**AOC 1001 Demonstrates DMPK Reduction and Spliceopathy Improvement in a Phase 1/2 Study in Myotonic Dystrophy Type 1 (DM1) (MARINA™)**

**Yiming Zhu, Tanya Kwan, Qingying Meng, Li-Jung Tai, Michelle Lee, Husam Younis, Art Levin, Mike Flanagan**

Avidity Biosciences, Inc., San Diego, CA 92121

---

### Background

Myotonic dystrophy type 1 (DM1) is a rare, autosomal dominant, progressive neuromuscular disease with no US Food and Drug Administration (FDA)-approved therapies. The cause of DM1 is a mutation in myotonic dystrophy protein kinase (DMPK) messenger ribonucleic acid (mRNA) that contains expanded (CUG) repeats (Figure 1A).**†** Mutant DMPK is a toxic gain-of-function protein that leads to nuclear retention (nuclear focus) and sequestration of splicing factors, a muscular disease-like (MBD-like) resulting in global splicing dysregulation.**†**

Given the challenges with delivery of oligonucleotides to muscle, we utilized a transmembrane receptor 1 (TIR1)-mediated delivery system utilizing a DMPK-targeting siRNA and fusion protein to deliver siRNA (AOC™ comprised of an siRNA targeting DMPK mRNAs (AOC-DMPK) conjugated to a humanized monoclonal antibody (MAb) targeting human TIR1 that is designed to reduce DMPK mRNA in muscle tissue and subsequent correct splicing events that are responsible for DM1 pathogenesis (Figure 1B).**†**

**Figure 1: Avidity’s Approach to Targeting DM1**

#### 1a. Mechanism of Disease

- **DMPK** and Drug Administration (FDA)-approved therapies. The cause of DM1 is a mutation in myotonic dystrophy protein kinase (DMPK) mRNA that contains expanded (CUG) repeats (Figure 1A).**†** Mutant DMPK is a toxic gain-of-function protein that leads to nuclear retention (nuclear focus) and sequestration of splicing factors, a muscular disease-like (MBD-like) resulting in global splicing dysregulation.**†**

#### 1b. Potential Therapeutic Approach

- **Lin X, et al.**
- **Weeks Post Second Dose**
- **Ctrl_mock**
- **Tanner MK, et al.**

### Results

**Figure 4: AOC 1001 Reduces DMPK mRNA Levels in DM1 Patients**

#### 4a. DM1 Myotubes in a Clinical Trial

- **3a. Knockdown of DMPK mRNA Expression and Improves Spliceopathy and Nuclear Foci in DM1 Myotubes**
- **3b. Reduction of Nuclei Foci**

#### 4b. Mean Reduction in 22-Gene Splicing Panel

- **3c. 22-Gene Splicing Panel Score Change from Baseline**

### Conclusion

We demonstrate the translation of patient in vitro activity to proof-of-mechanism (DMPK reduction and spliceopathy improvement) of AOC 1001 in a first-in-human clinical study in DM1 patients, supporting AOC 1001 as a potential therapy addressing the underlying cause of DM1.

### Acknowledgments

Investigators, participants, and their families in MARINA™ Association Institut de Myologie for providing control and participants and their families in MARINA™.

### References


### Abbreviations

AOC, antibody oligonucleotide conjugate; CFPM, count per million; DM1, myotonic dystrophy type 1; DMPK, myotonic dystrophy protein kinase; FDA, US Food and Drug Administration; IA, interventricular, MI, muscular dystrophy; MBNL, muscular disease-like; mRNAs, messenger ribonucleic acid; PSI, percent spliced-in; PSO, percent spliced-out; SEM, standard error of the mean; siRNA, small interfering ribonucleic acid; TIR1, transmembrane receptor 1.

---

28th Annual Congress of the World Muscle Society | Charleston, SC | October 3rd–7th, 2023