Antibody-Oligonucleotide Conjugates (AOCs) Demonstrate Potent and Durable Exon Skipping and Dystrophin Restoration in a Mouse Model of Duchenne Muscular Dystrophy

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DISCLOSURES:
• Dr. Karamanlidis is an employee of Avidity Biosciences
• He has received stock or an ownership interest from Avidity Biosciences
DMD is a Rare and Severe Genetic Disorder With Unmet Medical Need

- DMD is an X-linked neuromuscular disorder that affects ~1:5,000 male births, equivalent to ~300,000 worldwide\(^1,2\)
- Progressive muscle degeneration, wasting, and paralysis generally leads to death via respiratory and/or cardiac failure in the third-to-fourth decade of life\(^3\)
- DMD is caused by no-to-minimal production of dystrophin protein due to frameshift mutations in the\(^{DMD}\) gene; one or more missing exons\(^4\)

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DMD, Duchenne muscular dystrophy.
Restoration of Dystrophin Protein by Oligonucleotide-Mediated Exon Skipping

Example of exon 44 skipping in DMD patients with Δ45

DMD, Duchenne muscular dystrophy; mRNA, messenger ribonucleic acid; WT, wild type.
The *mdx* Mouse is the Most Widely Used Animal Model for DMD Research

The *mdx* mouse has a stop codon mutation in exon 23 on the DMD gene that disrupts full-length dystrophin expression.
AOCs: A Powerful New Class of Drugs That Efficiently Delivers Oligonucleotides to Striated Muscle

Antibody–Oligonucleotide Conjugate (AOC)

AOC, antibody–oligonucleotide conjugate; BLOQ, below limit of quantification; mAb, monoclonal antibody; PMO, phosphorodiamidate morpholino oligomer; PPMO, peptide-conjugated PMO; RxR, peptide sequence (RXR)4XB; TfR1, transferrin receptor 1.
mAOC-23 Treatment Produces Dose-Dependent and Long-Lasting Dystrophin Restoration in *mdx* Mice

**Exon 23 Skipping (RNA)**

28 Days Post Dose (*mdx* Mice)

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<tr>
<th>Time (Days Post Dose)</th>
<th>PBS</th>
<th>mAOC-23 10 mg/kg</th>
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**Homogeneous Dystrophin (Red)**

Restoration in a Quadriceps Cross-Section (28 Days Post Dose)

**Dystrophin Protein Restoration**

28 Days Post Dose (*mdx* Mice)

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* *p*<0.05

AOC, antibody–oligonucleotide conjugate; PBS, phosphate buffered saline; RNA, ribonucleic acid; WT, wild type.
mAOC-23 Improved Muscle Function in *mdx* Mice

*mdx* mice treated with a single dose of mAOC-23 show functional improvement *in vivo* (28 days post dose)

*AOC, antibody–oligonucleotide conjugate; PBS, phosphate buffered saline; WT, wild type.*

* *p*<0.05
mAOC-23 Improved Serum Biomarkers of Muscle Damage in *mdx* Mice, in Addition to Muscle Function

Serum Creatine Kinase

Serum Alanine Aminotransferase

Serum Aspartate Aminotransferase

*p*<0.05

AOC, antibody–oligonucleotide conjugate; PBS, phosphate buffered saline; WT, wild type.
Antibody–Oligonucleotide Conjugates Have the Potential to be Promising Therapeutics for DMD

- AOC technology effectively delivers RNA therapeutics to muscle and heart tissues, primary tissues impacted by DMD
- In a mouse model of DMD, a surrogate AOC demonstrated exon skipping, restoration of dystrophin protein, and subsequent improvement in muscle function
  - The pharmacologic activity was long lasting following a single dose, suggesting the potential for infrequent dose regimens
  - These data support the development of Avidity’s three AOC programs in DMD
- Avidity is advancing AOC 1044 targeting exon 44 skipping for the potential treatment of DMD, which is anticipated to be in the clinic by the end of 2022
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