - Part B assessed effects of multiple ascending doses of *del-zota* at 5 mg/kg given Q6W or 10 mg/kg given Q8W versus placebo over 4–5 months in ambulatory and non-ambulatory participants with DMD44 aged 7–26 years
- EXPLORE44-OLE™ is an open-label extension study of EXPLORE44® evaluating the long-term safety and efficacy of *del-zota* in participants that completed EXPLORE44® and *de novo* participants
  - Participants were initially treated at dose level in EXPLORE44® and transitioned to 5 mg/kg Q6W after dose selection; *de novo* participants (N=16) initiated at 5 mg/kg

Clinical Outcomes

- This poster compares clinical outcomes (**1**) between placebo (N=6) and *del-zota* (N=17) at Month 4/5 in the EXPLORE44® trial and (**2**) between DMD44 natural history (N=22) and *del-zota* (N=17) at 1 year (patients from EXPLORE44® who received an additional 6 months of treatment with *del-zota* in EXPLORE44-OLE™)
  - DMD44 natural history datasets included the PRO-DMD-01 database (CureDuchenne, analyzed by Analysis Group®) for ambulatory assessments (4-stair climb [4SC], 10-meter walk/run test [10MWRT], time to rise [TTR], and North Star Ambulatory Assessment [NSAA]) and Brogna et al (2023)[8] for performance of upper limb (PUL)
    - Matching criteria for PRO-DMD-01 were: ambulatory, exon 44 skip amenable, 7–27 years old, if on steroid stable ≥1 month, weight ≥23 kg; reported values were used for PUL

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RESULTS

Table 1. BLC of DMD44 Natural History Comparators and EXPLORE44®/ EXPLORE44-OLE™

	PRO-DMD-01 DMD44 (N=22)	EXPLORE44®/ OLE (N=10)*
Age (yrs)	10.6	11.0
4SC (s)	4.3	7.5
10MWRT (s)	5.7	8.1
TTR (s)	7.2	10.2
NSAA (total)	23.6	19.6

	Brogna DMD44 (N=27)†	EXPLORE44® / OLE (N=17)
Age (yrs)	12.2	13.3
Ambulatory, n (%)	48 (72.7%)	12 (70.6%)
Non-ambulatory, n (%)	18 (27.3%)	5 (29.4%)
PUL (total)	35.6	36.3

Data are presented as means unless otherwise indicated. *Ambulatory participants only, with one participant excluded due to ankle sprain and one participant unable to complete assessment due to fractured femur. BLC shown of participants with functional data at one year. †66 unique intervals. BLC, baseline characteristics.

RESULTS (CONTINUED)

Table 2. *Del-zota* demonstrated an acceptable safety profile

Treatment Emergent Adverse Events (TEAEs)	Placebo N=7	EXPLORE44® *Del-zota* N=19	EXPLORE44-OLE™ *Del-zota* N=39
Any TEAE	6 (86%)	16 (84%)	33 (85%)
Related to study drug	0	6 (32%)	10 (26%)
Serious TEAE	0	1 (5%)	3 (8%)‡
Serious TEAE related to study drug	0	1 (5%)	1 (3%)
TEAE leading to treatment discontinuation	0	2 (11%)†	1 (3%)‡
TEAE leading to death	0	0	0

Placebo data are pooled and *del-zota* data are pooled (5 mg/kg and 10 mg/kg). January 2025 data cutoff for EXPLORE44® (final cut) and June 2025 data cutoff for EXPLORE44-OLE™ (interim cut). Safety data represents the number of participants (%) with ≥1 TEAE unless indicated. †1 participant discontinued due to serious TEAE of anaphylaxis and 1 discontinued due to moderate infusion-related reaction. ‡SAEs considered unrelated to treatment include femur fracture and suicidal behavior, and one SAE of hypersensitivity was considered related to study drug and resulted in discontinuation.

Figure 1. Treatment with *del-zota* was associated with trends toward improvements in (A) timed functional tests and (B) functional and QoL assessments in participants with DMD44 relative to placebo at month 4/5

