Top-Line Data from the Phase 1/2 Clinical Trial Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AOC 1001 Administered Intravenously to Adult Patients with Myotonic Dystrophy Type 1 (DM1) (MARINA™)

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DISCLOSURES:

- Dr. Johnson has received personal compensation for serving as a consultant for Acceleron Pharma, Arthex, Avidity Biosciences, Dyne Therapeutics, Juvena, ML Bio, Sarepta Therapeutics, Triplet Therapeutics and Vertex Pharma
- He has received personal compensation for serving on data safety monitoring board for Biogen
- He has stock or an ownership in ML Bio
- He has received research support paid to his institution from AMO Pharma, AveXis, Dyne Therapeutics, Fulcrum Therapeutics, ML Bio, Sarepta Therapeutics, Triplet Therapeutics and Vertex Pharma

Myotonic Dystrophy Type 1 (DM1) is a Rare, Progressive, Neuromuscular Disease With a High Unmet Need and No FDA-Approved Disease-Modifying Therapies[1,2]

AFFECTS

>40,000

PEOPLE IN THE US[1,3]

0

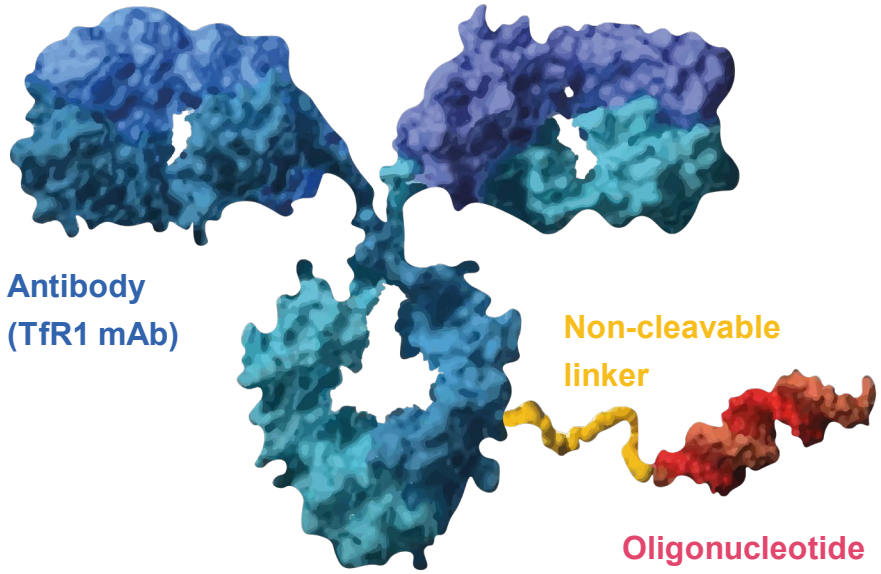
APPROVED THERAPIES[1]

- DM1 is a complex disease with symptoms that present with high variability from patient to patient[1]
- Autosomal-dominant, progressive disease that primarily affects muscle (skeletal, cardiac, and smooth)[4,5]
- Increases in severity from generation to generation[4,5]
- Significant impact on quality of life[6,7]
- Shortened life expectancy due to respiratory failure and sudden death[6-9]

DM1, myotonic dystrophy type 1; FDA, US Food and Drug Administration; US, United States.

1. LoRusso S, et al. *Neurotherapeutics.* 2018;15(14):872–84; 2. Ashizawa T, et al. *Neurol Clin Pract.* 2018;8(6):507–20; 3. US Census Bureau. 2021. https://www.census.gov/quickfacts/fact/table/US/ [Last Accessed March 2022]; 4. Udd B, Krahe R. *Lancet Neurol*. 2012;11(10):891–905; 5. Gourdon G, Meola G. *Front Cell Neurosci.* 2017;11:101; 6. Hagerman KA, et al. *Muscle Nerve*. 2019;59(4):457–64; 7. Landfeldt E, et al. *J Neurol*. 2019;266(4):998–1006; 8. Mathieu J, et al. *Neurology*. 1999;52(8):1658-62; 9. Groh WJ, et al. *N Engl J Med.* 2008; 358: 2688-97.

