Phase 1/2 Clinical Trial Evaluating the Safety and Pharmacokinetics of AOC 1001 in Adults with Myotonic Dystrophy Type 1: MARINA Trial in Progress

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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

Data previously presented at the Avidity Virtual Investor and Analyst Event on December 14th, 2022.

There are no FDA-Approved Disease-Modifying Therapies for DM1, and Current Medical Treatment is Focused on Symptom Management[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[6,7]

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

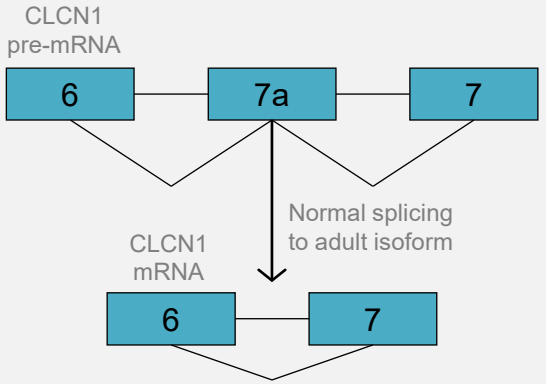
1. LoRusso S, et al. *Neurotherapeutics.* 2018;15(14):872–84; 2. Ashizawa T, et al. *Neurol Clin Pract.* 2018;8(6):507–20; 3. US Census Bureau. 2021. https://www.census.gov/quickfacts/fact/table/US/ [Last Accessed March 2022]; 4. Udd B, Krahe R. *Lancet Neurol*. 2012;11(10):891–905; 5. Gourdon G, Meola 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.

DM1 is Caused by a Toxic Gain-of-Function mRNA due to Increased CUG Repeats

Normal Conditions[1-3]

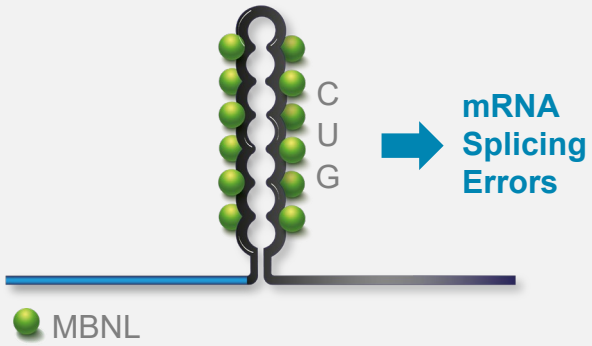
DMPK mRNA

CLCN1 pre-mRNA Splicing



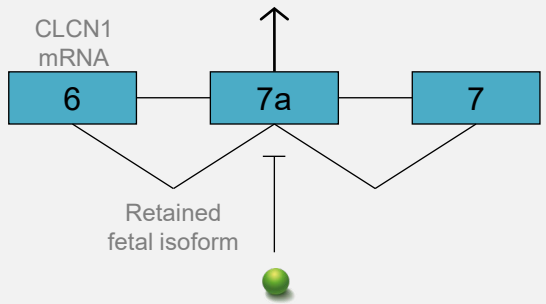
Mechanism of Disease[1-3]

Mutant DMPK mRNA sequesters RNA regulatory proteins such as MBNL



mRNA Splicing Errors

CLCN1 pre-mRNA Splicing Error Leading to Decreased CIC-1 Density (Myotonia)

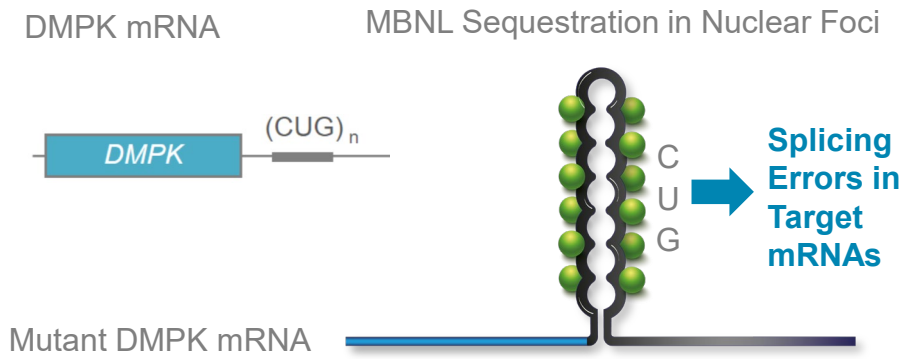


DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; MBNL, muscleblind like; mRNA, messenger ribonucleic acid.

