Phase 1/2 Clinical Trial Evaluating the Safety and Pharmacokinetics of AOC 1001 in Adults with Myotonic Dystrophy Type 1: MARINA Trial in Progress

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DISCLOSURES:
- Dr. Johnson has received personal compensation for serving as a consultant for Acceleron Pharma, Arthex, Avidity Biosciences, Dyne Therapeutics, Juvena, ML Bio, Sarepta Therapeutics, Triplet Therapeutics, and Vertex Pharma
- He has received personal compensation for serving on data safety monitoring board for Biogen
- He has stock or an ownership in ML Bio
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Data previously presented at the Avidity Virtual Investor and Analyst Event on December 14th, 2022.
There are no FDA-Approved Disease-Modifying Therapies for DM1, and Current Medical Treatment is Focused on Symptom Management\textsuperscript{1,2}

DM1, myotonic dystrophy type 1; FDA, US Food and Drug Administration; US, United States.

- DM1 is a complex disease with symptoms that present with high variability from patient to patient\textsuperscript{1}
- Autosomal-dominant, progressive disease that primarily affects muscle (skeletal, cardiac, and smooth)\textsuperscript{4,5}
- Increases in severity from generation to generation\textsuperscript{4,5}
- Significant impact on quality of life\textsuperscript{6,7}
- Shortened life expectancy\textsuperscript{6,7}
DM1 is Caused by a Toxic Gain-of-Function mRNA due to Increased CUG Repeats

**Normal Conditions**

DMPK mRNA

![Diagram of normal splicing](image)

**Mechanism of Disease**

Mutant DMPK mRNA sequesters RNA regulatory proteins such as MBNL

![Diagram of disease splicing](image)

DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; MBNL, muscleblind like; mRNA, messenger ribonucleic acid.

DM1 is Caused by a Toxic Gain-of-Function mRNA and is Well Suited to an siRNA Approach

**Mechanism of Disease**¹⁻³

- DMPK mRNA
- MBNL Sequestration in Nuclear Foci
- Mutant DMPK mRNA

AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; MBNL, muscleblind like; mRNA, messenger ribonucleic acid; siRNA, small inhibitory ribonucleic acid.

**Potential Therapeutic Approach**

AOC 1001

- MBNL Release Reduce Nuclear Foci
- Knock Down of DMPK

Reduces mRNA Splicing Errors

AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; MBNL, muscleblind like; mRNA, messenger ribonucleic acid; siRNA, small inhibitory ribonucleic acid.

AOC 1001 is an Investigational AOC

• The main components of AOC 1001 are:
  • Antibody: human TfR1-targeting, effector function-null, humanized IgG1 antibody (TfR1 mAb)
  • Non-cleavable linker
  • Oligonucleotide: double-stranded siRNA oligonucleotide (siDMPK.19) that is complementary to a sequence in the 3’ untranslated region (exon 15) of both wild-type and mutant-human DMPK mRNA

• The TfR1 mAb targets muscles for delivery of siDMPK.19 into the cytoplasm and nucleus where it mediates DMPK mRNA degradation

• We are currently evaluating the safety and tolerability of single and multiple ascending doses of AOC 1001 in adults with DM1 in a Phase 1/2 clinical study

AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; IgG, immunoglobulin G; mAb, monoclonal antibody; mRNA, messenger ribonucleic acid; siDMPK, small inhibitory DM1 protein kinase; siRNA, small inhibitory ribonucleic acid; TfR1, transferrin receptor 1.

MARINA™ and MARINA-OLE™ Allow for Both Short- and Long-term Data Collection to Evaluate AOC 1001*

- **N = ~44 Ages 18-65 (3:1 randomization)**
- **Part A** receives single IV dose
- **Part B** receives multi-ascending IV doses
  - Quarterly doses - 1 booster after first 6 weeks
  - 6-month treatment and observation duration

*Sept. 2022, FDA placed a partial clinical hold on new participant enrollment. All current participants may continue in their current dosing cohort. Avidity is working to resolve the partial clinical hold as quickly as possible.
Early Data from MARINA Mid-Point at 6 Weeks Post 1 or 2 Doses of AOC 1001

- Safety includes all cohorts (including 4mg/kg) with a data cutoff of November 17, 2022
- Day 92 biopsy in 2mg/kg cohort taken prior to third dose of AOC 1001

*One participant in the 1mg/kg cohort had insufficient tissue for analysis
**Due to timing, one splicing sample from the 2 mg/kg cohort will be evaluated in the next batch analysis

Data at 3 Months: n=19 participants*
- 1mg/kg Cohort (n=5 active participants)
- 2mg/kg Cohort (n=9 active participants)
- Pooled placebo (n=5 participants)
Baseline Demographics* Generally Well Matched Between Cohorts

Cohort A and B1 Enrolled Participants with Mild-Moderate Disease Severity

<table>
<thead>
<tr>
<th>Mean (Range) or Number of subjects</th>
<th>Cohort A (1 mg/kg) N=8</th>
<th>Cohort B1 (2 mg/kg) N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37.9 (21–64)</td>
<td>38.8 (18-60)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male: 2 / Female: 6</td>
<td>Male: 1 / Female: 11</td>
</tr>
<tr>
<td>BMI</td>
<td>22.0 (16.1–29.2)</td>
<td>25.0 (17.5–32.0)</td>
</tr>
<tr>
<td>Mean CTG repeat length (range)</td>
<td>504 (150-725)</td>
<td>707 (150-1250)</td>
</tr>
<tr>
<td>Baseline splicing (composite of 22 splicing events; higher number is more severe)</td>
<td>74 (38-96)</td>
<td>72 (39-105)</td>
</tr>
</tbody>
</table>

