Topline Data Analysis of the Phase 1/2 Clinical Trial Evaluating AOC 1001 in Adult Patients with Myotonic Dystrophy Type 1: MARINA™

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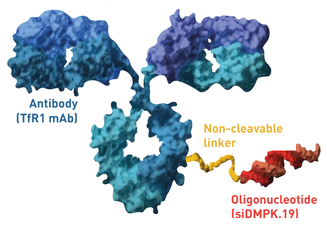
INTRODUCTION

- Myotonic dystrophy type 1 (DM1) is a rare, progressive, neuromuscular disease with a high unmet need and no US Food and Drug Administration (FDA)-approved disease-modifying therapies[1,2]
- DM1 is an autosomal-dominant, progressive disease that primarily affects muscle (skeletal, cardiac, and smooth)[3,4]
- The genetic cause of DM1 is due to expansion of the CTG repeat in the 3' untranslated region of the DM1 protein kinase (*DMPK*) gene, leading to sequestration of RNA regulating proteins and consequently the mis-splicing of multiple downstream genes which results in multiorgan manifestations of DM1[5–7]
- DM1 is typically characterized by myotonia and muscle weakness leading to dysarthria, dysphagia, immobility, and respiratory insufficiency[3,4]
- These clinical manifestations of disease place a significant burden on patients, affecting their quality of life across multiple domains[8,9]
- Current medical treatment for DM1 is focused on symptom management[2]

Mechanism of Action

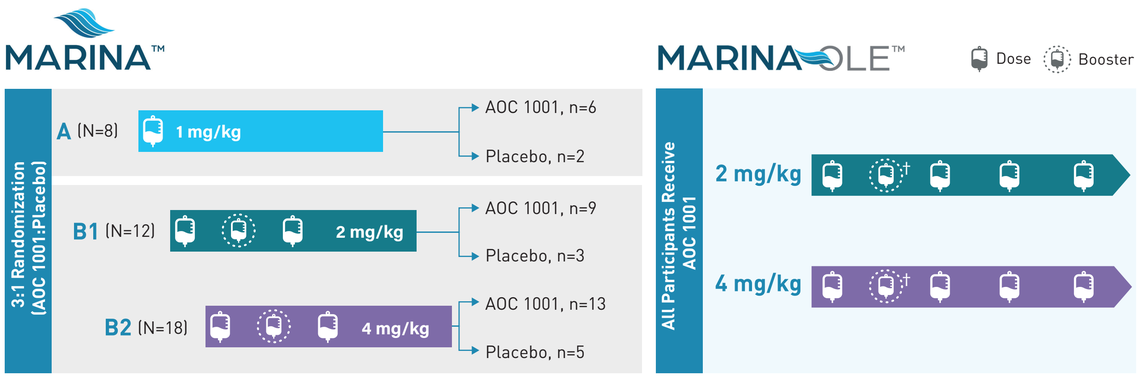
- AOC 1001 is an antibody oligonucleotide conjugate (AOC)
- Figure 1 illustrates the structure of AOC 1001 and its three components:
  - **Antibody:** human transferrin receptor 1 (TfR1) targeting, effector function-null, humanized IgG1 antibody (TfR1 mAb)
  - **Non-cleavable linker**
  - **Oligonucleotide:** double-stranded, siRNA oligonucleotide complementary to both wild-type and mutant DMPK mRNA (siDMPK.19)
- The TfR1 mAb targets muscles for delivery of siDMPK.19 into the cytoplasm and nucleus where it mediates DMPK mRNA degradation

Figure 1: AOC 1001



MARINA™ Trial Design

Figure 2: MARINA™ Trial Designed to Evaluate Safety and Tolerability of AOC 1001*



- One participant receiving 4 mg/kg AOC 1001 discontinued treatment due to a severe adverse event (SAE)
- As of July 28, 2023, 37 participants 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;
†Booster dose was only given to participants who were in Cohort A1 and placebo B1/B2. Dose listed is siRNA. The diagram for the MARINA-OLE™ trial includes the first 12 of the 24 months with quarterly dosing