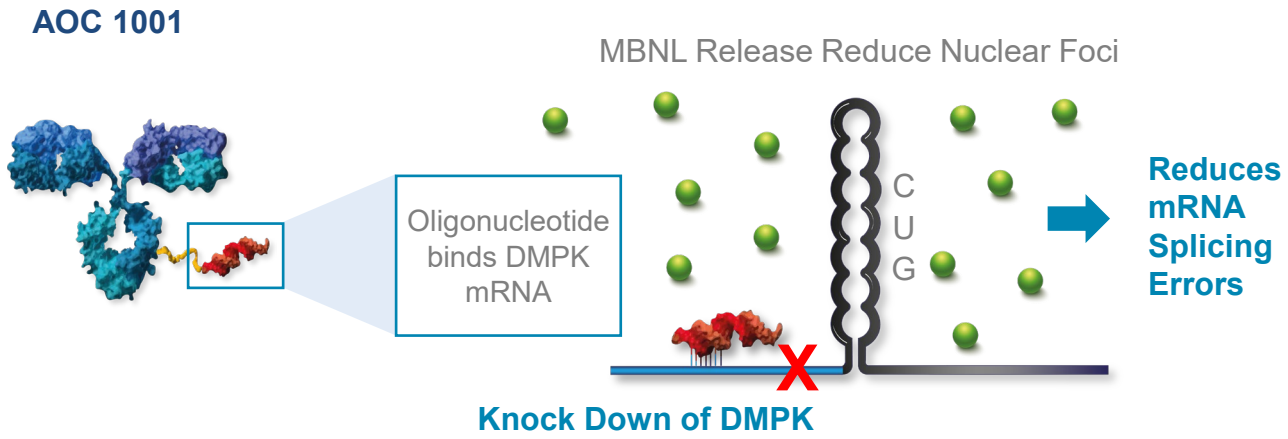
1. Brook JD, et al. *Cell.* 1992;68(4):799–808; 2. Lin X, et al. *Hum Mol Genet.* 2006;15(13):2087–97; 3. Lee JE, Cooper TA. *Biochem Soc Trans*. 2009;37(Pt 6):1281–6.

DM1 is Caused by a Toxic Gain-of-Function mRNA and is Well Suited to an siRNA Approach

Mechanism of Disease[1-3]



Potential Therapeutic Approach



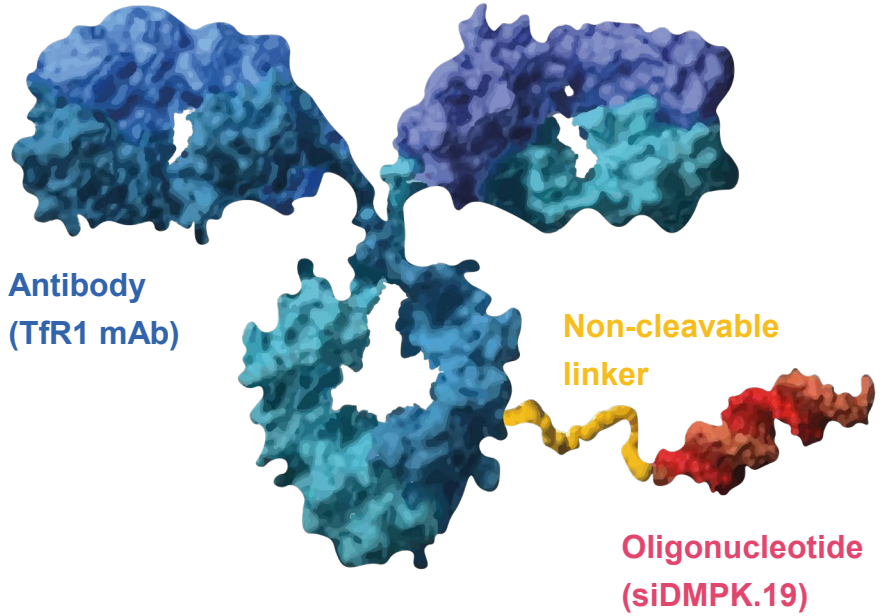
MBNL

AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; MBNL, muscleblind like; mRNA, messenger ribonucleic acid; siRNA, small inhibitory ribonucleic acid.

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.