*Preliminary results based on live, unlocked clinical database – numbers subject to change
<table>
<thead>
<tr>
<th>Subjects with ≥ 1 AE n (%)</th>
<th>Placebo n=10</th>
<th>1mg/kg n=6</th>
<th>2mg/kg n=9</th>
<th>4mg/kg n=13</th>
<th>Total AOC 1001 N=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>8 (80%)</td>
<td>6 (100%)</td>
<td>9 (100%)</td>
<td>12 (92%)</td>
<td>27 (96%)</td>
</tr>
<tr>
<td>Related to study drug</td>
<td>2 (20%)</td>
<td>1 (17%)</td>
<td>3 (33%)</td>
<td>10 (77%)</td>
<td>14 (50%)</td>
</tr>
<tr>
<td>Serious AE (SAE)</td>
<td>0</td>
<td>0</td>
<td>1 (11%)</td>
<td>1 (8%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>AE leading to study discontinuation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

- **Majority of treatment emergent adverse events (AEs) were mild or moderate**
  - The most common in the study were COVID-19 (16%) and headache (16%)
  - Other AEs include:
    - Infusion related reactions
    - Reductions in hemoglobin
    - Elevations in ASTs or ALTs
      - No changes in bilirubin
    - No thrombocytopenia and no renal impairment reported

- **2 Serious Adverse Events (SAEs)**
  - 1 SAE in the 4mg/kg cohort resulted in a partial clinical hold†
  - 1 unrelated SAE in reaction to opioid pain medication after an elective surgery

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*Preliminary results based on live, unlocked clinical database – numbers subject to change
†Patient discontinued from the study after the database cut 17-Nov-2022 data cutoff.
AOC 1001 Delivered siRNA to Muscle in a Dose-Proportional Manner

Dose Proportional Increase in Tibialis Anterior Muscle siRNA Concentrations

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Concentrations in the 1 mg/kg cohort that were measurable but below lower limit of quantitation were imputed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg single dose (n=6)</td>
<td>1</td>
<td>Box plots represent median, 25th and 75th percentiles, and 1.5x interquartile range</td>
</tr>
<tr>
<td>2 mg/kg Q6W x 2 (n=8)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4 mg/kg Q6W x 2 (n=3)</td>
<td>4</td>
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</table>
All AOC 1001-Treated Participants Showed *DMPK* mRNA Reduction

All Treated Participants Demonstrate *DMPK* mRNA Reduction

Data shown at 6 weeks post a single dose of the 1 mg/kg and 6 weeks post two doses of 2 mg/kg

Mean % *DMPK* mRNA Reduction

Placebo group combined from both cohorts and shown as standard error of the mean

*One participant in the 1mg/kg cohort had insufficient tissue for analysis
Muscle-Specific Biomarkers Shows 31% Splicing Improvement

**Muscle-Specific Splicing Panel in Tibialis Anterior for Individual Patients**

Muscle panel: CLCN1, CACNA1S, ATP2A1, BIN1
Data shown at 6 weeks post a single dose of the 1 mg/kg and 6 weeks post two doses of 2 mg/kg

Splicing measured by targeted RNA sequencing and calculated using published formula (Tanner et. al 2021)
Splicing index for each participant is calculated as absolute change from baseline (4-gene panel)
Data represented as 6 weeks post last dose with placebo group combined from all cohorts
AOC 1001 Shows Early Signs of Myotonia Reduction

Early Responder from **Cohort A (1 mg/kg)**

**Participant from 1 mg/kg Single Dose**

- **Baseline vHOT**
- **Day 43 vHOT**
  - 6 weeks after single dose
- **Day 92 vHOT**
  - 12 weeks after single dose
- **Day 183 vHOT**
  - 24 weeks after single dose

Improvement visible at Day 43 but myotonia benefit wanes by 6 months following a single dose at 1 mg/kg

vHOT, video hand opening time.
AOC 1001 Shows Early Signs of Myotonia Reduction
Early Responder from **Cohort B1 (2 mg/kg)**

**Participant from 2 mg/kg Multidose**

- **Baseline vHOT**
- **Day 43 vHOT** 6 weeks after first dose
- **Day 92 vHOT** 6 weeks after second dose
- **Day 183 vHOT** 12 weeks after third dose

Improvement visible at Day 43 that is sustained for at least 12 weeks following the third dose at 2 mg/kg

vHOT, video hand opening time.
Delivering on the Platform and Impacting Disease Mechanism

- DM1 is an underrecognized, progressive, and often fatal neuromuscular disease with a high unmet need and no approved therapies
- Data presented provide an early mid-point look at MARINA 6 weeks post 1 or 2 doses of AOC 1001
  - Baseline demographics are generally well matched between cohorts
  - Generally favorable safety and tolerability profile
- AOC 1001 has demonstrated successful delivery of siRNA to muscle and meaningful DMPK reduction in 100% of treated participants
- Splicing improvements demonstrated AOC 1001 activity in the nucleus
  - 31% improvement in key muscle-specific panel
- AOC 1001 showed early signs of myotonia improvement just weeks after dosing with the two lowest doses in the trial
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