Results

Table 1: Baseline Demographics and Disease Characteristics

Mean (SD) or n (%)	Placebo n=10	1 mg/kg n=6	2 mg/kg n=9	4 mg/kg n=13
Age	46.5 (8.7)	37.0 (18.0)	37.6 (13.6)	44.0 (12.4)
Female	5 (50)	5 (83.3)	9 (100)	9 (69.2)
Body mass index	24.7 (3.5)	21.8 (5.2)	23.9 (5.0)	22.2 (4.5)
Spliceopathy score*	82.9 (11.8)	70.0 (20.2)	70.2 (20.8)	83.6 (20.2)
CTG repeat length, mean (SD)	616 (380)	463 (198)	675 (274)	585 (250)
Video hand opening time (vHOT) (seconds)†	10.1 (18.6)	6.8 (5.3)	8.0 (6.4)	10.2 (8.4)
10-meter walk run test (10mWRT) (seconds)	6.8 (2.8)	5.2 (3.2)	6.7 (3.1)	7.7 (3.1)
Timed up and go (TUG) (seconds)	6.6 (2.6)	5.7 (2.0)	6.6 (1.5)	7.5 (2.2)
Quantitative muscle testing (QMT)‡ (% pred. nl.)§	51.5 (16.3)	56.3 (13.3)	50.1 (12.0)	41.6 (19.3)

n = number of participants who received at least one dose.
*Composite of 22 splicing events; higher number is more severe; 1 participant in the placebo group and 3 participants in the 4 mg/kg cohort had insufficient tissue for analysis;
†As measured by the middle finger opening time;
‡QMT is a total composite score based on 6 muscle groups tested: hand grip, elbow extension, elbow flexion, ankle dorsiflexion, knee extension, knee flexion;
§% predicted normal.

Table 2: Summary of Treatment–Emergent Adverse Events

Subjects with ≥1 AE n (%)	Placebo n=10	1 mg/kg n=6	2 mg/kg n=9	4 mg/kg n=13
Any AE	8 (80%)	6 (100%)	9 (100%)	13 (100%)
Related to study drug	2 (20%)	1 (17%)	3 (33%)	10 (77%)
SAE	0	0	1 (11%)	1 (8%)
AE leading to study discontinuation*	0	0	0	1 (8%)
AE leading to death	0	0	0	0

*Patient discontinued treatment in the study due to SAE and was lost to follow-up;
†Most common AEs are defined as those above 30% in combined 2 and 4 mg/kg treated participants.

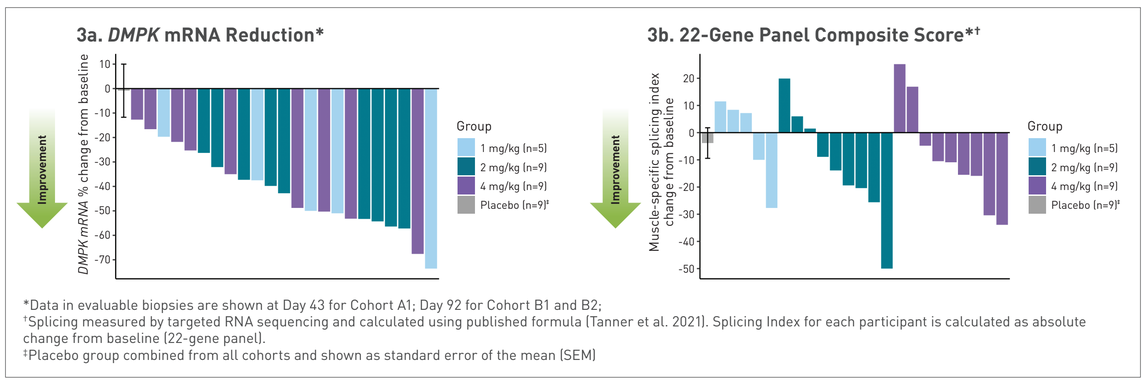
Most treatment-emergent adverse events (AE) were mild or moderate

- Most common AEs†
  - Procedural pain (36%)
  - Anemia (32%)
- 3 severe AEs: 2 unrelated to treatment and 1 related to treatment was also reported as the SAE discussed below

2 SAEs

- 1 SAE considered related to AOC 1001 4 mg/kg (resulted in a partial clinical hold*): bilateral ischemia in the region of the lateral geniculate nuclei in the thalamus with subsequent hemorrhagic transformation
- 1 SAE considered unrelated to treatment: reaction to opioid pain medication after an exlective surgery

