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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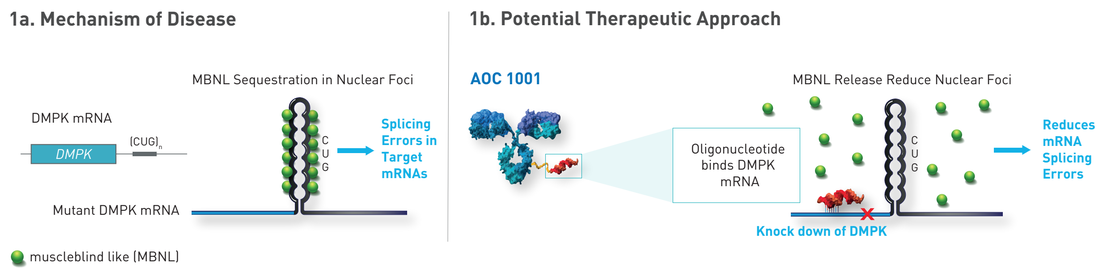
Background

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).[1–5] 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.[6]

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).

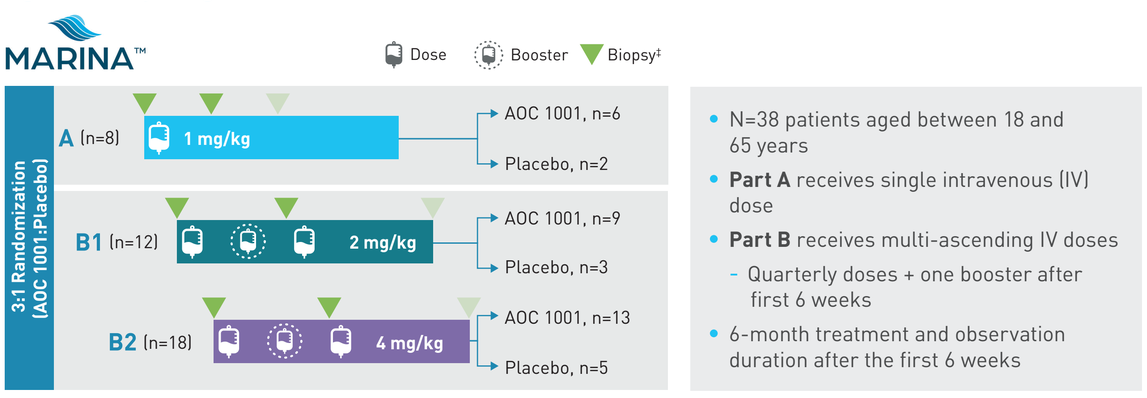
Figure 1: Avidity's Approach to Targeting DM1



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.†

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



- N=38 patients aged between 18 and 65 years
- **Part A** receives single intravenous (IV) dose
- **Part B** receives multi-ascending IV doses
  - Quarterly doses + one booster after first 6 weeks
- 6-month treatment and observation duration after the first 6 weeks

*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 Nuclei Foci in DM1 Myotubes