AOC 1001 is an Investigational AOC

- The main components of AOC 1001 are:
  - **Antibody:** human TfR1-targeting, effector function-null, humanized IgG1 antibody (TfR1 mAb)
  - **Non-cleavable linker**
  - **Oligonucleotide:** double-stranded siRNA oligonucleotide (siDMPK.19) that is complementary to a sequence in the 3' untranslated region (exon 15) of both wild-type and mutant-human DMPK mRNA
- The TfR1 mAb targets muscles for delivery of siDMPK.19 into the cytoplasm and nucleus where it mediates DMPK mRNA degradation
- We are currently evaluating the safety and tolerability of single and multiple ascending doses of AOC 1001 in adults with DM1 in a Phase 1/2 clinical study

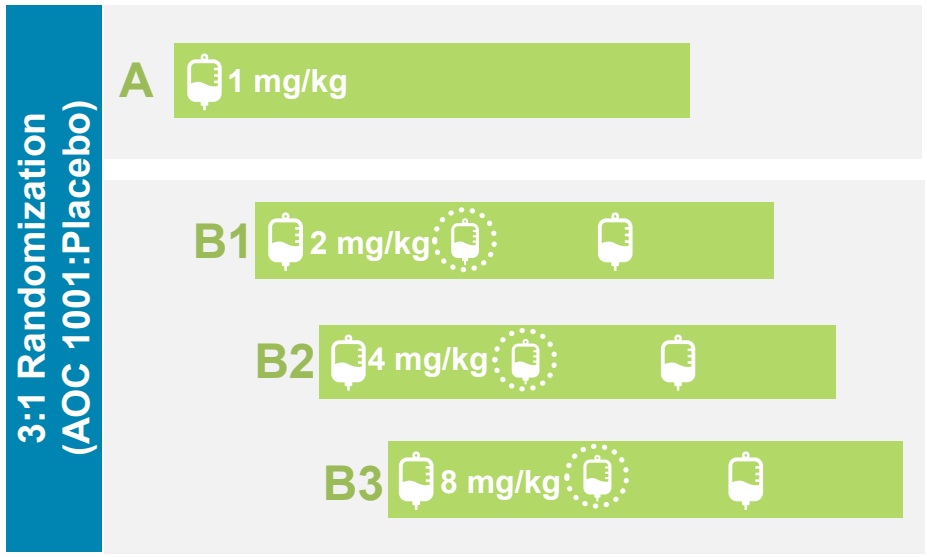


AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; IgG, immunoglobulin G; mAb, monoclonal antibody; mRNA, messenger ribonucleic acid; siDMPK, small inhibitory DM1 protein kinase; siRNA, small inhibitory ribonucleic acid; TfR1, transferrin receptor 1.

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.

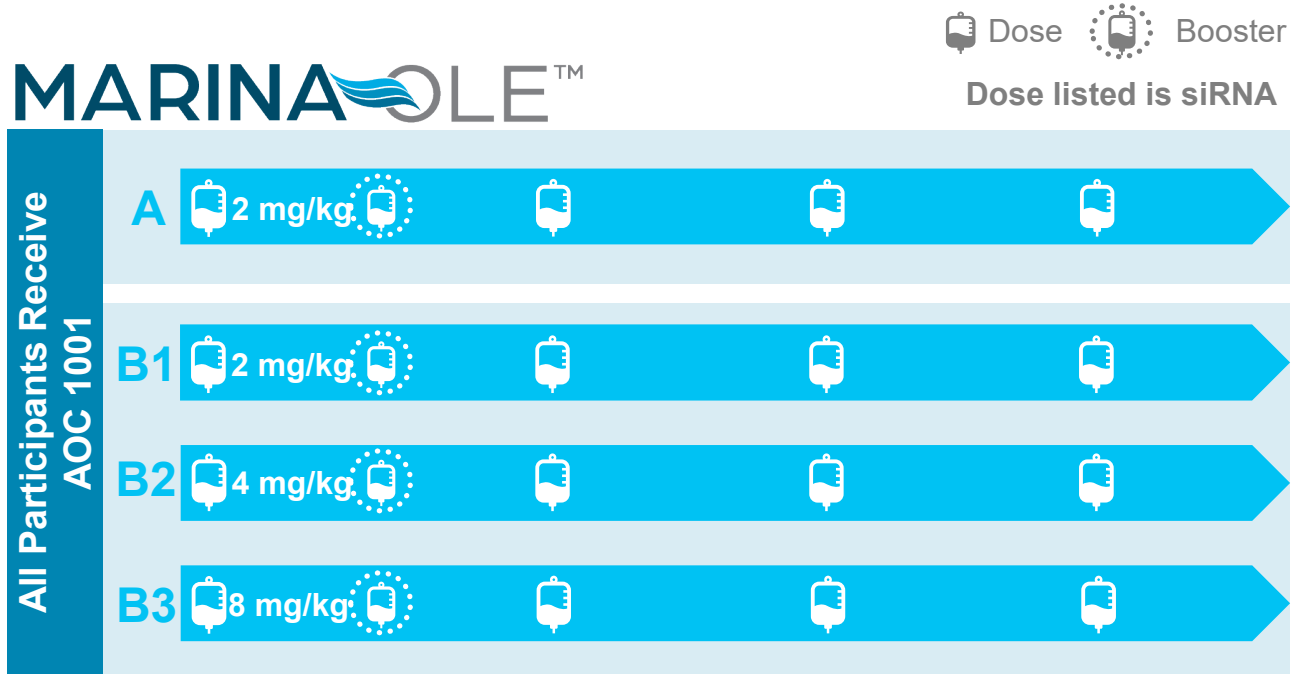
MARINA™ and MARINA-OLE™ Allow for Both Short- and Long-term Data Collection to Evaluate AOC 1001*

