

# From Myotube to Patient: AOC 1001 Demonstrates DMPK Reduction and Spliceopathy Improvement in a Phase 1/2 Study in Myotonic Dystrophy Type 1 (DM1) (MARINA™)



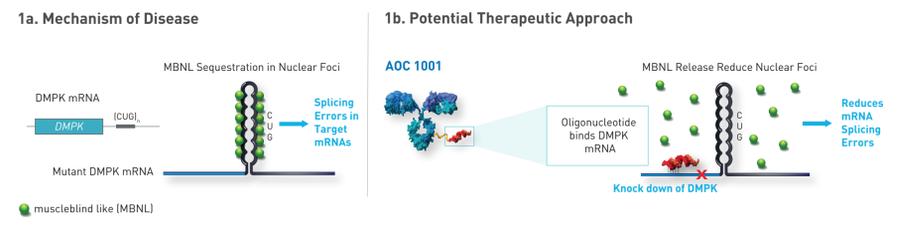
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## Background

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 (>50) CUG repeats (Figure 1a).<sup>1-5</sup> Mutant *DMPK* is a toxic gain-of-function mRNA that leads to nuclear retention (nuclear foci) and sequestration of splicing factors (e.g., muscleblind-like [MBNL]) resulting in global splicing dysregulation.<sup>6</sup>

Given the challenges with delivery of oligonucleotides to muscle, we utilized transferrin receptor 1 (TfR1)-mediated endocytosis to deliver siRNA to skeletal muscle and heart. Thus, AOC 1001 is an antibody oligonucleotide conjugate (AOC™) comprised of an siRNA targeting *DMPK* mRNA (siDMPK) conjugated to a humanized monoclonal antibody (mAb) targeting human TfR1 that is designed to reduce *DMPK* mRNA in muscle tissue and subsequently correct splicing events that are responsible for DM1 pathogenesis (Figure 1b).

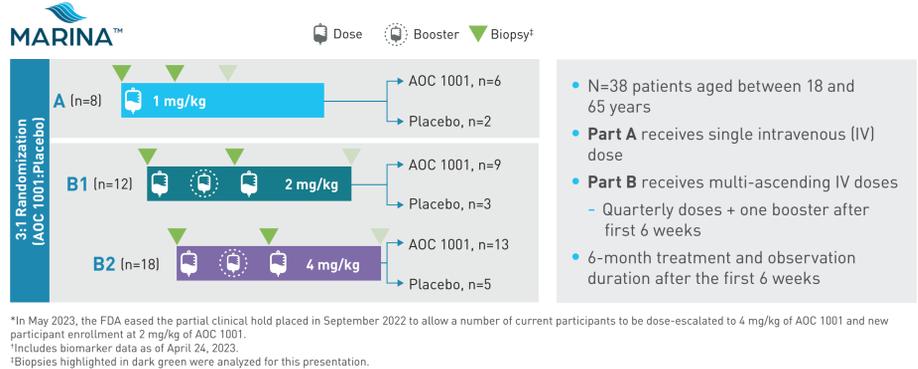
Figure 1: Avidity's Approach to Targeting DM1



## Avidity's Approach to Treating DM1

- The activity of AOC 1001 was evaluated *in vitro* in DM1 patient myotubes and in a clinical trial of patients with DM1.
- DM1 patient myotubes were transfected with siDMPK. Levels of *DMPK* mRNA and splicing events (RNA sequencing) as well as nuclear foci (immunohistochemistry) were evaluated.
- MARINA™ is a Phase 1/2 study (NCT05027269) to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AOC 1001 in adult patients with DM1 (Figure 2)\*. Pre- and 6 weeks post-dose muscle biopsy samples were evaluated for *DMPK* mRNA expression and splicing changes by qPCR and RNA sequencing, respectively.<sup>7</sup>

Figure 2: Study Design of MARINA™ to Evaluate AOC 1001 in DM1



\*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.  
\*Includes biomarker data as of April 24, 2023.  
\*Biopsies highlighted in dark green were analyzed for this presentation.

