Topline Safety and Efficacy Data Analysis of Phase 1/2 Clinical Trial Evaluating AOC 1001 in Adults with Myotonic Dystrophy Type 1: MARINA™

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Disclosures

- Dr. Johnson has received personal compensation for serving as a consultant for Arthex Biotech, Avidity Biosciences, Dyne Therapeutics, Juvena Therapeutics, Kate Therapeutics, Pepgen, Rgenta Therapeutics, Sarepta Therapeutics, Takeda Pharmaceuticals, and Vertex Pharmaceuticals
- He has received personal compensation for serving on data safety monitoring board for Biogen
- He has stock or an ownership in Juvena Therapeutics
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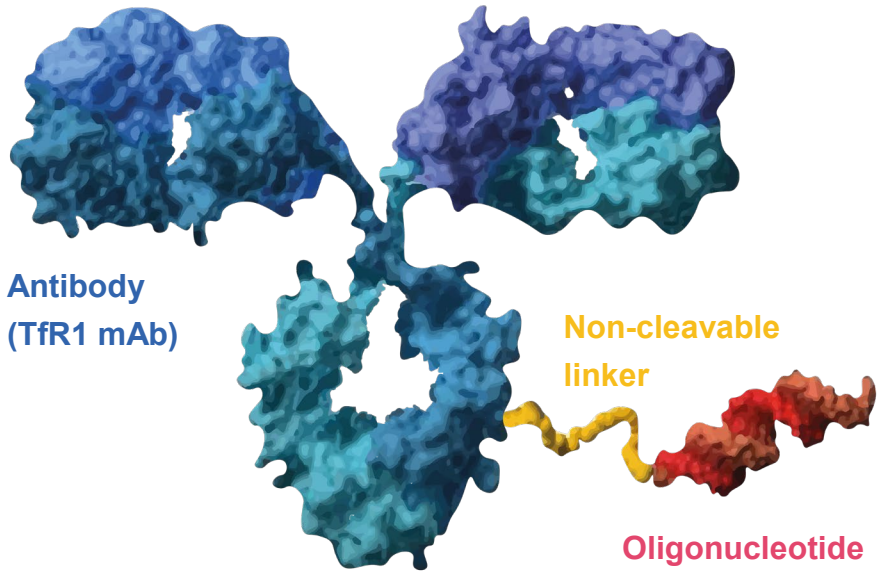
The Underlying Mechanism of DM1 is Well Suited to an siRNA Approach Using an Antibody Oligonucleotide Conjugate (AOC)



- DM1 is caused by the mutant *DMPK* mRNA with CUG expansion sequestering CUG binding proteins which leads to mis-splicing of downstream genes[1,2]
- Decreasing the amount of mutant *DMPK* mRNA has the potential to free up the CUG binding proteins and reverse mis-splicing[3]