MARINA™



- N = ~44 Ages 18-65 (3:1 randomization)
- **Part A** receives single IV dose
- **Part B** receives multi-ascending IV doses
  - Quarterly doses - 1 booster after first 6 weeks
- 6-month treatment and observation duration

MARINA-OLE™

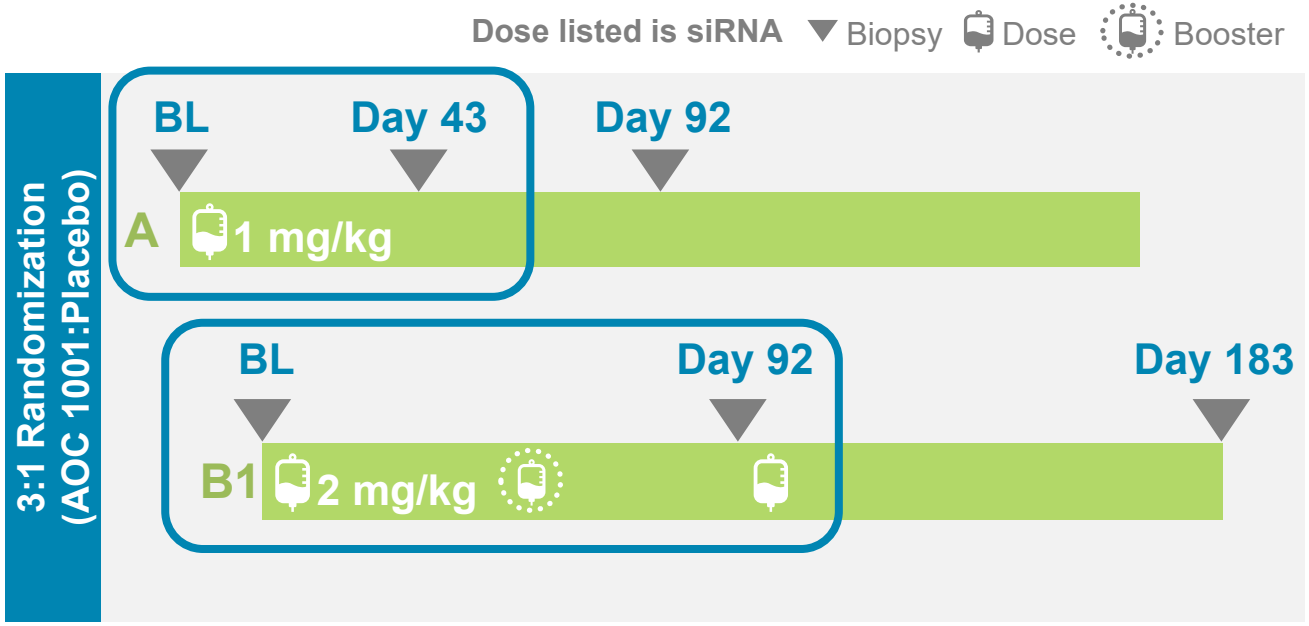


- N = ~44 Ages 18-65
- **All participants receive AOC 1001**
- Quarterly doses - 1 booster after first 6 weeks
- 24-month treatment and 9-month observation duration

*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.

Early Data from MARINA Mid-Point at 6 Weeks Post 1 or 2 Doses of AOC 1001

MARINA™



Biopsy	1 mg/kg (n=8 Participants)		2 mg/kg (n=12 Participants)	
	Baseline	Day 43	Baseline	Day 92
DMPK	6 Active 2 Placebo	5* Active 2 Placebo	9 Active 3 Placebo	9 Active 3 Placebo
Splicing				8** Active 3 Placebo

- Safety includes all cohorts (including 4mg/kg) with a data cutoff of November 17, 2022
- Day 92 biopsy in 2mg/kg cohort taken prior to third dose of AOC 1001

Data at 3 Months: n=19 participants*

- 1mg/kg Cohort (n=5 active participants)
- 2mg/kg Cohort (n=9 active participants)
- Pooled placebo (n=5 participants)

*One participant in the 1mg/kg cohort had insufficient tissue for analysis
**Due to timing, one splicing sample from the 2 mg/kg cohort will be evaluated in the next batch analysis

