INTRODUCTION

• Myotonic dystrophy type 1 (DM1) is a rare, progressive, neuromuscular disease with a high-uncertain need and no US Food and Drug Administration (FDA)-approved disease-modifying therapies.

• DM1 is an autosomal-dominant, progressive disease that primarily affects muscle (skeletal, cardiac, and smooth).

• The genetic cause of DM1 is due to expansion of the CTG repeat in the 3’ untranslated region of the DM1 protein kinase (encoded by the DMPK gene).

• DM1 is typically characterized by myotonia and muscle weakness leading to dysrhythmia, dysphagia, insomnolence, and respiratory insufficiency.

• These clinical manifestations of disease place a significant burden on patients, affecting their quality of life across multiple domains.

• Current medical treatment for DM1 is focused on symptom management.

Mechanism of Action

• AOC 1001 is an antibody oligonucleotide conjugate (AOC).

• Figure 1 illustrates the structure of AOC 1001 and its components.

• Antibody human transcriber-1 (TfR1) targets, effector function-null humanized IgG1 antibody (TfR1 mAb)

• Oligonucleotides—double-stranded, siRNA oligonucleotides compliment to both 5’ and 3’ ends of the nontoxic drug marker mARNA (NMARNA).

• The TfR1 mAb targets muscle for delivery of siRNA to the cytoplasm and nucleus where it mediates DMPK mRNA degradation.

Table 1: Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Mass (kg)</th>
<th>Median (IQR)</th>
<th>Placebo (n=9)</th>
<th>1 mg/kg (n=9)</th>
<th>2 mg/kg (n=9)</th>
<th>4 mg/kg (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.9 (7.7)</td>
<td>43.8 (5.3)</td>
<td>44.8 (7.2)</td>
<td>44.8 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 / 8</td>
<td>2 / 7</td>
<td>3 / 6</td>
<td>4 / 5</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.7 (3.5)</td>
<td>21.8 (2.5)</td>
<td>23.9 (5.5)</td>
<td>22.7 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Sporicthyropy score</td>
<td>82.9 (11.8)</td>
<td>76.0 (23.0)</td>
<td>76.2 (23.0)</td>
<td>84.3 (10.2)</td>
<td></td>
</tr>
<tr>
<td>GM1C total score (5%)</td>
<td>81.9 (28)</td>
<td>75.7 (27)</td>
<td>79.5 (27)</td>
<td>85.9 (27)</td>
<td></td>
</tr>
<tr>
<td>Video hand opening time (VHOT) (seconds)</td>
<td>10.1 (11.4)</td>
<td>8.0 (4)</td>
<td>9.2 (4)</td>
<td>9.2 (4)</td>
<td></td>
</tr>
<tr>
<td>10-meter walk run test (10mWRT) (meters)</td>
<td>6.4 (2.8)</td>
<td>6.2 (1.1)</td>
<td>6.7 (1.1)</td>
<td>7.7 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Timed hand grip (Handgrip) (N=12)</td>
<td>5.7 (1.5)</td>
<td>5.7 (1.5)</td>
<td>5.7 (1.5)</td>
<td>6.7 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Quantitative muscle testing (QMT) % predicted</td>
<td>5.1 (7.9)</td>
<td>5.1 (7.9)</td>
<td>5.1 (7.9)</td>
<td>5.1 (7.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Number of participants who received a treatment.
†Number of participants who received a treatment in Phase 2/3.
‡Number of participants who received a treatment in Phase 2/3.
§Number of participants who received a treatment in Phase 2/3.

Table 2: Summary of Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Subjects with ≥1 AE</th>
<th>Placebo (n=9)</th>
<th>1 mg/kg (n=9)</th>
<th>2 mg/kg (n=9)</th>
<th>4 mg/kg (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>% moderate or severe</td>
<td>25%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>% severe</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
</tr>
</tbody>
</table>

The most treatment-emergent adverse events (AE) were mild or moderate.