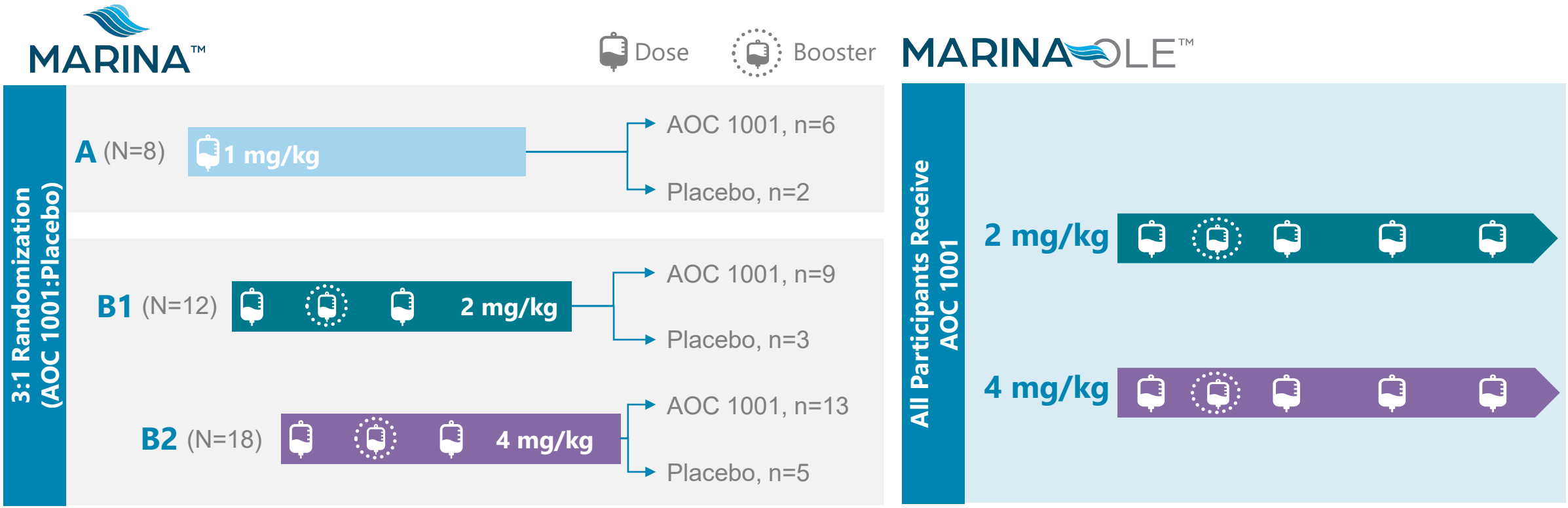
AOC 1001 includes[4]:

- **Antibody:** human 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

AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; IgG, immunoglobulin G; mAb, monoclonal antibody; MBNL, muscleblind-like RNA-binding protein; mRNA, messenger ribonucleic acid; siRNA, small inhibitory ribonucleic acid; TfR1, transferrin receptor 1.

1. Brook JD, et al. *Cell.* 1992;68(4):799-808; 2. Lin X, et al. *Hum Mol Genet.* 2006;15(13):2087-2097; 3. Lee JE, Cooper TA. *Biochem Soc Trans*. 2009;37(Pt 6):1281-1286;
4. Johnson N. A Phase 1/2 Clinical Trial Evaluating the Safety and Pharmacokinetics of AOC 1001 in Adults with Myotonic Dystrophy Type 1 (DM1): MARINA™ Study Design. Poster presented at Muscular Dystrophy Association Clinical & Scientific Conference, Nashville, TN; March 13-15, 2022.

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



- One participant receiving 4 mg/kg AOC 1001 discontinued treatment due to SAE
- All eligible participants (N=37) have enrolled in the MARINA-OLE™

Dose listed is siRNA. The diagram for the MARINA-OLE™ trial includes the first 12 of the 24 months with quarterly dosing.
*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.
FDA, US Food and Drug Administration; SAE, serious adverse event; siRNA; small inhibitory ribonucleic acid.

Generally Favorable Safety and Tolerability

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Summary of Treatment Emergent Adverse Events

	MARINA				MARINA-OLE
Subjects with ≥ 1 AE n (%)	Placebo N=10	1 mg/kg N=6	2 mg/kg N=9	4 mg/kg N=13	Total N=37
Any AE	8 (80%)	6 (100%)	9 (100%)	13 (100%)	30 (81%)
AE related to study drug	2 (20%)	1 (17%)	3 (33%)	10 (77%)	7 (19%)
Serious AE (SAE)*	0	0	1 (11%)	1 (8%)	1 (3%)ǂ
SAE related to study drug	0	0	0	1 (8%)	0
AE leading to study discontinuation*	0	0	0	1 (8%)	0
AE leading to death	0	0	0	0	0

10 participants treated with placebo in MARINA were newly treated with AOC 1001 in MARINA-OLE