Baseline Demographics* Generally Well Matched Between Cohorts

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Cohort A and B1 Enrolled Participants with Mild-Moderate Disease Severity

Mean (Range) or Number of subjects	Cohort A (1 mg/kg) N=8	Cohort B1 (2 mg/kg) N=12
Age	37.9 (21–64)	38.8 (18-60)
Sex	Male: 2 / Female: 6	Male: 1 / Female: 11
BMI	22.0 (16.1–29.2)	25.0 (17.5–32.0)
Mean CTG repeat length (range)	504 (150-725)	707 (150-1250)
Baseline splicing (composite of 22 splicing events; higher number is more severe)	74 (38-96)	72 (39-105)

*Preliminary results based on live, unlocked clinical database – numbers subject to change

Generally Favorable Safety and Tolerability*

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Subjects with ≥ 1 AE n (%)	Placebo n=10	1mg/kg n=6	2mg/kg n=9	4mg/kg n=13	Total AOC 1001 N=28
Any AE	8 (80%)	6 (100%)	9 (100%)	12 (92%)	27 (96%)
Related to study drug	2 (20%)	1 (17%)	3 (33%)	10 (77%)	14 (50%)
Serious AE (SAE)	0	0	1 (11%)	1 (8%)	2 (7%)
AE leading to study discontinuation	0	0	0	0	0
AE leading to death	0	0	0	0	0

- **Majority of treatment emergent adverse events (AEs) were mild or moderate**
  - The most common in the study were COVID-19 (16%) and headache (16%)
  - Other AEs include:
    - Infusion related reactions
    - Reductions in hemoglobin
    - Elevations in ASTs or ALTs
      - No changes in bilirubin
    - No thrombocytopenia and no renal impairment reported
- **2 Serious Adverse Events (SAEs)**
  - 1 SAE in the 4mg/kg cohort resulted in a partial clinical hold†
  - 1 unrelated SAE in reaction to opioid pain medication after an elective surgery

*Preliminary results based on live, unlocked clinical database – numbers subject to change
†Patient discontinued from the study after the database cut 17-Nov-2022 data cutoff.

AOC 1001 Delivered siRNA to Muscle in a Dose-Proportional Manner

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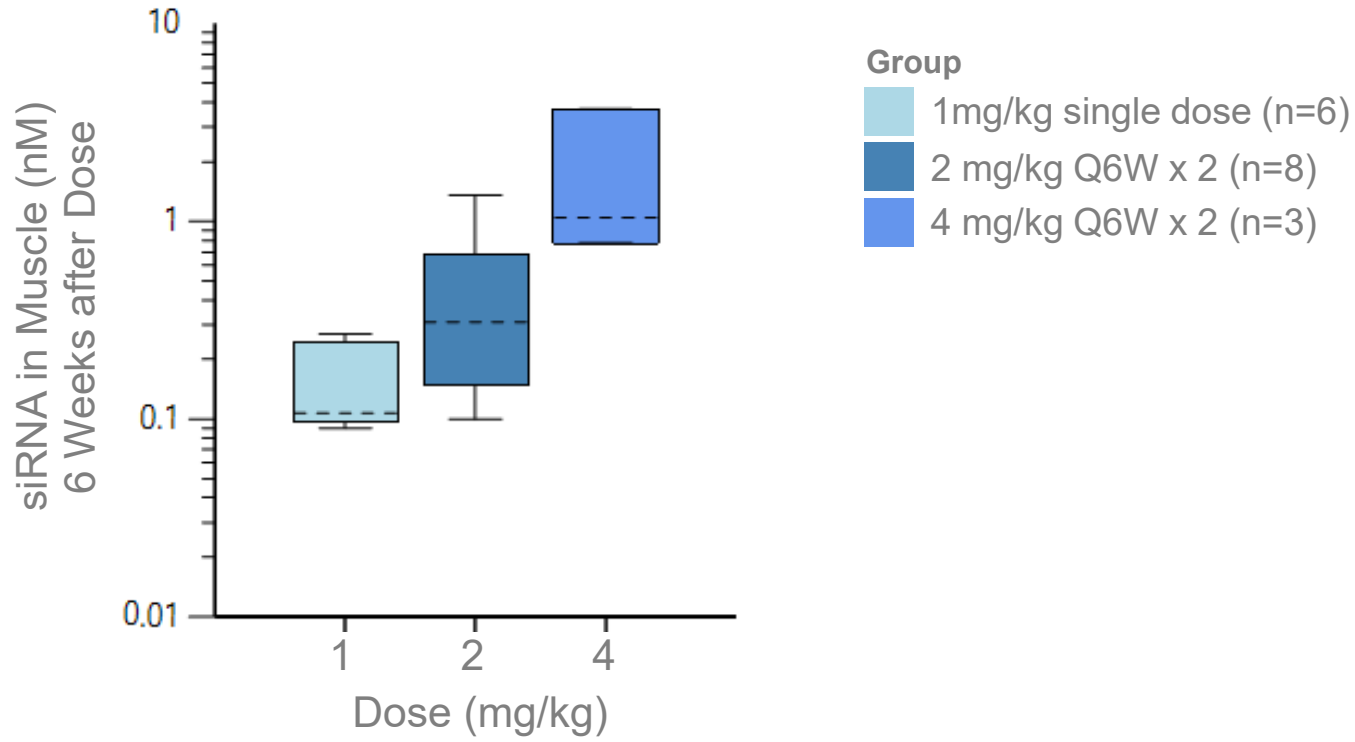
Dose Proportional Increase in Tibialis Anterior Muscle siRNA Concentrations