Figure 3: AOC 1001 Treatment Led to *DMPK* Reduction and Splicing Improvement

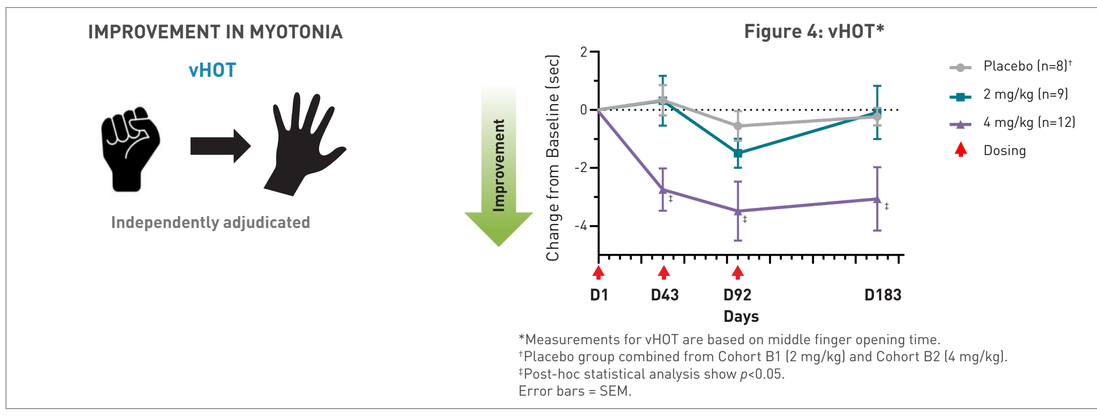


*Data in evaluable biopsies are shown at Day 43 for Cohort A1; Day 92 for Cohort B1 and B2;
†Splicing measured by targeted RNA sequencing and calculated using published formula (Tanner et al. 2021). Splicing Index for each participant is calculated as absolute change from baseline (22-gene panel).
‡Placebo group combined from all cohorts and shown as standard error of the mean (SEM)

Results (continued)

Directional Improvements in Myotonia were Seen in Participants Treated With AOC 1001

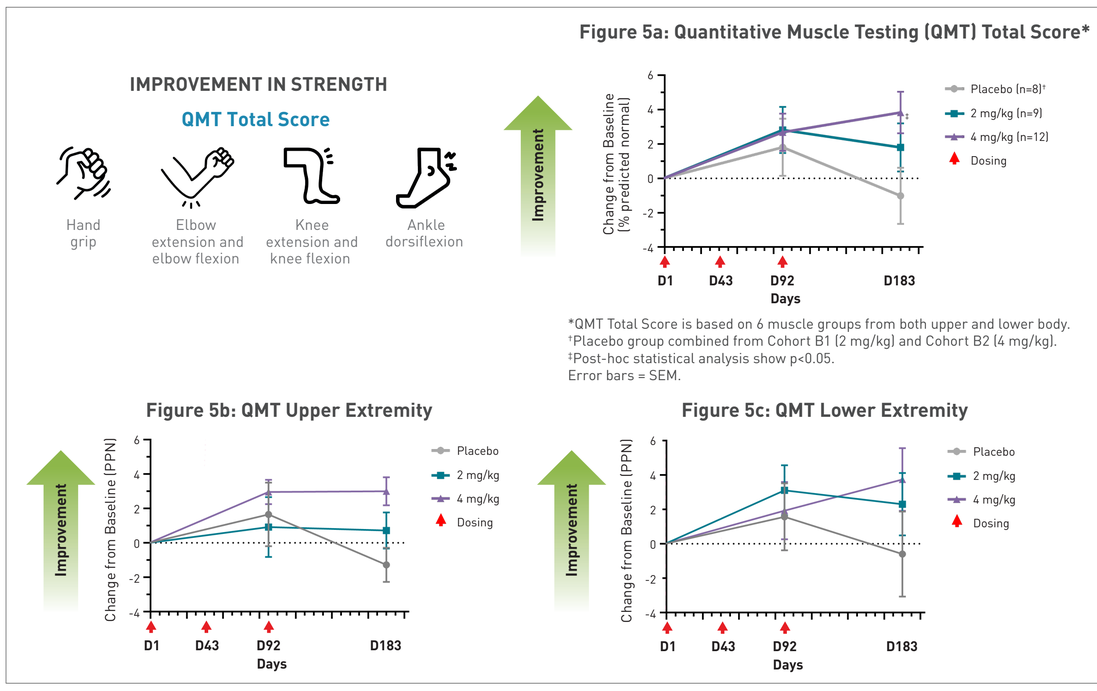
- Participants treated with AOC 1001 demonstrated improvements in myotonia, a hallmark of DM1, at 2 mg/kg and 4 mg/kg
- AOC 1001 achieved statistical significance at 4 mg/kg compared to placebo in a post-hoc analysis at all time points



*Measurements for vHOT are based on middle finger opening time.
†Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
‡Post-hoc statistical analysis show $p<0.05$.
Error bars = SEM.