Over 200 infusions of AOC 1001 totaling 46.2 patient-years of exposure#

Most treatment emergent adverse events (AEs) were mild or moderate †

- MARINA: Most common AEs
  - procedural pain (36%), anemia† (32%), COVID-19 (23%), headache (23%), nausea (23%)
  - 1 discontinuation due to an SAE
- MARINA-OLE: Most common AEs
  - Procedural pain (22%)
  - Pain in extremity and headache (16%)
  - No discontinuations

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*1 SAE considered related to AOC 1001 4 mg/kg: resulted in a partial clinical hold & patient discontinuing from treatment; 1 SAE considered unrelated to treatment: reaction to opioid pain medication after an elective surgery

ǂ 2 SAEs in same patient, considered unrelated to treatment (cholelithiasis which resulted in pancreatitis; resolved by cholecystectomy)

As of August 2023

†Anemia was asymptomatic except for 1 participant who did not require medical intervention

Update on FDA Partial Clinical Hold on AOC 1001

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- In September 2022, the FDA placed a partial clinical hold on new participant enrollment in the MARINA™ study in response to a serious adverse event reported in a single participant in the 4 mg/kg cohort comprising bilateral ischemia in the region of the lateral geniculate nuclei in the thalamus with subsequent hemorrhagic transformation. This was described as thalamic hemorrhage
- Comprehensive investigation by Avidity found no plausible biological link to any component of AOC 1001, the AOC platform, the transferrin receptor delivery mechanism or reduction of DMPK
- In May 2023, partial hold was eased to allow enrollment of new participants at the 2 mg/kg dose and to dose escalate 12 participants from 2 mg/kg to 4 mg/kg

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AOC, antibody oligonucleotide conjugate; DMPK, DM1 protein kinase; FDA, US Food and Drug Administration.

Participants Treated With AOC 1001 Demonstrated Improvements in Myotonia and Hand Strength

