AOC 1044 as a Novel Therapeutic Approach for DMD Patients Amenable to Exon 44 Skipping: EXPLORE44™ Phase 1/2 Healthy Volunteer Data

Mark Stahl, Yiming Zhu, Varun Goel, Laura Leung, Tara Carmack, Yvonne Tami, Trista Hardin, Usue Etxaniz, Philip Kovach, Josiah Herzog, Steve Hughes, Elizabeth J. Ackermann

Avidity Biosciences, San Diego, CA, USA

Disclosures: This poster is sponsored by Avidity Biosciences, Inc. Some authors are employees of Avidity Biosciences, Inc. and may have stock options or an ownership interest.
Acknowledgments: Avidity would like to acknowledge the patients, families, and study staff involved in the EXPLORE44™ trial.

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[1]
- Lack of functional dystrophin leads to stress and tears of muscle cell membranes, 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
- 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 patients, ~7% have mutations amenable to exon 44 skipping (DMD44)[3]
  - There are ~900 people with DMD44 in the US (ultra rare)
- Although several oligonucleotides targeting different exons have been approved, their clinical efficacy is limited by poor muscle delivery.[4] Currently, there is no approved exon skipping therapy for patients with exon 44 skip-amenable mutations
- Avidity's antibody-oligonucleotide conjugate (AOC™) technology is designed to optimize the delivery of oligonucleotides to muscle tissue
- AOC 1044 is comprised of a humanized anti-transferrin receptor 1 (TfR1) antibody conjugated to multiple copies of a phosphorodiamidate morpholino oligomer (PMO) (Figure 1) designed to exclude exon 44 from the mature dystrophin mRNA to restore the reading frame and result in the production of dystrophin protein in patients with amenable mutations (Figure 2)

Figure 1: AOC 1044, an Antibody Oligonucleotide Conjugate Targeting Exon 44 Skipping

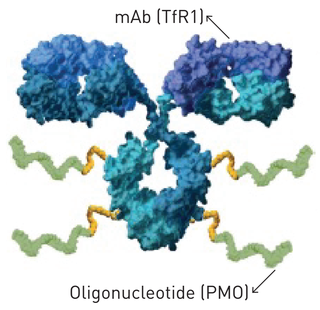
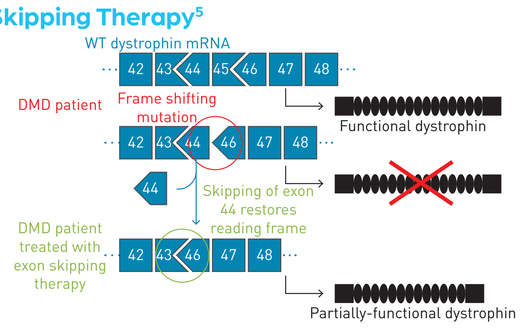


Figure 2: Example of a DMD Patient With Exon 45 Deletion, Amenable to Exon 44 Skipping Therapy[5]



Methodology

- EXPLORE44™ (AOC 1044-CS1) Part A is a randomized, placebo-controlled, double-blind Phase 1/2 trial (Clinicaltrials.gov identifier: NCT05670730)[6]
- Part A assessed the effects of AOC 1044 in single-dose cohorts of healthy volunteers (HVs), who were monitored for 3 months
- Part A included up to 5 single-dose cohorts randomized 3:1 (AOC 1044:placebo) with doses to be evaluated ranging from 1.5 to a maximum of 20 mg/kg
- This poster reports interim data from the first 4 cohorts (1.5, 3.0, 5.0, and 10.0). Each AOC 1044 arm enrolled 6 to 8 participants
- Biopsies were taken at dose levels ≥5 mg/kg at Day 8 and Day 29. Biopsy results from 5 and 10 mg/kg cohort are shown
- The primary objective of Part A is safety and tolerability of single doses in HVs. Secondary objectives of Part A include pharmacokinetics. Exploratory objectives include pharmacodynamics and exon 44 skipping
- Part A of this study was conducted at a single center

Interim Results

- Thirty-seven male HVs were randomized 3:1 and 36 (18-55 years) were treated in 4 ascending-dose cohorts to receive a single dose of AOC 1044 or placebo

Table 1: Baseline Demographics

Mean (SD) or n (%)	Pooled placebo (N=8)	1.5 mg/kg (N=6)	3 mg/kg (N=6)	5 mg/kg (N=8)	10 mg/kg (N=8)	Pooled AOC 1044 (N=28)
Age	34.0 (11.88)	27.2 (4.02)	36.3 (6.47)	38.4 (6.99)	42.8 (6.94)	36.8 (8.23)
BMI	26.26 (3.561)	25.67 (4.140)	23.43 (2.784)	28.18 (1.566)	26.74 (2.032)	26.21 (3.053)