## Results

Figure 3: siDMPK Reduces *DMPK* mRNA Expression and Improves Spliceopathy and Nuclear Foci in DM1 Myotubes

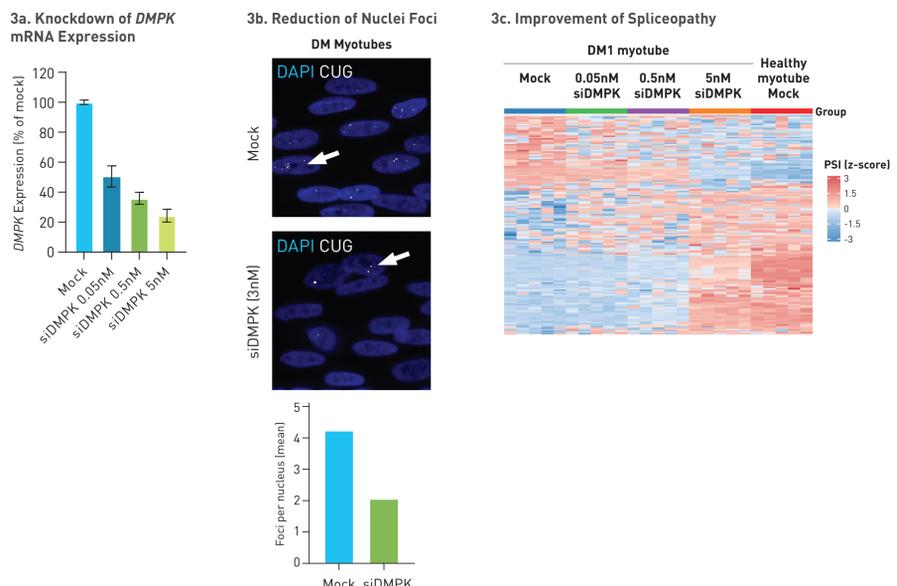


Figure 3: (a) *DMPK* expression in DM1 myotubes after treatment with siDMPK (N=5 replicates, mean + standard deviation). (b) Representative images of CUG-containing nuclei foci and mean foci number per nucleus in mock and siDMPK-treated DM1 myotubes. (c) Over 100 mis-spliced events in DM1 myotubes (FDR<0.05 and  $\Delta$ PSI>20 in DM1 myotube versus healthy myotube) were corrected by siDMPK treatment (N=5 replicates). PSI, percent spliced-in.

## Results (Continued)

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

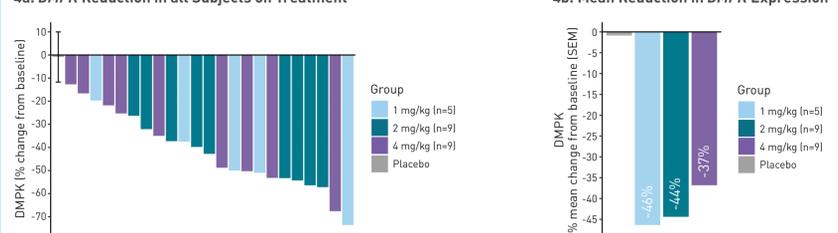


Figure 4: (a) Individual percent change from baseline and (b) mean percent change from baseline of *DMPK* expression 6 weeks post one dose of 1 mg/kg or two doses of 2 or 4 mg/kg AOC 1001. Placebo group combined and shown as mean and standard error of the mean (SEM).