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 lead to mis-splicing of downstream genes
- Decrease the amount of mutant *DMPK* mRNA has the potential to free up the CUG binding proteins and reverse mis-splicing

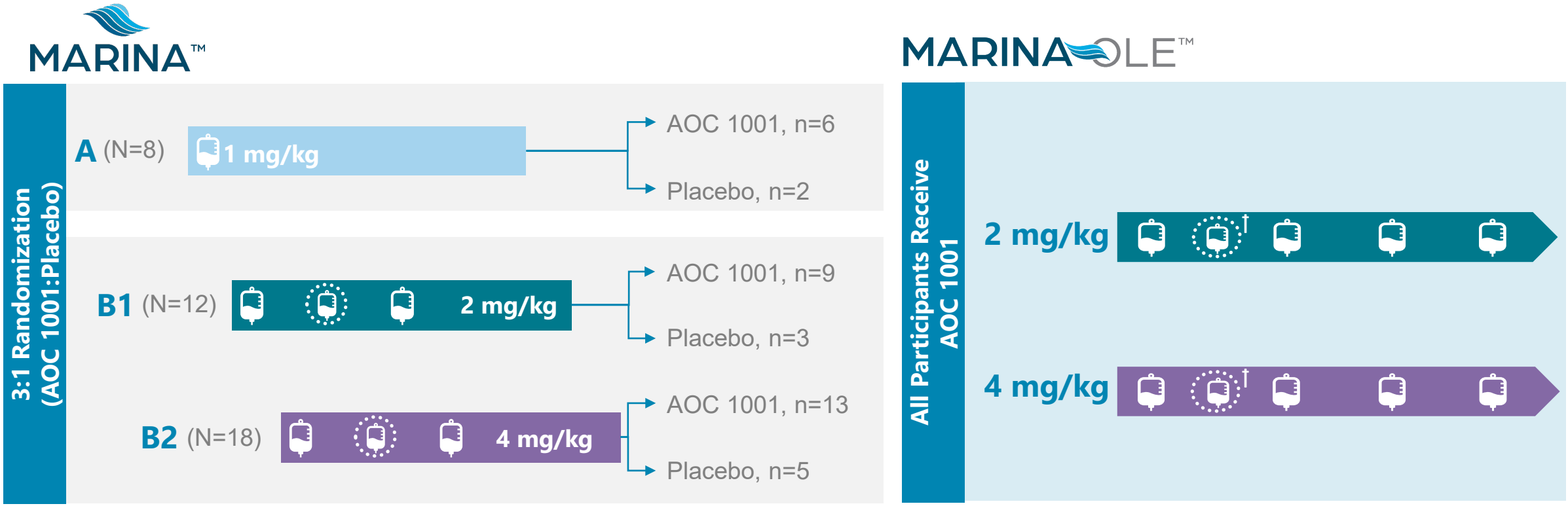
AOC 1001 includes[4]:

- **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; siDMPK, small inhibitory DM1 protein kinase; 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):2087–97; 3. Lee JE, Cooper TA. *Biochem Soc Trans*. 2009;37(Pt 6):1281–6;
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; 13-15 March 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
- As of April 20, 36 participants have enrolled in the MARINA-OLE™

Dose Booster

*Sept. 2022, FDA placed a partial clinical hold on new participant enrollment. All current participants may continue in their current dosing cohort. Avidity is working to resolve the partial clinical hold as quickly as possible.
†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.

Baseline Demographics and Disease Characteristics

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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)
BMI	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

Generally Favorable Safety and Tolerability

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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%)
Serious AE (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

Most treatment emergent adverse events (AEs) 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 serious AE discussed below