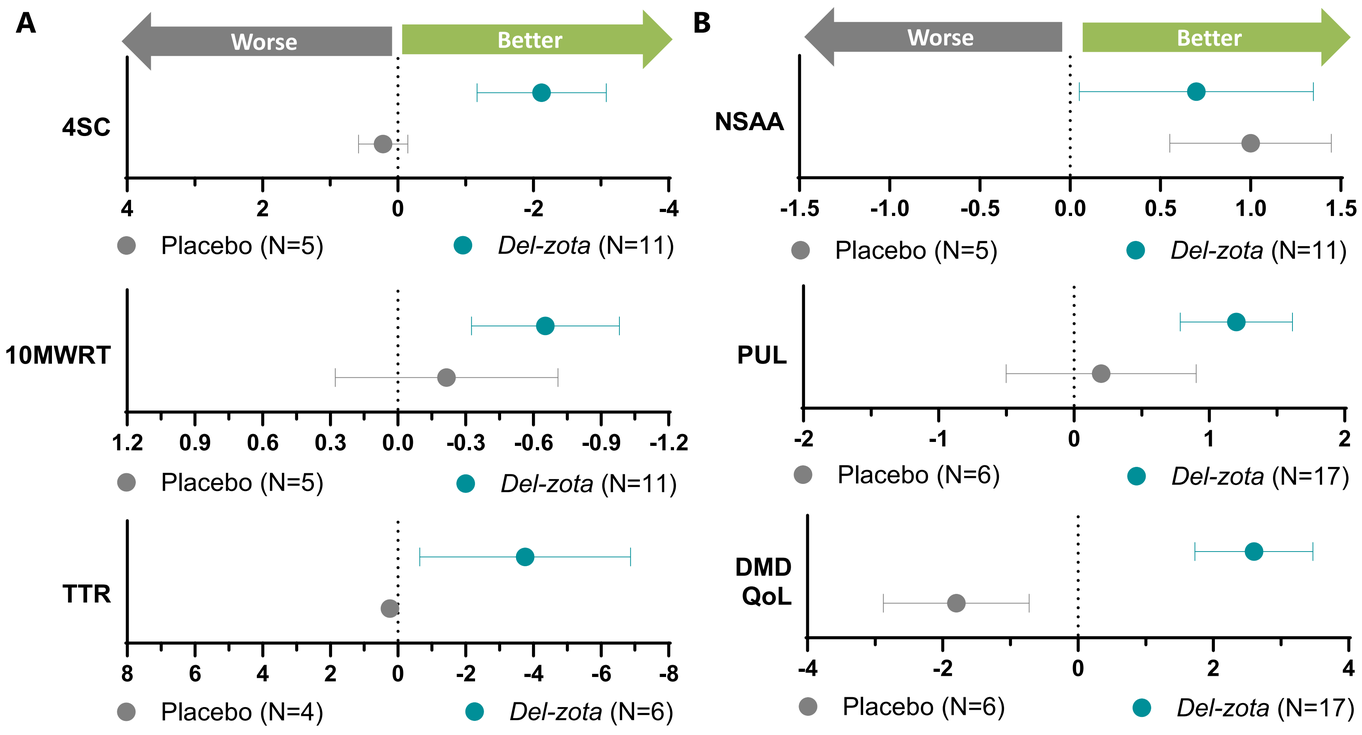
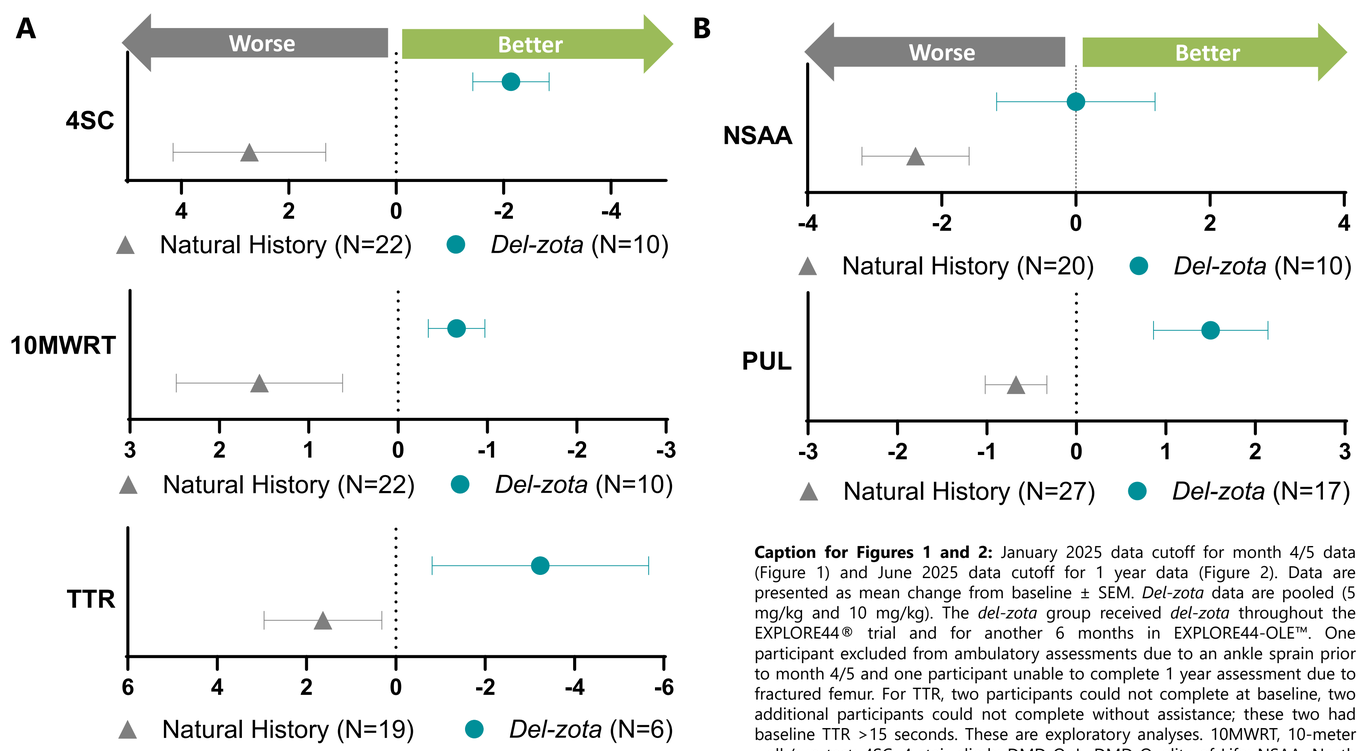