Figure 5: AOC 1001 Improves Splicing of 22-Gene Panel in DM1 Patients

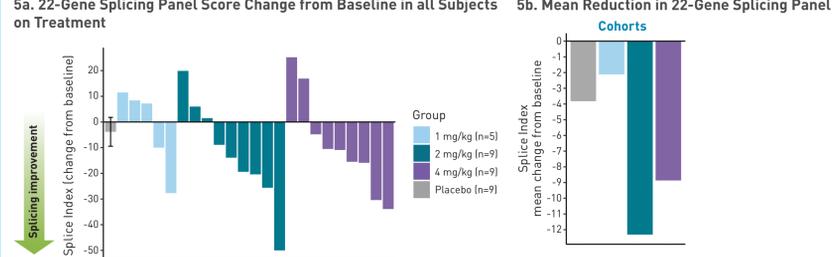
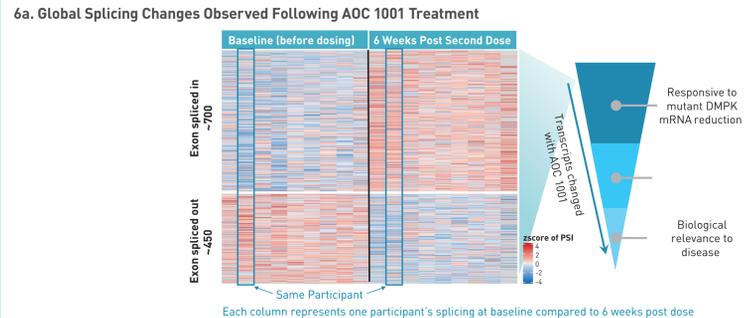
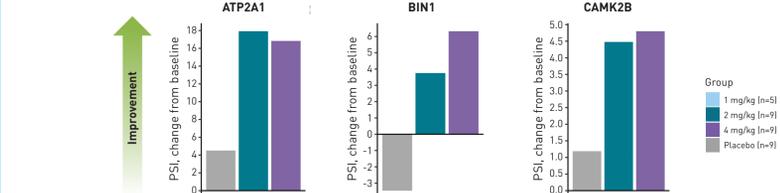


Figure 5: Splicing improvements in 22-gene panel demonstrates AOC 1001 is impacting DM1 disease mechanism. (a) Individual change from baseline and (b) mean change from baseline in 22-gene splicing score 6 weeks post one dose of 1 mg/kg or two doses of 2 or 4 mg/kg AOC 1001. Placebo group combined and shown as mean +/- SEM. Splicing measured by targeted RNA sequencing and calculated using published formula.<sup>8</sup> Mean change from baseline is the mean change from baseline score across all matched samples in a cohort.

Figure 6: AOC 1001 Improves Spliceopathy in DM1 Patients



6b. Mean Splicing Improvement in Genes Related to Muscle Function



6c. Mean Increase of Correctly Spliced Isoform in Genes Related to Muscle Function

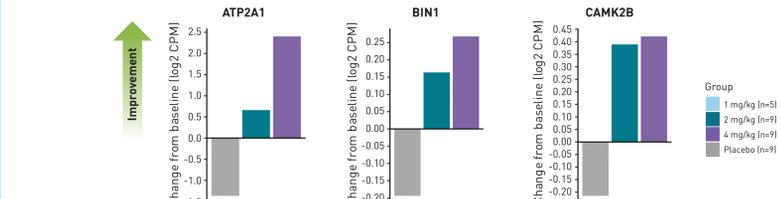


Figure 6: (a) Example of the broad impact AOC 1001 has on global splicing. Bulk RNA sequencing utilized to identify mRNA transcripts with significant splicing changes 6 weeks post second dose of AOC 1001 (2 mg/kg) relative to baseline (p<0.05, mean PSI difference >0.05). (b) PSI change (mean) and (c) expression change of the correctly spliced isoform (mean) of splicing events related to DM1 pathogenesis and muscle function in MARINA participants 6 weeks post second dose of 2 mg/kg or 4 mg/kg AOC 1001.

## Conclusion

We demonstrate the translation of potent *in vitro* activity to proof-of-mechanism (*DMPK* reduction and spliceopathy improvement) of AOC 1001 in a first-in-human clinical study in DM1 participants, 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 DM1 cell lines. CHU de Québec-Université Laval, Canada for providing DM1 patient-derived human primary myoblasts.

## References

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## Abbreviations

AOC, antibody oligonucleotide conjugate; CPM, count per million; DM1, myotonic dystrophy type 1; *DMPK*, myotonic dystrophy protein kinase; FDA, US Food and Drug Administration; IV, intravenous; mAb, monoclonal antibody; MBNL, muscleblind like; mRNA, messenger ribonucleic acid; PSI, percent spliced-in; PS0, percent spliced-out; SEM, standard error of the mean; siRNA, small interfering ribonucleic acid; TfR1, transferrin receptor 1.