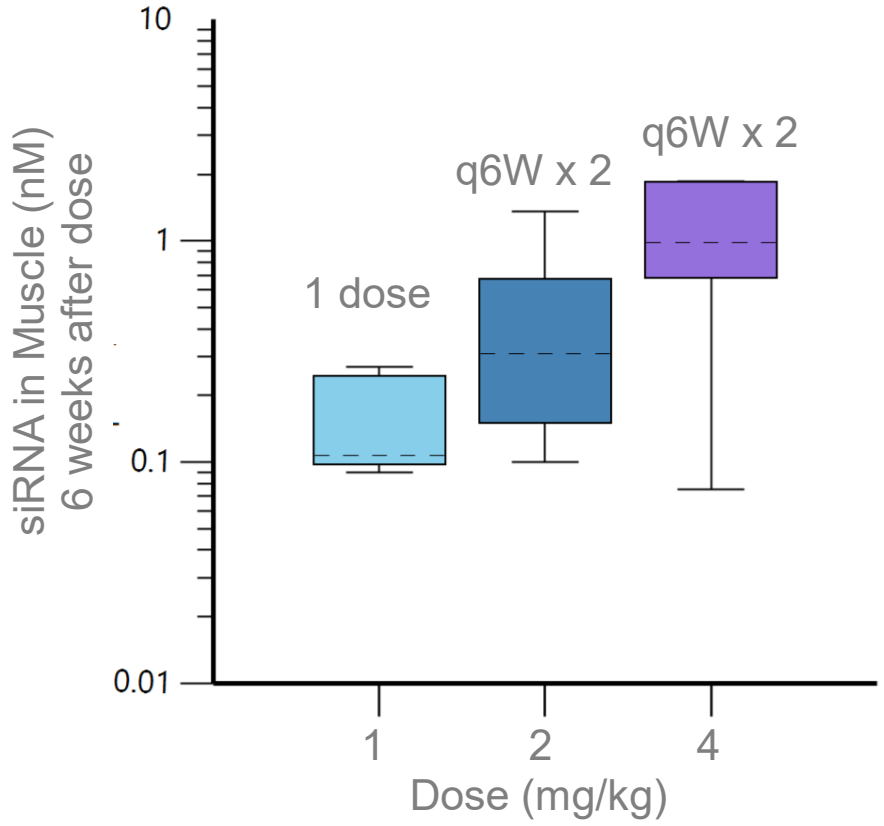
2 Serious Adverse Events (SAEs)

- 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 elective surgery

*Patient discontinued from the study due to the SAE
†Most common AEs are defined as those above 30% in combined 2 and 4 mg/kg treated participants

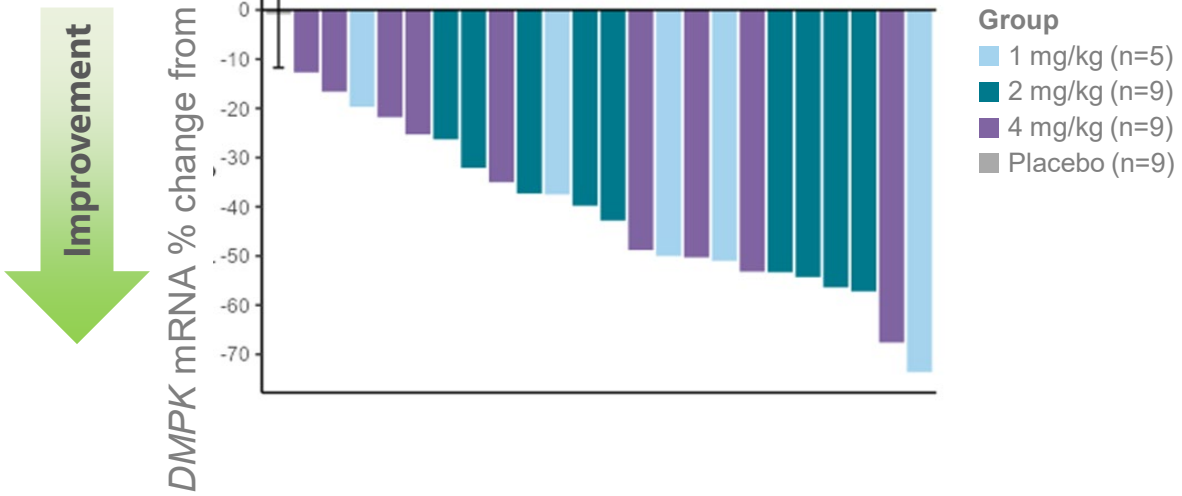
AOC 1001 Delivered siRNA to Muscle and Expands siRNA Therapeutics Beyond Liver