Figure 2. Treatment with *del-zota* was associated with trends toward improvements in (A) timed functional tests and (B) functional assessments in participants with DMD44 relative to matched external DMD44 natural history controls at 1 year



Caption for Figures 1 and 2: January 2025 data cutoff for month 4/5 data (Figure 1) and June 2025 data cutoff for 1 year data (Figure 2). Data are presented as mean change from baseline ± SEM. *Del-zota* data are pooled (5 mg/kg and 10 mg/kg). The *del-zota* group received *del-zota* throughout the EXPLORE44® trial and for another 6 months in EXPLORE44-OLE™. One participant excluded from ambulatory assessments due to an ankle sprain prior to month 4/5 and one participant unable to complete 1 year assessment due to fractured femur. For TTR, two participants could not complete at baseline, two additional participants could not complete without assistance; these two had baseline TTR >15 seconds. These are exploratory analyses. 10MWRT, 10-meter walk/run test; 4SC, 4-stair climb; DMD QoL, DMD Quality of Life; NSAA, North Star Ambulatory Assessment; PUL, performance of upper limb; TTR, time to rise.

CONCLUSIONS

- *Del-zota* treatment led to trends towards improvement in functional and quality of life outcomes compared to placebo at 4/5 months and matched DMD44 natural history controls at 1 year
- Improvements were seen compared to both placebo and DMD44 natural history, despite *del-zota* participants' baseline characteristics (age and ambulatory assessments) suggesting that a decline would have been expected
- These findings, along with a favorable safety profile, support continued clinical development of *del-zota* for the treatment of DMD44

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DISCLOSURES

PRO-DMD-01 disclosure: This publication is based on research using data from data contributor CureDuchenne that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication. KMF 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. **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. **JE** has participated in advisory meetings for Sarepta Therapeutics, received grant funding from Prime Therapeutics, is a site investigator for clinical trials sponsored by Avidity and Scholar Rock, and received support for attending and traveling to meetings from the Muscular Dystrophy Association and CureSMA, which is outside the scope of this presentation. **CGL** declares contracts (as principal investigator) from Sarepta Therapeutics, Dyne Therapeutics, Avidity Biosciences, FibroGen, Scholar Rock, and Biohaven; consulting fees from Sarepta Therapeutics (payments to her institution), NS Pharma (payments to herself), and Avidity (payments to her institution and to herself); payments for participation in a speakers bureau from Biogen; and support for attending meetings and/or travel from the Muscular Dystrophy Association, CureCMD, and CureSMA, all outside the scope of this presentation. **CMM** has served as a consultant for clinical trials with Astellas Pharma, Avidity Biosciences, Capricor Therapeutics, Catabasis Pharmaceuticals, Edgewise Therapeutics, Entrada Therapeutics, Epirium Bio (formerly Cardero Therapeutics), FibroGen, Italfarmaco, Pfizer, PTC Therapeutics, Hoffman La Roche, Santhera Pharmaceuticals, Sarepta Therapeutics, and Solid Biosciences. He has received research support for clinical trials from Capricor Therapeutics, Catabasis Pharmaceuticals, Edgewise Therapeutics, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics, and Solid Biosciences. He serves on external advisory boards related to DMD for Capricor Therapeutics, Edgewise Therapeutics, Eli Lilly, Entrada Therapeutics, Italfarmaco, NS Pharma, Percheron, PTC Therapeutics, Sarepta Therapeutics, Santhera Pharmaceuticals and Solid Biosciences. **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, JC, PK, JJH, SGH, 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.

ACKNOWLEDGMENTS

Medical writing support was provided by Lauren Todd, Ph.D., CMPP of Sixsense Strategy Group, Inc., a Herspiegel company (Toronto, Canada), funded by Avidity Biosciences, Inc., in accordance with Good Publication Practice guidelines.

Analysis Group ® analyzed the PRO-DMD-01 natural history data.

FUNDING

This study was supported by Avidity Biosciences, Inc.

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