Box plots represent median, 25th and 75th percentiles, and 1.5x interquartile range
Concentrations in the 1 mg/kg cohort that were measurable but below lower limit of quantitation were imputed

All AOC 1001-Treated Participants Showed *DMPK* mRNA Reduction*

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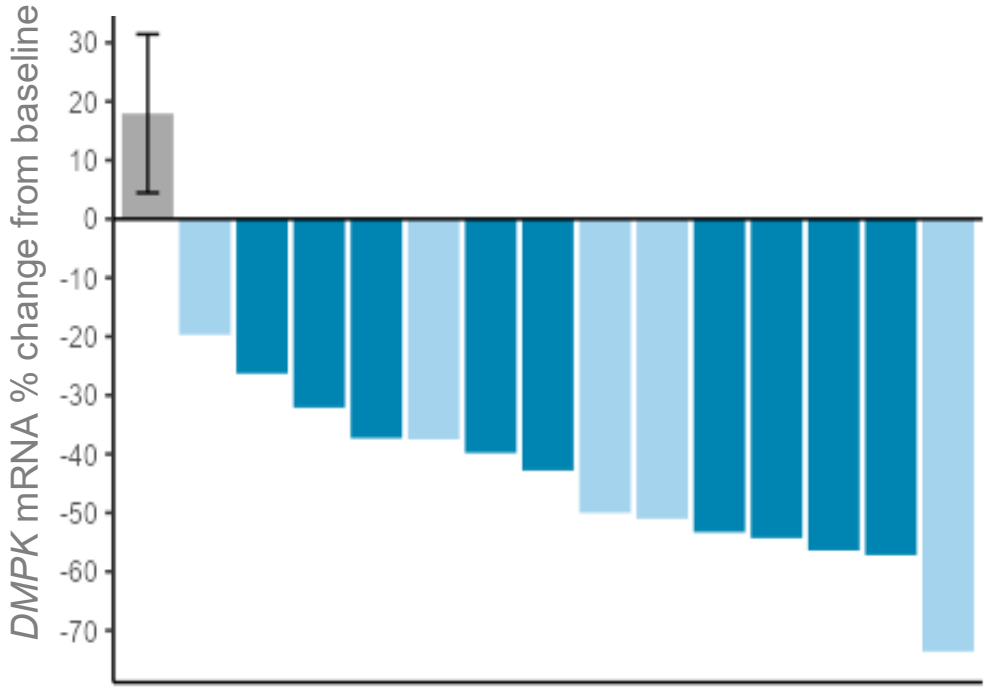
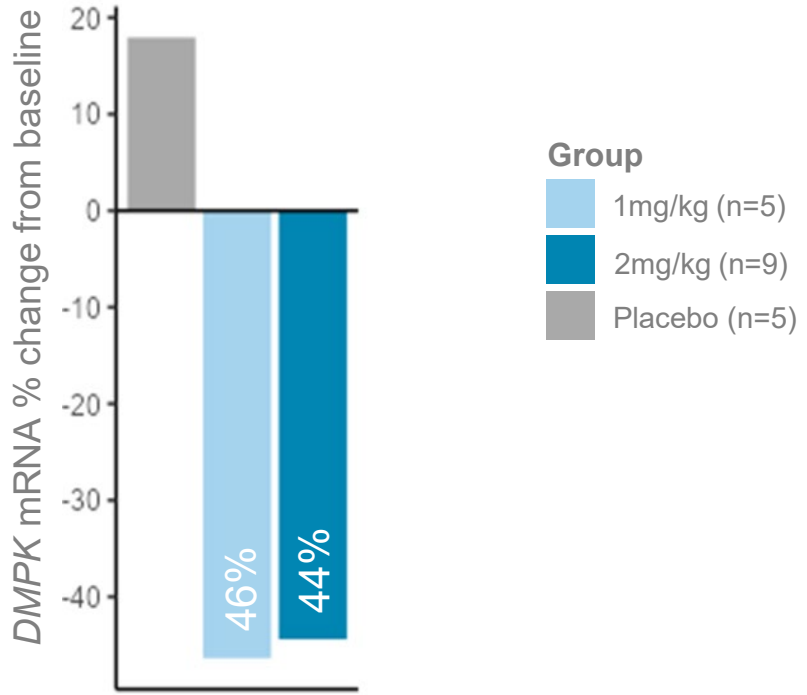
All Treated Participants Demonstrate *DMPK* mRNA Reduction