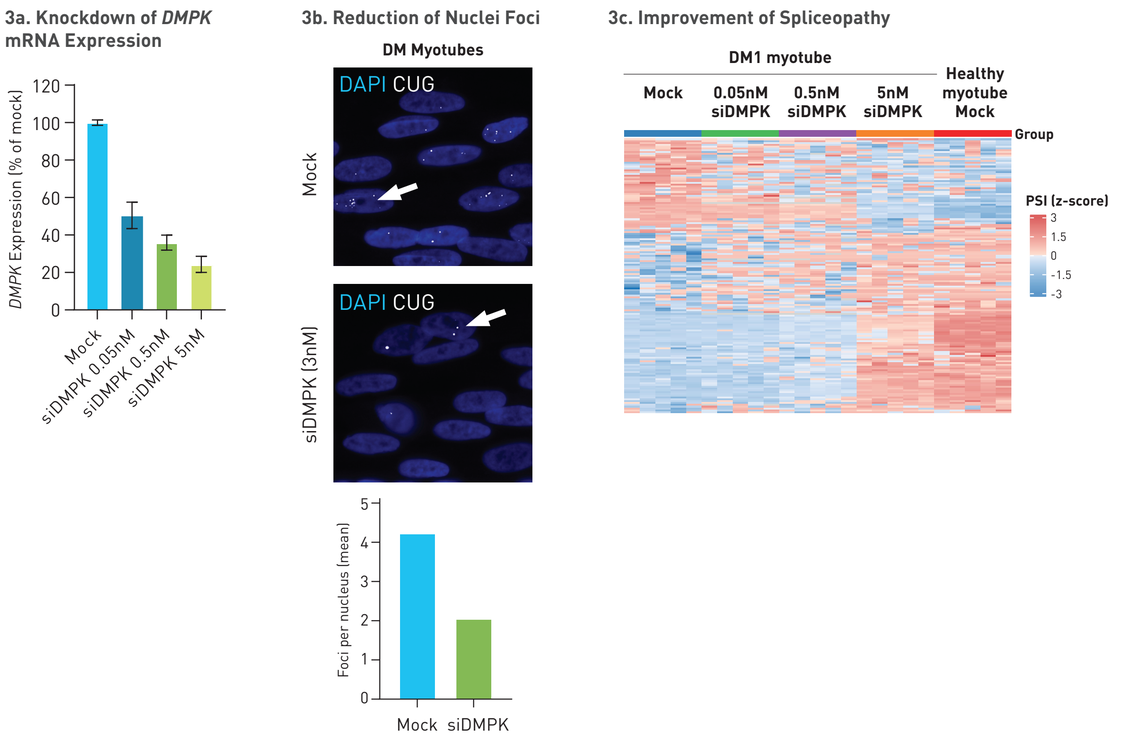


Figure 3: (a) DMPK expression in DM1 myotubes after treatment with siDMPK (N=5 replicates, mean + standard deviation). (b) Representative images of CUG-containing nuclei foci and mean foci number per nucleus in mock and siDMPK-treated DM1 myotubes. (c) Over 100 mis-spliced events in DM1 myotubes (FDR<0.05 and |ΔPSI|>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

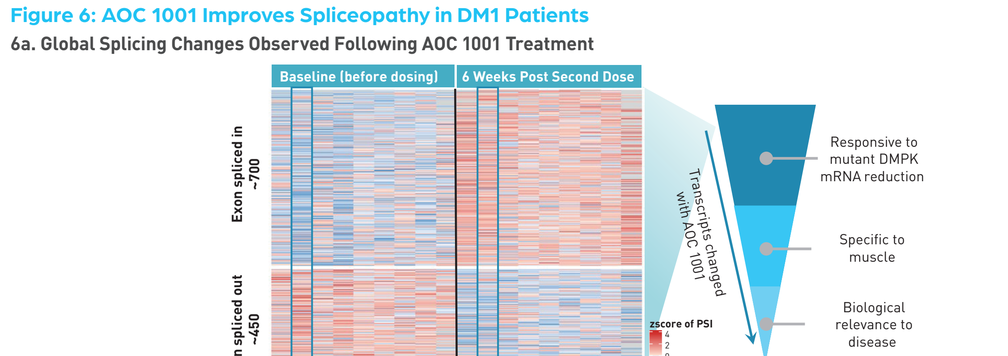


Figure 4: (a) Individual percent change from baseline and (b) mean percent change from baseline of DMPK expression 6 weeks post one dose of 1 mg/kg or two doses of 2 or 4 mg/kg AOC 1001. Placebo group combined and shown as mean and standard error of the mean (SEM).