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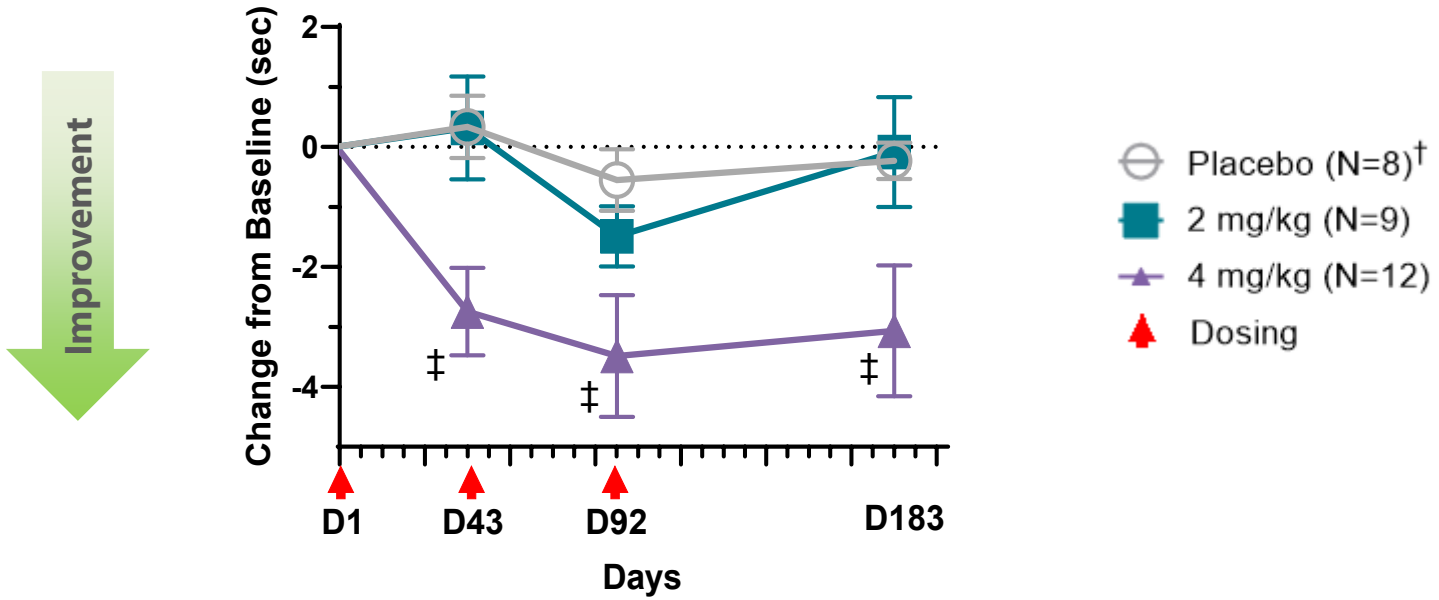
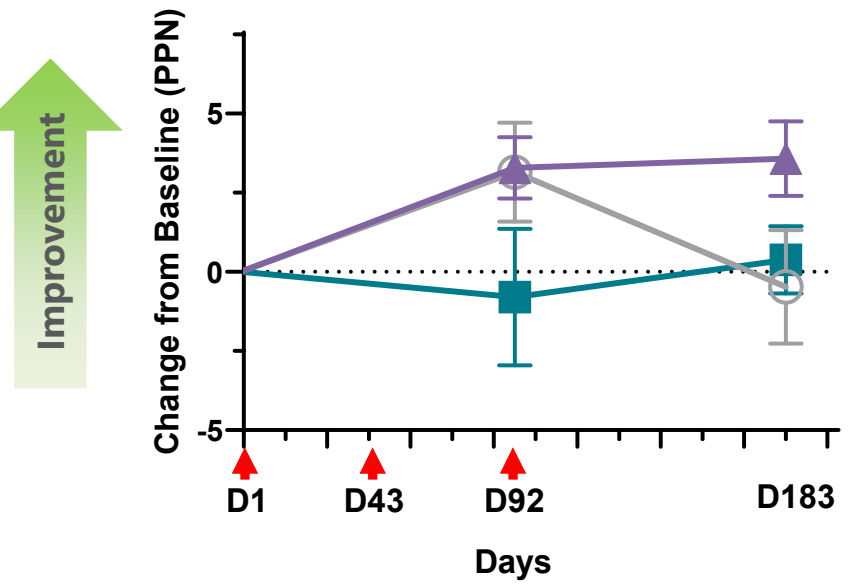
Video Hand Opening Time (vHOT)*



Hand Grip



Error bars = standard error of the mean (SEM)
*Measurements for vHOT are based on middle finger opening time. Statistical analysis was post-hoc.
†Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
‡Post-hoc statistical analysis show $p<0.05$.
DM1, myotonic dystrophy type 1; vHOT, video hand opening time.

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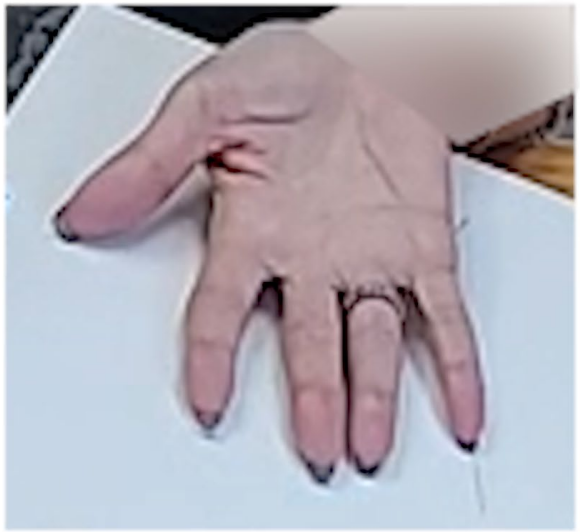
AOC 1001 Demonstrates Myotonia Reduction Across 4 mg/kg Cohort*