Data shown at 6 weeks post a single dose of the 1 mg/kg and 6 weeks post two doses of 2 mg/kg

Mean % *DMPK* mRNA Reduction



45% *DMPK* mRNA reduction after a single dose at 1 mg/kg or two doses at 2 mg/kg

Placebo group combined from both cohorts and shown as standard error of the mean
*One participant in the 1mg/kg cohort had insufficient tissue for analysis

Muscle-Specific Biomarkers Shows 31% Splicing Improvement

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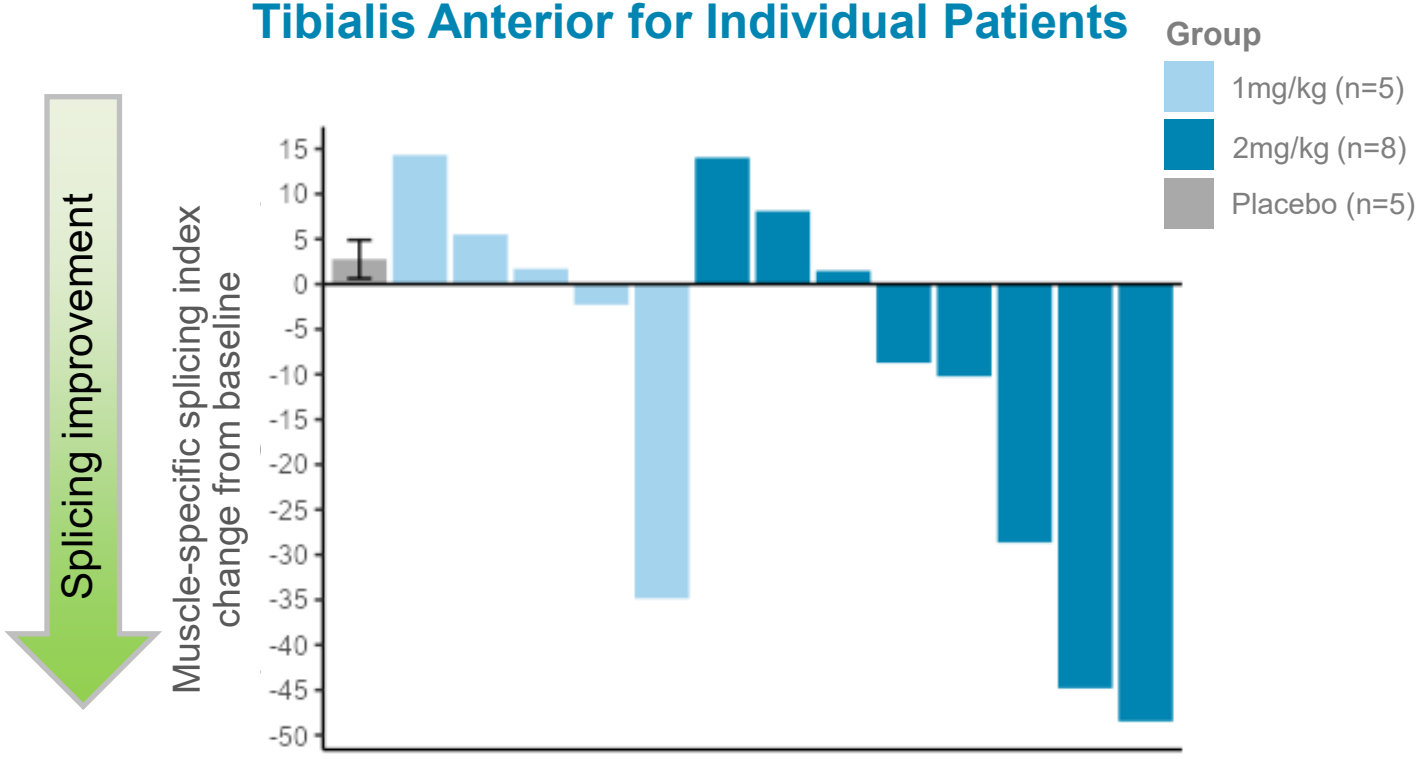
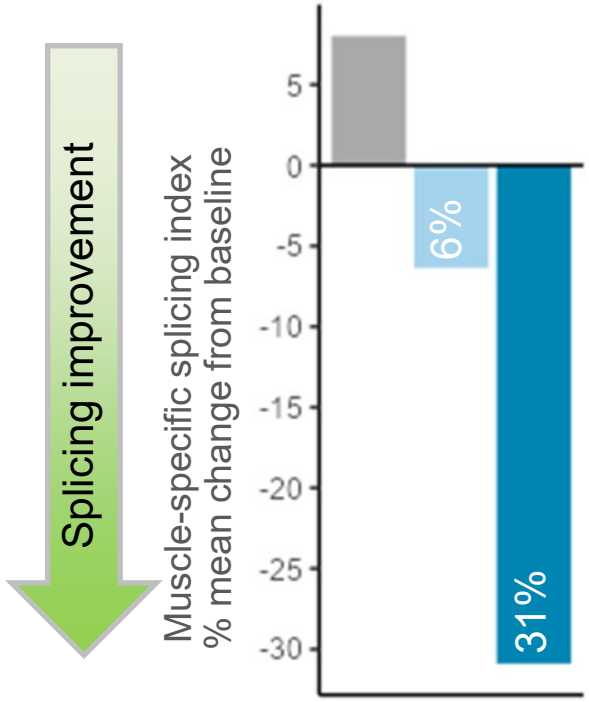
Muscle-Specific Splicing Panel in Tibialis Anterior for Individual Patients



