Topline Safety and Efficacy Data Analysis of Phase 1/2 Clinical Trial Evaluating AOC 1001 in Adults with Myotonic Dystrophy Type 1: MARINA™

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Disclosures

• Dr. Johnson has received personal compensation for serving as a consultant for Arthex Biotech, Avidity Biosciences, Dyne Therapeutics, Juvena Therapeutics, Kate Therapeutics, Pepgen, Rgenta Therapeutics, Sarepta Therapeutics, Takeda Pharmaceuticals, and Vertex Pharmaceuticals
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The Underlying Mechanism of DM1 is Well Suited to an siRNA Approach Using an Antibody Oligonucleotide Conjugate (AOC)

- DM1 is caused by the mutant DMPK mRNA with CUG expansion sequestering CUG binding proteins which leads to mis-splicing of downstream genes\(^1\)\(^,\)\(^2\)
- Decreasing the amount of mutant DMPK mRNA has the potential to free up the CUG binding proteins and reverse mis-splicing\(^3\)

AOC 1001 includes\(^4\):
- **Antibody**: human TfR1-targeting, effector function-null, humanized IgG1 antibody (TfR1 mAb)
- **Non-cleavable linker**
- **Oligonucleotide**: double-stranded siRNA oligonucleotide complementary to both wild-type and mutant DMPK mRNA

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AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; IgG, immunoglobulin G; mAb, monoclonal antibody; MBNL, muscleblind-like RNA-binding protein; mRNA, messenger ribonucleic acid; siRNA, small inhibitory ribonucleic acid; TfR1, transferrin receptor 1.

MARINA™ Trial Designed to Evaluate Safety and Tolerability of AOC 1001*

<table>
<thead>
<tr>
<th>Dose Booster</th>
<th>MARINA™</th>
<th>MARINA-OLE™</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg</td>
<td>A (N=8)</td>
<td>AOC 1001, n=6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo, n=2</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>B1 (N=12)</td>
<td>AOC 1001, n=9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo, n=3</td>
</tr>
<tr>
<td>4 mg/kg</td>
<td>B2 (N=18)</td>
<td>AOC 1001, n=13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo, n=5</td>
</tr>
</tbody>
</table>

- One participant receiving 4 mg/kg AOC 1001 discontinued treatment due to SAE
- All eligible participants (N=37) have enrolled in the MARINA-OLE™

In May 2023, the FDA eased the partial clinical hold placed in September 2022 to allow a number of current participants to be dose-escalated to 4 mg/kg of AOC 1001 and new participant enrollment at 2 mg/kg of AOC 1001.

3Booster dose was only given to participants who were in Cohort A1 and placebo B1/B2.

FDA, US Food and Drug Administration; SAE, serious adverse event; siRNA; small inhibitory ribonucleic acid.
### Generally Favorable Safety and Tolerability

#### Summary of Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>Subjects with ≥ 1 AEv (%)</th>
<th>MARINA</th>
<th>MARINA-OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=10</td>
<td>1 mg/kg N=6</td>
</tr>
<tr>
<td>Any AE</td>
<td>8 (80%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>AE related to study drug</td>
<td>2 (20%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Serious AE (SAE)*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAE related to study drug</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to study discontinuation*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

10 participants treated with placebo in MARINA were newly treated with AOC 1001 in MARINA-OLE

Over 200 infusions of AOC 1001 totaling 46.2 patient-years of exposure#

Most treatment emergent adverse events (AEs) were mild or moderate†

- **MARINA:** Most common AEs
  - procedural pain (36%), anemia† (32%), COVID-19 (23%), headache (23%), nausea (23%)
  - 1 discontinuation due to an SAE
- **MARINA-OLE:** Most common AEs
  - Procedural pain (22%)
  - Pain in extremity and headache (16%)
  - No discontinuations

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*1 SAE considered related to AOC 1001 4 mg/kg: resulted in a partial clinical hold & patient discontinuing from treatment; 1 SAE considered unrelated to treatment: reaction to opioid pain medication after an elective surgery

2 SAEs in same patient, considered unrelated to treatment (cholelithiasis which resulted in pancreatitis; resolved by cholecystectomy)

# As of August 2023

†Anemia was asymptomatic except for 1 participant who did not require medical intervention
Update on FDA Partial Clinical Hold on AOC 1001

• In September 2022, the FDA placed a partial clinical hold on new participant enrollment in the MARINA™ study in response to a serious adverse event reported in a single participant in the 4 mg/kg cohort comprising bilateral ischemia in the region of the lateral geniculate nuclei in the thalamus with subsequent hemorrhagic transformation. This was described as thalamic hemorrhage.