Dose Proportional Increase in Muscle siRNA Concentrations

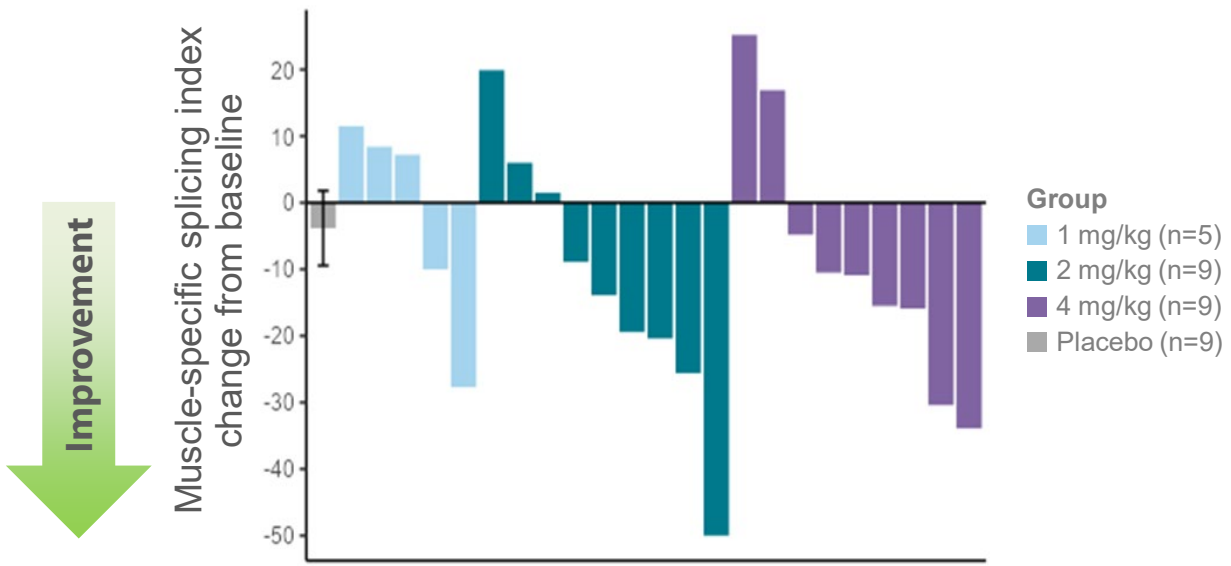


AOC-1001 Treatment Led to DMPK Reduction and Splicing Improvement

DMPK mRNA Reduction*



22 Gene Panel Composite Score *,†



~42% reduction in *DMPK* mRNA across all cohorts weeks after one or two doses of AOC 1001*

*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

Improvement in Myotonia and Total Muscle Strength was Seen in Participants Treated With AOC 1001