Table 2: AOC 1044 Was Well-Tolerated: Safety Summary in Healthy Volunteers

	Pooled placebo (N=8) n (%), events	1.5 mg/kg (N=6) n (%), events	3 mg/kg (N=6) n (%), events	5 mg/kg (N=8) n (%), events	10 mg/kg (N=8) n (%), events	Pooled AOC 1044 (N=28) n (%), events
TEAE	2 (25.0), 4	0	3 (50.0), 5	6 (75.0), 10	7 (87.5), 22	16 (57.1), 37
TEAE related to study drug	0	0	2 (33.3), 2	3 (37.5), 3	5 (62.5), 6	10 (35.7), 11
TEAE related to study procedure	1 (12.5), 2	0	0	0	3 (37.5), 4	3 (10.7), 4
Severe TEAE	1 (12.5), 1	0	0	0	0	0
Severe TEAE related to study drug	0	0	0	0	0	0
Serious TEAE	0	0	0	0	0	0
Serious TEAE related to study drug	0	0	0	0	0	0
TEAE with a fatal outcome	0	0	0	0	0	0

- Safety and tolerability were monitored for 3 months post-dose
- All TEAEs were mild or moderate with no serious or severe TEAEs in participants dosed with AOC 1044
- No symptomatic hemoglobin changes, hypomagnesemia, or renal events
- One severe adverse event of elevated creatine phosphokinase was reported in the placebo group

Interim Results (Continued)

Figure 3: PMO44 Concentration in Skeletal Muscle of Healthy Volunteers Receiving AOC 1044

- AOC 1044 treatment resulted in highly efficient, dose-dependent delivery of PMO to skeletal muscle. Tissue concentrations substantially exceed those that result in >5% dystrophin in DMD44 mouse model

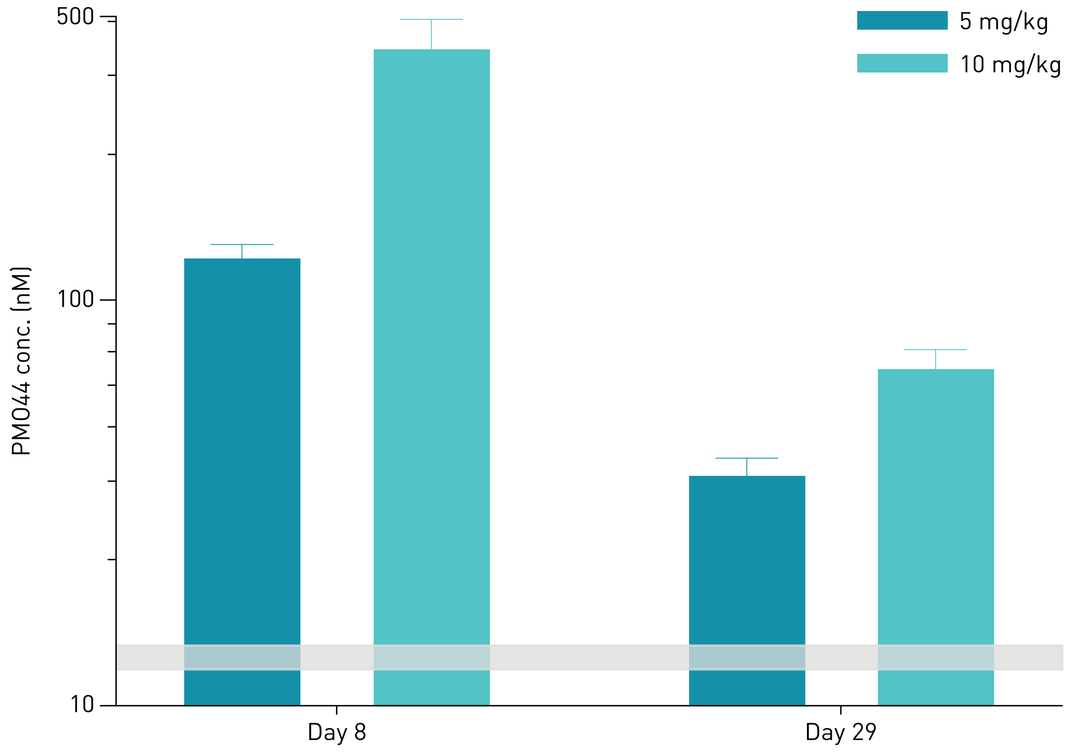


Figure 3: Data shown as mean and standard error. Gray bar indicates PMO44 muscle concentration associated with 5% dystrophin production in preclinical model.