• Comprehensive investigation by Avidity found no plausible biological link to any component of AOC 1001, the AOC platform, the transferrin receptor delivery mechanism or reduction of DMPK.

• In May 2023, partial hold was eased to allow enrollment of new participants at the 2 mg/kg dose and to dose escalate 12 participants from 2 mg/kg to 4 mg/kg.
Participants Treated With AOC 1001 Demonstrated Improvements in Myotonia and Hand Strength

**Video Hand Opening Time (vHOT)**

- Participants treated with AOC 1001 demonstrated improvements in myotonia and hand strength.

**Hand Grip**

- Error bars = standard error of the mean (SEM)
- Measurements for vHOT are based on middle finger opening time. Statistical analysis was post-hoc.
- Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
- Post-hoc statistical analysis show p<0.05.
- DM1, myotonic dystrophy type 1; vHOT, video hand opening time.
AOC 1001 Demonstrates Myotonia Reduction Across 4 mg/kg Cohort*
vHOT is measuring hand flexor myotonia and hand extensor muscle strength

Participant from 4 mg/kg Multidose

Baseline vHOT

Day 183 vHOT
12 weeks after third dose

Improvement visible 12 weeks following the third dose at 4 mg/kg

vHOT, video hand opening time.
*improvements also seen in participants in 1 and 2 mg/kg cohorts
Improvements in Strength Measured by Quantitative Muscle Testing (QMT) Total and Manual Muscle Testing (MMT) Composite Scores

Error bars = standard error of the mean.
*QMT Total Score is based on 6 muscle groups from both upper and lower body: Ankle dorsiflexion, hand grip, elbow flexion, elbow extension, knee flexion, knee extension
†Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
‡Post hoc statistical analysis show p<0.05 for Cohort B2 (4 mg/kg)

MMT, manual muscle testing; QMT, quantitative muscle testing.
Consistent with Improvement in Total QMT Score, Improvements also Demonstrated in Both Upper and Lower Extremities

Error bars = standard error of the mean.

1Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
2Post hoc statistical analysis show *p*<0.05.
3QMT, quantitative muscle testing.
Directional Improvements Were Observed in Functional & Patient Reported Measures:
10-Meter Walk Run Test (10mWRT), Timed Up and Go (TUG), and the DM1-Activ Patient Reported Outcome (PRO)

Error bars = standard error of the mean.
†Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
10mWRT, 10-meter walk run test; TUG, timed up and go test; DM1-ACTIV patient reported outcome
MARINA™ Phase 1/2 Trial Demonstrates AOC 1001 Impacts Disease Mechanism and Demonstrates Functional Improvement

- AOC 1001 consistently demonstrated directional improvement across multiple aspects of DM1 including measures of myotonia, strength, function and patient reported outcome
- MARINA™ trial concluded with 38 participants enrolled and treated with study drug
  - All 37 participants that completed MARINA™ have rolled into the MARINA-OLE™ at 2-4 mg/kg of AOC 1001 and remain ongoing
- Generally favorable safety and tolerability profile
  - ~46 total patient years of exposure accumulated with over 200 doses of AOC 1001 administered*
- Discussions with the FDA on resolving the partial clinical hold are ongoing
- Based on the solid data package from MARINA™, Avidity is now finalizing the AOC 1001 pivotal dose and Phase 3 design
- First look at data from the MARINA-OLE™ study in the first-half of 2024

*As of August 2023, and based on 38 participants treated with AOC 1001 in MARINA™ and/or MARINA-OLE™. FDA, US Food and Drug Administration.