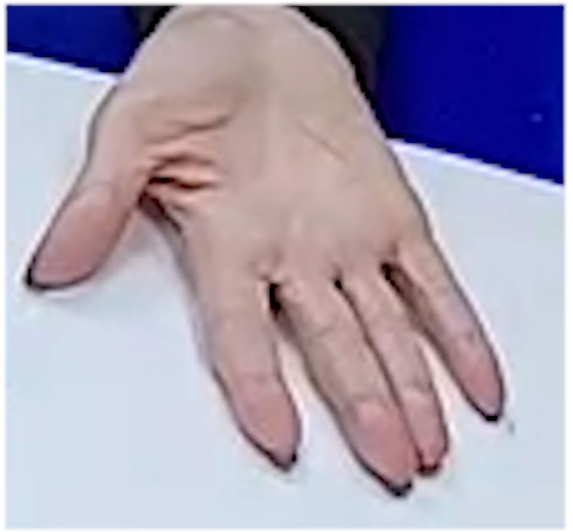
vHOT is measuring hand flexor myotonia and hand extensor muscle strength

Participant from 4 mg/kg Multidose

Baseline vHOT



Day 183 vHOT
12 weeks after third dose



Improvement visible 12 weeks following the third dose at 4 mg/kg

vHOT, video hand opening time.
*improvements also seen in participants in 1 and 2 mg/kg cohorts

Improvements in Strength Measured by Quantitative Muscle Testing (QMT) Total and Manual Muscle Testing (MMT) Composite Scores

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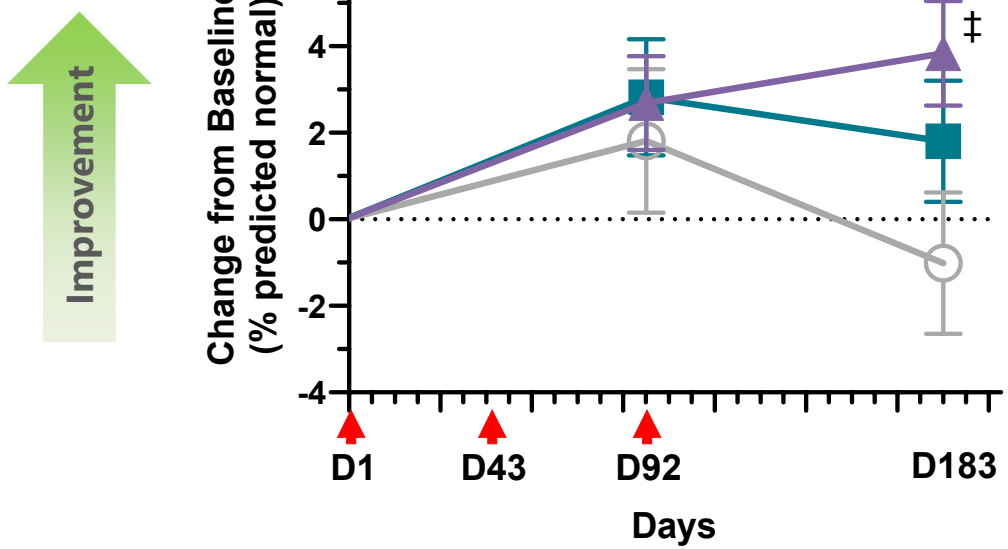
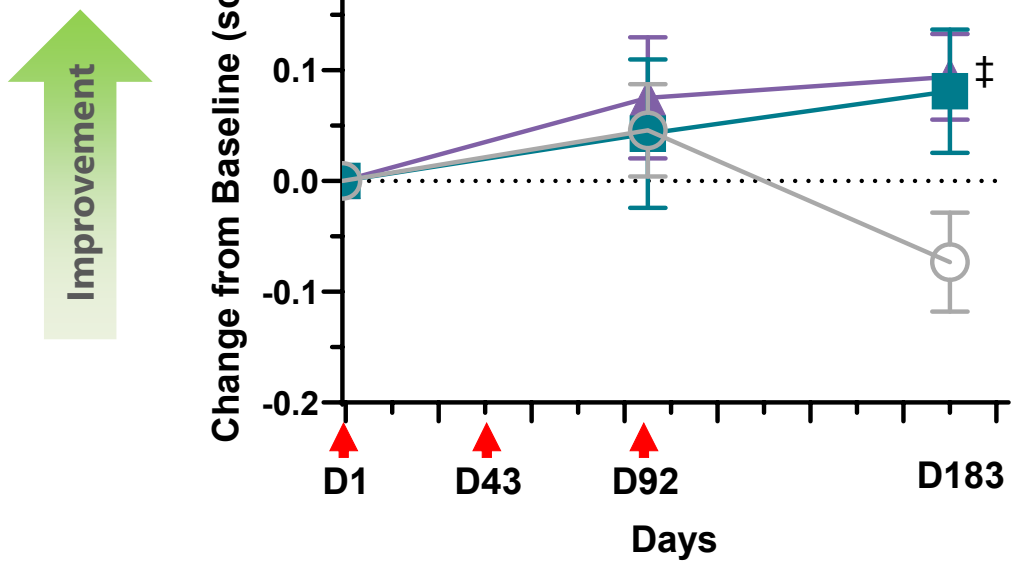
QMT Total Score*