Figure 4: Exon Skipping at Day 29 in Healthy Volunteers

- AOC 1044 treatment resulted in statistically significant levels of exon skipping following a single dose of 5 mg/kg or 10 mg/kg

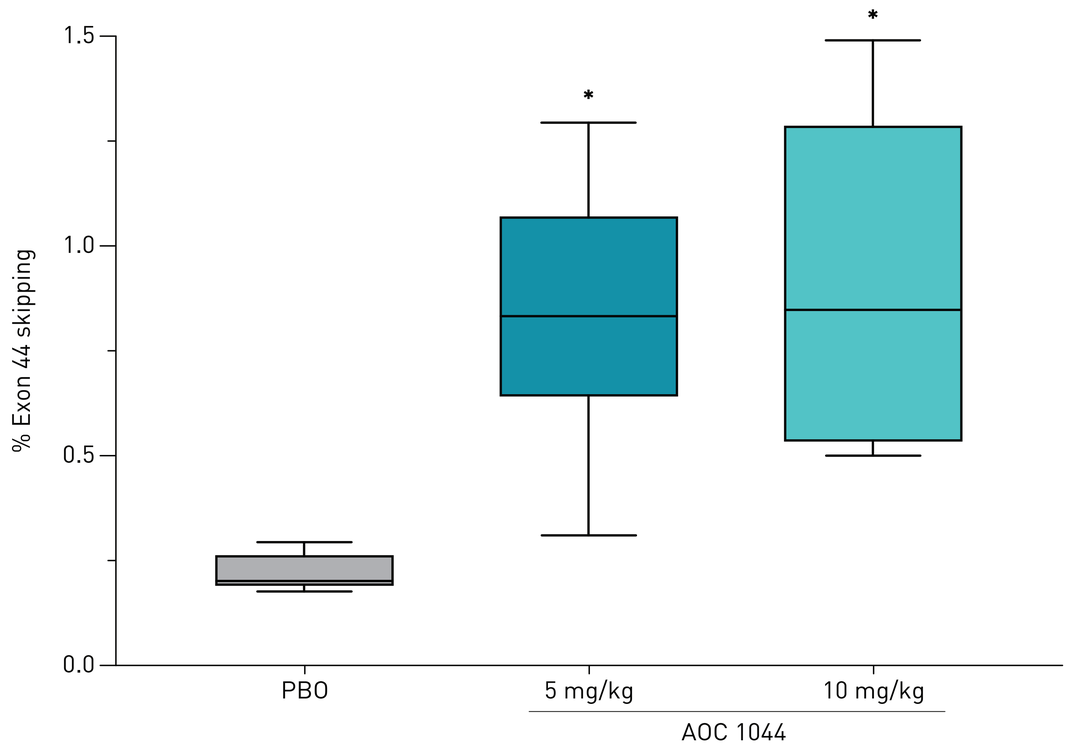


Figure 4: Data presented as a boxplot: 25th and 75th quartiles, line represents mean with 5% and 95% confidence interval.
* Indicates statistically significant difference relative to PBO utilizing Mann–Whitney test ($P<0.05$). One participant in the 10 mg/kg cohort did not have a Day 29 biopsy.

Conclusions

- These data represent the first-in-human experience using an AOC™ to deliver PMOs to muscle
- AOC 1044 was well tolerated in HVs up to 10 mg/kg. All treatment-emergent adverse events in participants dosed with AOC 1044 were mild to moderate
- AOC 1044 achieved robust delivery to muscle with tissue concentrations in HVs well above that required for 5% dystrophin levels seen in preclinical DMD44 models
- AOC 1044 delivered up to 50 times greater concentrations of PMO in skeletal muscle following a single dose compared with peptide conjugated PMOs in HVs
- AOC 1044 produced statistically significant exon 44 skipping compared with placebo of up to 1.5% in HVs after a single dose of 10 mg/kg AOC 1044 at Day 29. AOC 1044 increased exon skipping in all participants
- Persistently high levels of PMO and exon skipping on Day 29 support the potential for AOC 1044 to result in accumulation of exon 44-skipped transcripts and dystrophin protein in DMD patients over an extended dosing interval
- These data support the continued evaluation of AOC 1044 in Part B of the Phase 1/2 EXPLORE44™ trial in DMD patients amenable to exon 44 skipping

References and Abbreviations

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.** Roberts TC, et al. *Nat Rev Drug Discov*. 2020;19(10):673-94. **5.** Aartsma-Rus A, et al. *BMC Medical Genetics*. 2007;8(43);2. **6.** Clinicaltrials.gov. NCT05670730 [EXPLORE44]. https://clinicaltrials.gov/ct2/show/NCT05670730. Accessed February 2024.

AOC, antibody-oligonucleotide conjugate; BMI, body mass index; DMD, Duchenne muscular dystrophy; DMD44, Duchenne muscular dystrophy amenable to exon 44 skipping; HV, healthy volunteer; PBO, placebo; PMO, phosphorodiamidate morpholino oligomer; PMO44, phosphorodiamidate morpholino oligomer for skipping exon 44; TEAE, treatment-emergent adverse event.

MDA Clinical & Scientific Conference | Orlando, FL | March 3–6, 2024