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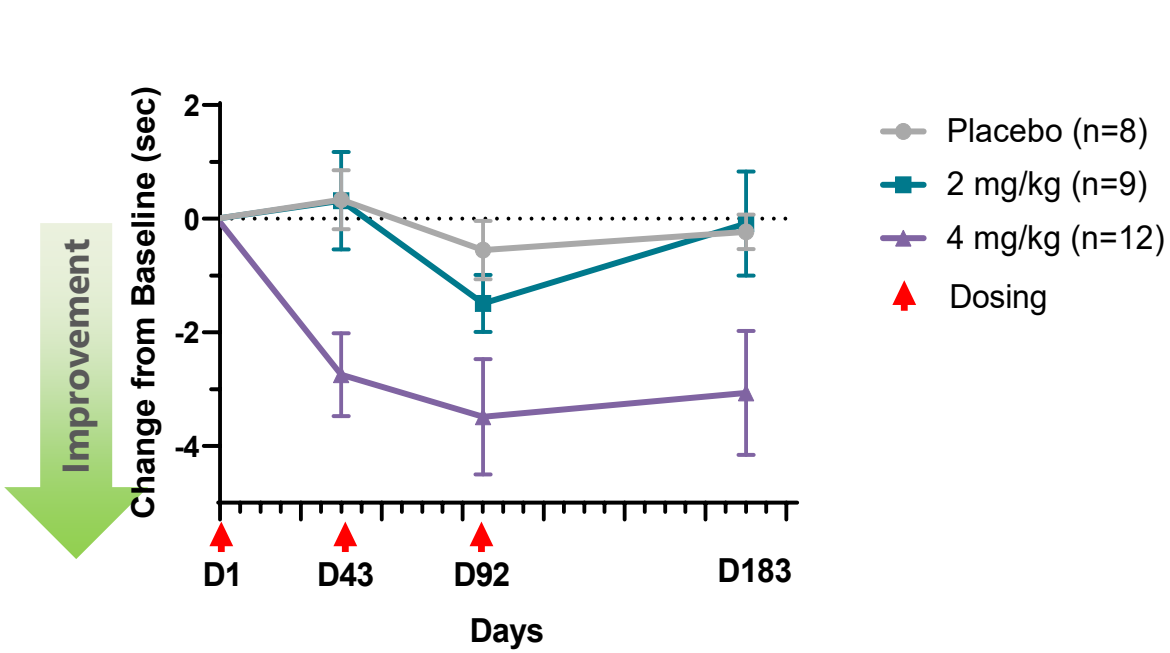
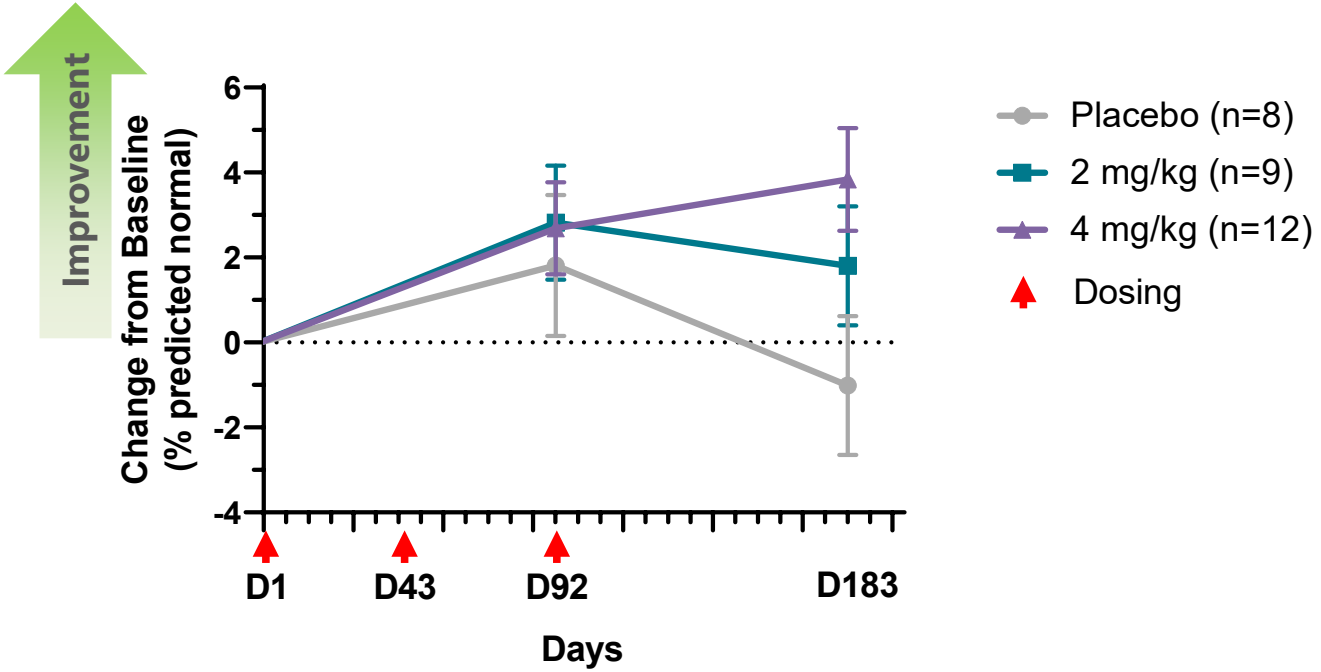
Video Hand Opening Time (vHOT)*



Quantitative Muscle Testing (QMT) Total Score†



*Measurements for vHOT are based on middle finger opening time.
†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)
Error bars = standard error of the mean (SEM)