Total MMT Composite Score



Error bars = standard error of the mean.
*QMT Total Score is based on 6 muscle groups from both upper and lower body: Ankle dorsiflexion, hand grip, elbow flexion, elbow extension, knee flexion, knee extension
†Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
‡Post hoc statistical analysis show $p<0.05$ for Cohort B2 (4 mg/kg)
MMT, manual muscle testing; QMT, quantitative muscle testing.

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Consistent with Improvement in Total QMT Score, Improvements also Demonstrated in Both Upper and Lower Extremities

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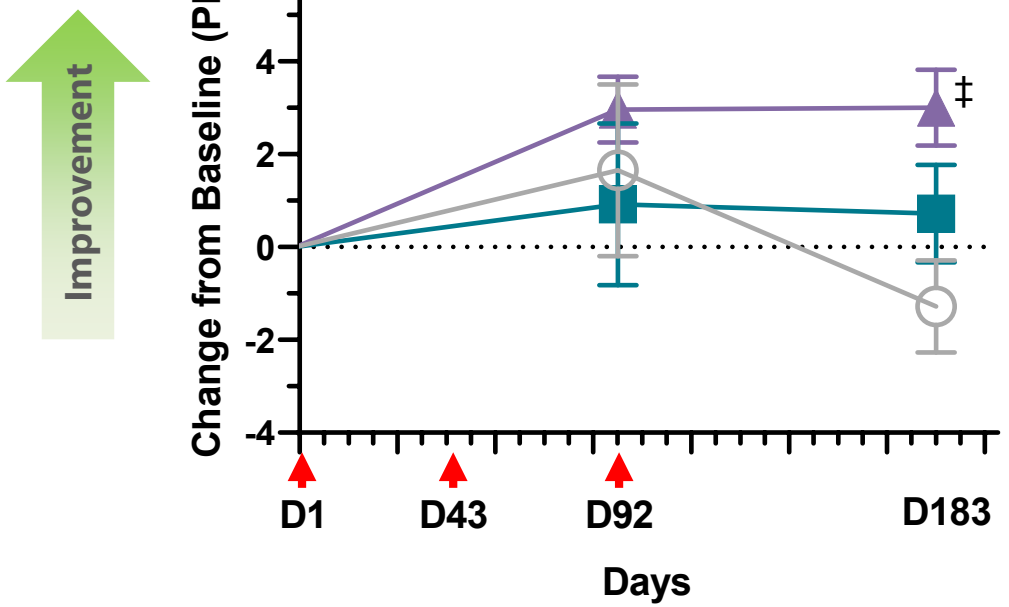
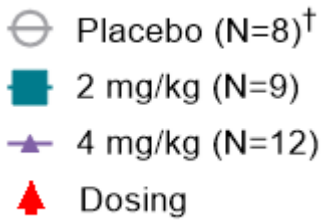
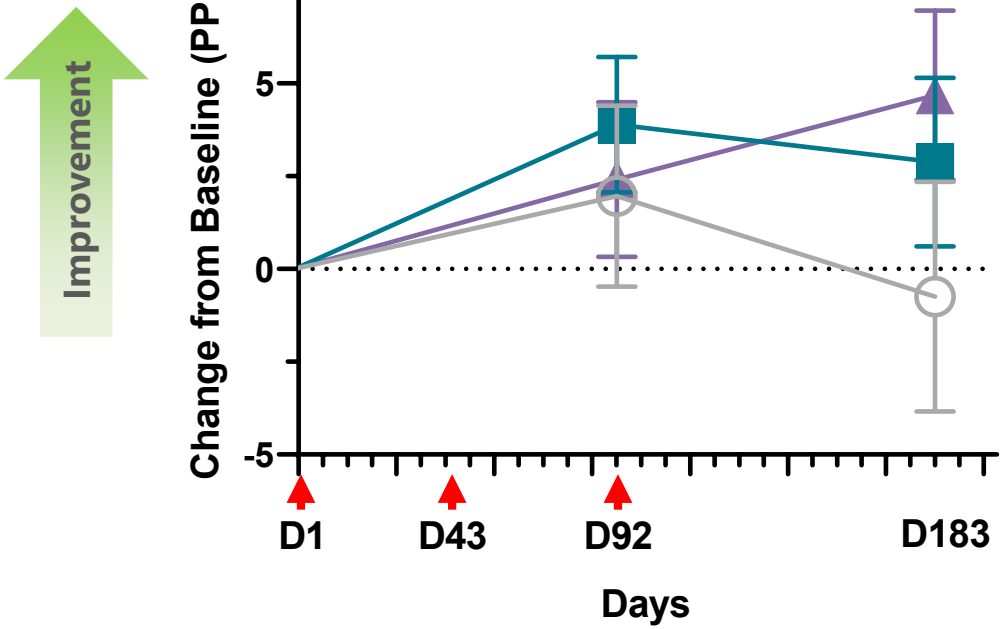
QMT Upper Extremity





QMT Lower Extremity



Error bars = standard error of the mean.
†Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
‡Post hoc statistical analysis show $p<0.05$.
QMT, quantitative muscle testing.

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Directional Improvements Were Observed in Functional & Patient Reported Measures: 10-Meter Walk Run Test (10mWRT), Timed Up and Go (TUG), and the DM1-Activ Patient Reported Outcome (PRO)