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

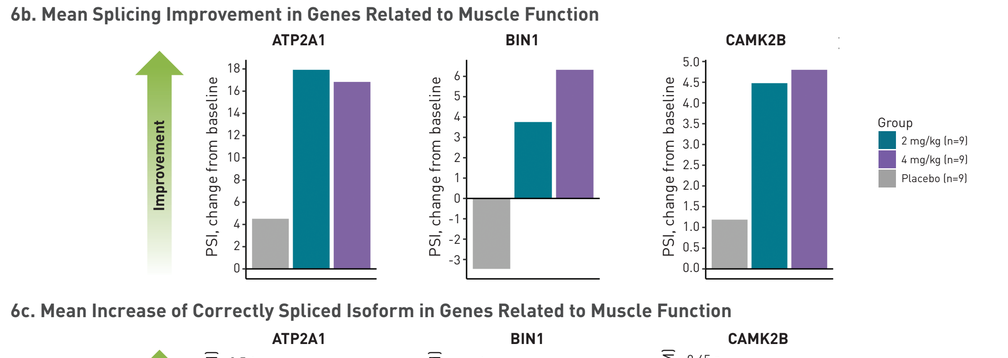


Figure 5: Splicing improvements in 22-gene panel demonstrates AOC 1001 is impacting DM1 disease mechanism. (a) Individual change from baseline and (b) mean change from baseline in 22-gene splicing score 6 weeks post one dose of 1 mg/kg or two doses of 2 or 4 mg/kg AOC 1001. Placebo group combined and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

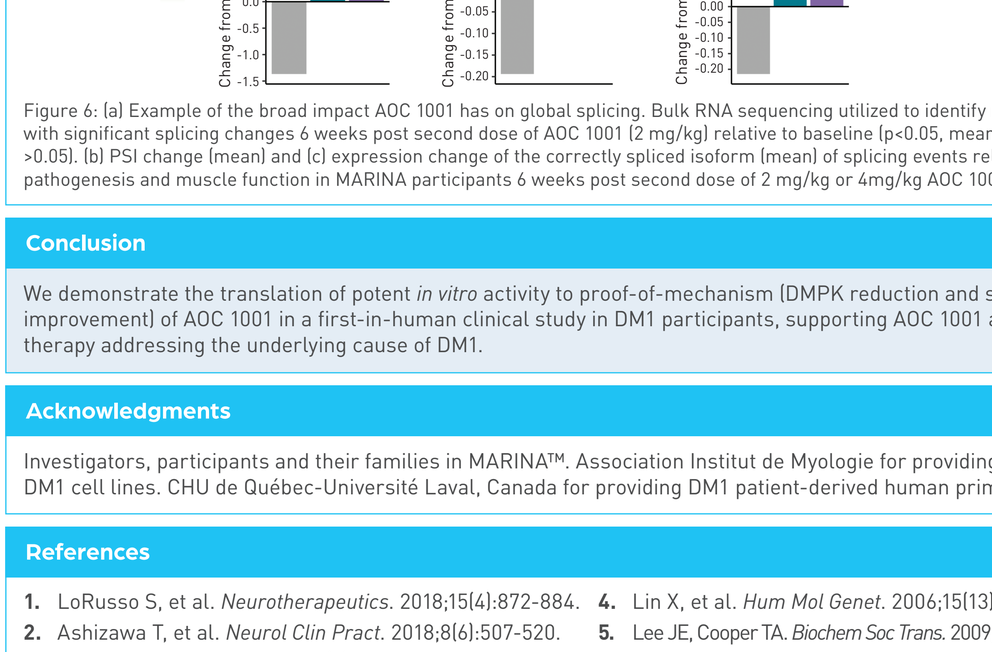


Figure 6: (a) Example of the broad impact AOC 1001 has on global splicing. Bulk RNA sequencing utilized to identify mRNA transcripts with significant splicing changes 6 weeks post second dose of AOC 1001 (2 mg/kg) relative to baseline (p<0.05, mean PSI difference >0.05). (b) PSI change (mean) and (c) 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 4mg/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; PSO, percent spliced-out; SEM, standard error of the mean; siRNA, small interfering ribonucleic acid; TfR1, transferrin receptor 1.

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