AOC 1001 Showed Early Signs of Improvement in Mobility Measures

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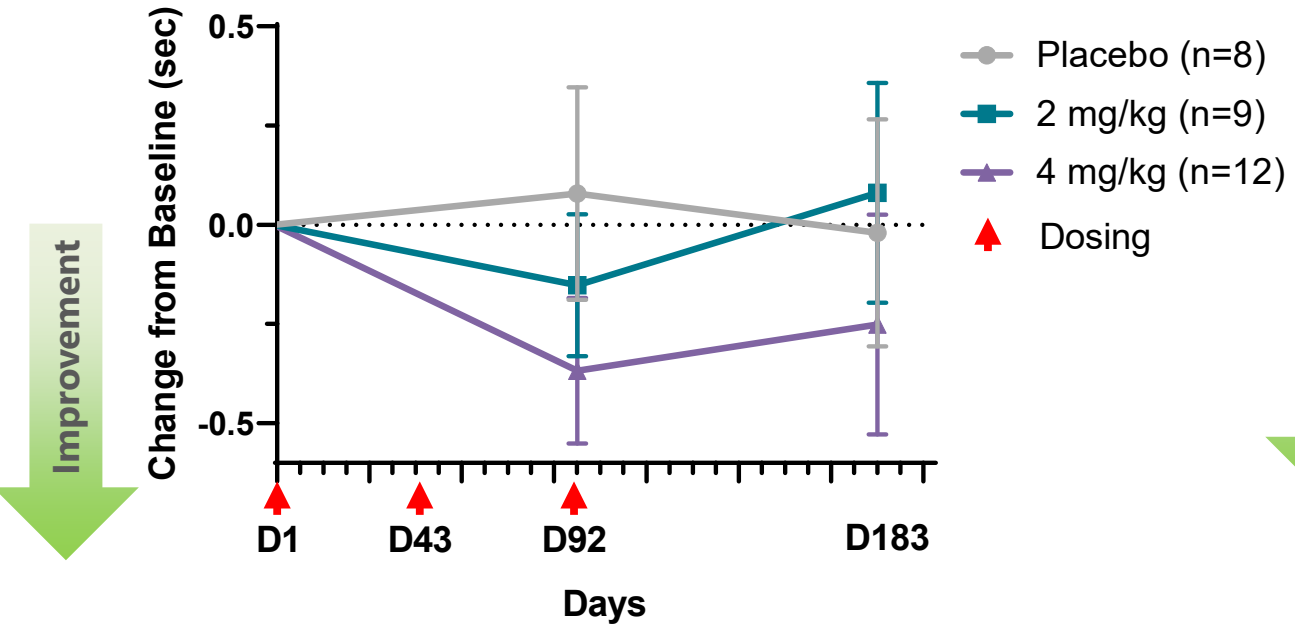
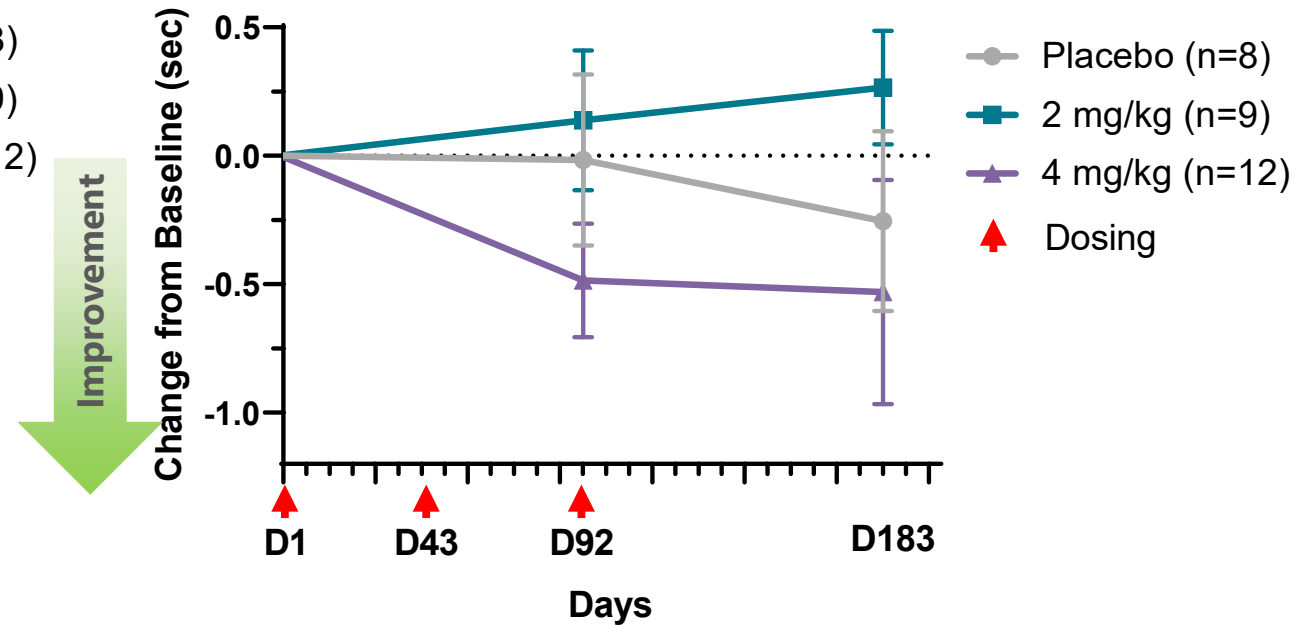
Timed Up and Go (TUG)