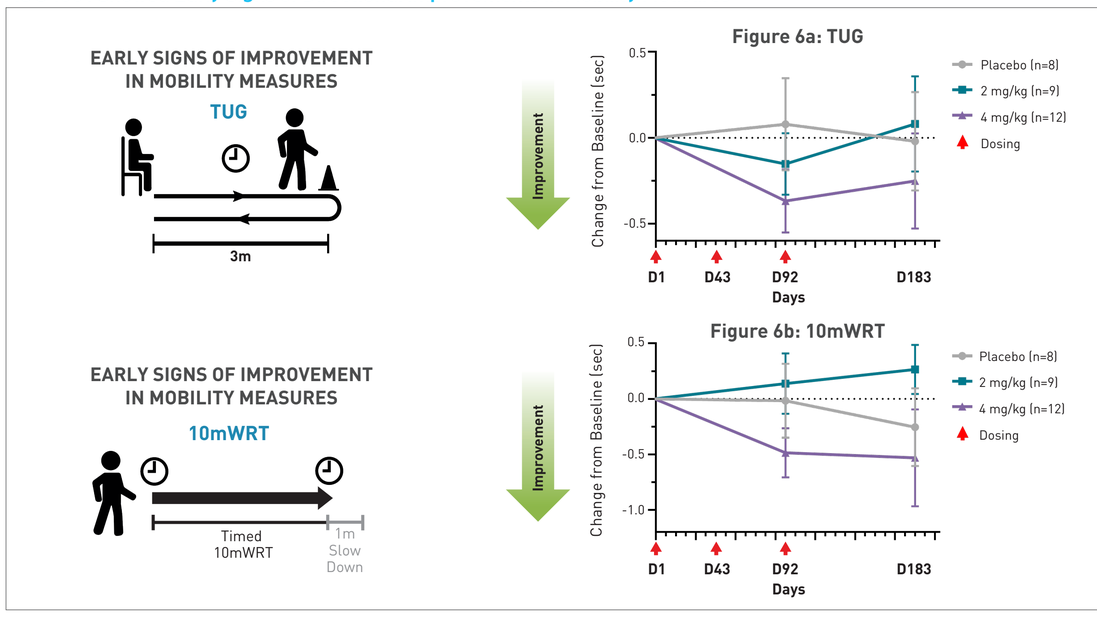
Directional Improvements in Total Muscle Strength were Seen in Participants Treated With AOC 1001

- Participants treated with AOC 1001 had improvements in total muscle strength at 2 mg/kg and 4 mg/kg
- AOC 1001 achieved statistical significance at 4 mg/kg in a post-hoc analysis at Day 183
- Improvement in total composite score is due to improvement in both upper and lower extremity



*QMT Total Score is based on 6 muscle groups from both upper and lower body.
†Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
‡Post-hoc statistical analysis show p<0.05.
Error bars = SEM.

AOC 1001 Showed Early Signs of Directional Improvements in Mobility Measures



Conclusions

- DM1 is an underrecognized, progressive, and often fatal neuromuscular disease with a high unmet need and no approved therapies
- AOC 1001 is an investigational antibody oligonucleotide conjugate that successfully delivered siRNA to muscle resulting in *DMPK* mRNA reductions and splicing improvements leading to functional improvements
- Top-line data from MARINA™ demonstrate directional improvement in multiple clinical endpoints in the dose range of 2–4 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 improvement in quantitative muscle strength assessments (QMT total, upper and lower extremities) observed at Month 6
  - Early signs of directional mobility improvements in the 10mWRT and the TUG
- AOC 1001 had a generally favorable safety and tolerability profile
- Data support advancement of AOC 1001 into Phase 3 study

Acknowledgments

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References

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Abbreviations

10mWRT, 10-meter walk run test; AE, adverse event; AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; FDA, US Food and Drug Administration; mAb, monoclonal antibody; mRNA, messenger ribonucleic acid; OLE, open-label extension; QMT, quantitative muscle testing; SAE, severe adverse event; SD, standard deviation; SEM, standard error of the mean; TfR1, human transferrin receptor 1; TUG, timed up and go test; US, United States; vHOT, video hand opening time.

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