Conclusions

• DM1 is an underoscognized, progressive, and often fatal neuromuscular disease with a high-uncertain need and no approved therapies.

• AOC 1001 is an investigational antibody oligonucleotide conjugate that successfully delivered siRNA to muscle resulting in DMPK mRNA reduction and splicing improvements leading to factorial improvements.

• Top-line data from MARINA™ show demonstration of clinical endpoints in the dose range of 2 mg/kg of AOC 1001 including:

  - Directional improvements in myotonia (VHOT) as early as 6 weeks after dosing with a sustained effect at Month 6
  - Directional improvements in quantitative muscle strength assessments (QMT total, upper and lower extremities) observed at Month 6
  - Early signs of directional mobility improvements in the TUG and the 10mWRT
  - AOC 1001 had a generally favorable safety and tolerability profile

• Data support advancement of AOC 1001 into Phase 3 study

Results

Results in Table 1: Baseline Demographics and Disease Characteristics:

- Age: 44.9 (7.7) years for Placebo, 43.8 (5.3) years for 1 mg/kg, 44.8 (7.2) years for 2 mg/kg, and 44.8 (7.2) years for 4 mg/kg.
- Female: 1/8 for Placebo, 2/7 for 1 mg/kg, 3/6 for 2 mg/kg, and 4/5 for 4 mg/kg.
- Body mass index: 24.7 (3.5) for Placebo, 21.8 (2.5) for 1 mg/kg, 23.9 (5.5) for 2 mg/kg, and 22.7 (4.6) for 4 mg/kg.
- Sporicthyropy score: 82.9 (11.8) for Placebo, 76.0 (23.0) for 1 mg/kg, 76.2 (23.0) for 2 mg/kg, and 84.3 (10.2) for 4 mg/kg.
- GM1C total score (5%): 81.9 (28) for Placebo, 75.7 (27) for 1 mg/kg, 79.5 (27) for 2 mg/kg, and 85.9 (27) for 4 mg/kg.
- Video hand opening time (VHOT) (seconds): 10.1 (11.4) for Placebo, 8.0 (4) for 1 mg/kg, 9.2 (4) for 2 mg/kg, and 9.2 (4) for 4 mg/kg.
- 10-meter walk run test (10mWRT) (meters): 6.4 (2.8) for Placebo, 6.2 (1.1) for 1 mg/kg, 6.7 (1.1) for 2 mg/kg, and 7.7 (1.1) for 4 mg/kg).
- Timed hand grip (Handgrip) (N=12): 5.7 (1.5) for Placebo, 5.7 (1.5) for 1 mg/kg, 5.7 (1.5) for 2 mg/kg, and 6.7 (1.5) for 4 mg/kg.
- Quantitative muscle testing (QMT) % predicted: 5.1 (7.9) for Placebo, 5.1 (7.9) for 1 mg/kg, 5.1 (7.9) for 2 mg/kg, and 5.1 (7.9) for 4 mg/kg.

Most treatment-emergent adverse events (AE) were mild or moderate:

- Most common AEs: Procedure pain (3%), Amnesia (2%), and Shoulder pain (2%).
- 1 severe AE—2 unrelated to treatment and 1 related to treatment was also reported as the SA discussed below.
- 2 SAE—1 SAE considered unrelated to AOC 1001: 1 mg/kg resulting in a partial visual field cut, bilateral ischemia in the region of the lateral geniculate nucleus in the thalamus with subsequent sensori-motor transloc motion.
- 1 SAE considered unrelated to treatment—reaction to spinal pain medication after an elective surgery.

AOC 1001 showed early signs of directional improvements in mobility measures:

- Directional improvements in myotonia were seen in participants treated with AOC 1001.
- Placebo-treated participants treated with AOC 1001 had improvements in total muscle strength at 3 mg/kg and 4 mg/kg.
- AOC 1001 achieved statistical significance at 4 mg/kg compared to placebo in a post-hoc analysis at all time points.