10 Meter Walk Run test (10mWRT)



Placebo group combined from Cohort B1 (2 mg/kg) and Cohort B2 (4 mg/kg)
Error bars = standard error of the mean (SEM)

AOC 1001 Demonstrates Myotonia Reduction in Early Responder from 2 mg/kg Cohort

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Participant from
2 mg/kg Multidose

Baseline vHOT

Day 183 vHOT
12 weeks after third dose

Improvement visible 12 weeks following the third dose at 2 mg/kg

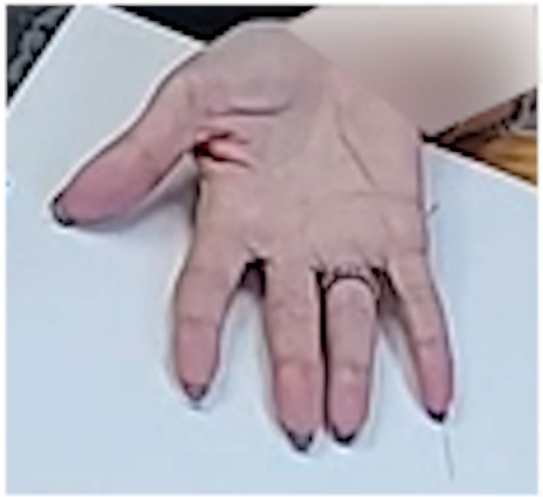
vHOT, video hand opening time.

AOC 1001 Demonstrates Myotonia Reduction Across 4 mg/kg Cohort

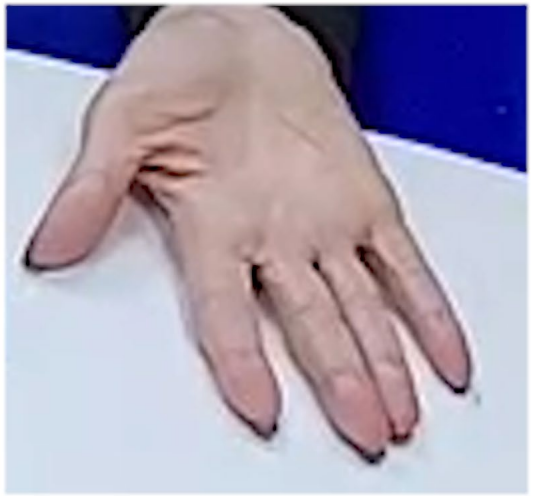
MARINA™

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.

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

- 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:
  - Improvements in myotonia (vHOT) as early as 6 weeks after dosing with a sustained effect at month 6
  - Improvement in QMT total strength measure observed at month 6
  - Early signs of 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

Authors and Acknowledgements

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