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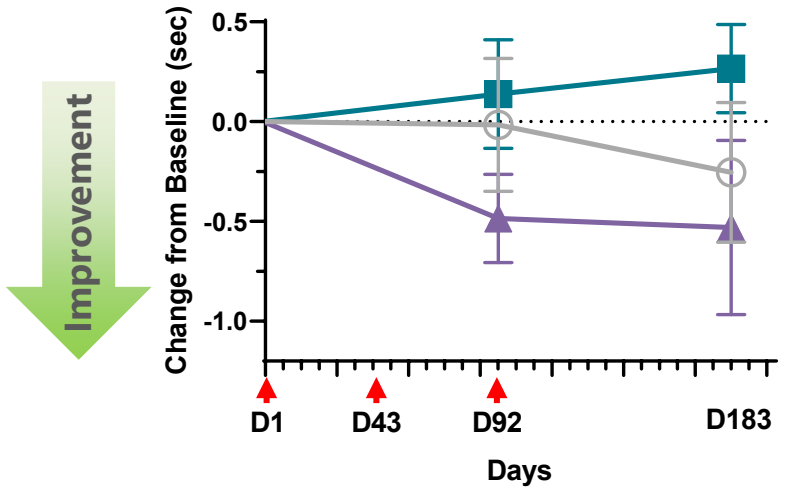
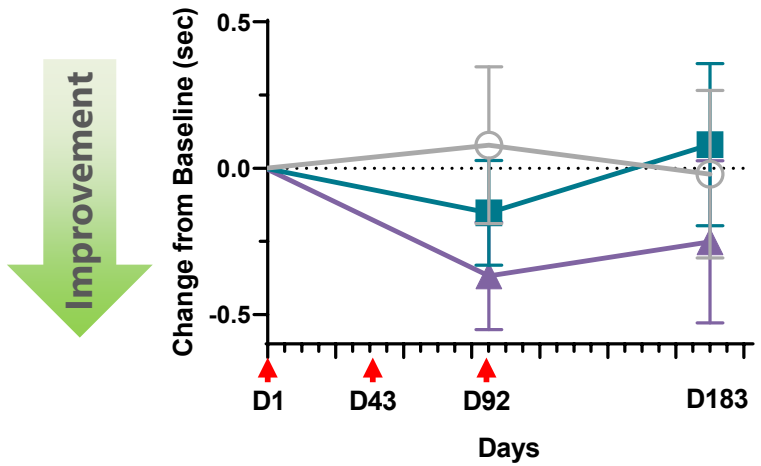
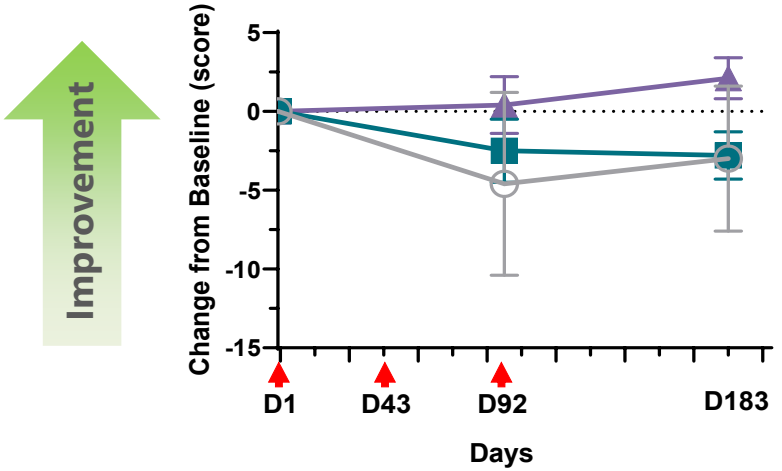
10mWRT

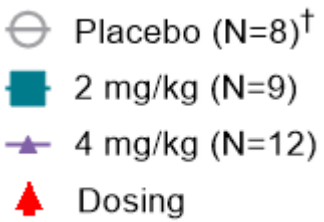


TUG



DM1-Activ





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Error bars = standard error of the mean.
†Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg).
10mWRT, 10-meter walk run test; TUG, timed up and go test; DM1-ACTIV patient reported outcome

MARINA™ Phase 1/2 Trial Demonstrates AOC 1001 Impacts Disease Mechanism and Demonstrates Functional Improvement

- AOC 1001 consistently demonstrated directional improvement across multiple aspects of DM1 including measures of myotonia, strength, function and patient reported outcome
- MARINA™ trial concluded with 38 participants enrolled and treated with study drug
  - All 37 participants that completed MARINA™ have rolled into the MARINA-OLE™ at 2-4 mg/kg of AOC 1001 and remain ongoing
- Generally favorable safety and tolerability profile
  - ~46 total patient years of exposure accumulated with over 200 doses of AOC 1001 administered*
- Discussions with the FDA on resolving the partial clinical hold are ongoing
- Based on the solid data package from MARINA™, Avidity is now finalizing the AOC 1001 pivotal dose and Phase 3 design
- First look at data from the MARINA-OLE™ study in the first-half of 2024

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*As of August 2023, and based on 38 participants treated with AOC 1001 in MARINA™ and/or MARINA-OLE™.
FDA, US Food and Drug Administration.