Muscle-Specific Panel for Each Cohort



Muscle panel: CLCN1, CACNA1S, ATP2A1, BIN1
Data shown at 6 weeks post a single dose of the 1 mg/kg and 6 weeks post two doses of 2 mg/kg

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 (4-gene panel)
Data represented as 6 weeks post last dose with placebo group combined from all cohorts

AOC 1001 Shows Early Signs of Myotonia Reduction

Early Responder from **Cohort A (1 mg/kg)**

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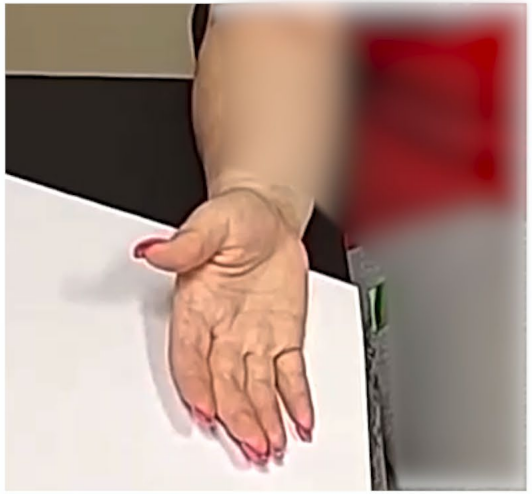
Participant from
1 mg/kg Single Dose

Baseline vHOT	Day 43 vHOT 6 weeks after single dose	Day 92 vHOT 12 weeks after single dose	Day 183 vHOT 24 weeks after single dose
			

Improvement visible at Day 43 but myotonia benefit wanes by 6 months following a single dose at 1 mg/kg

vHOT, video hand opening time.

AOC 1001 Shows Early Signs of Myotonia Reduction

Early Responder from **Cohort B1 (2 mg/kg)**

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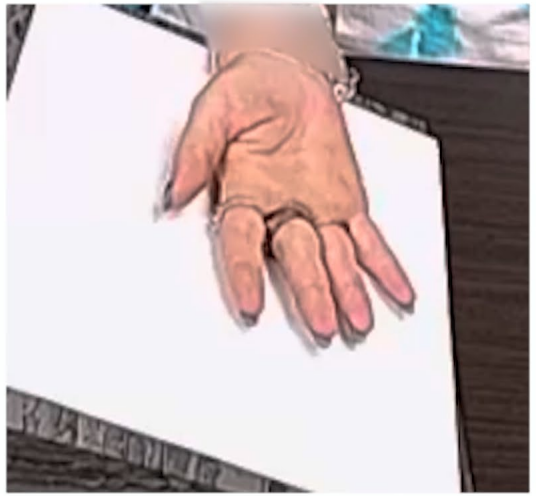
Participant from 2 mg/kg Multidose

Baseline vHOT	Day 43 vHOT 6 weeks after first dose	Day 92 vHOT 6 weeks after second dose	Day 183 vHOT 12 weeks after third dose
			

Improvement visible at Day 43 that is sustained for at least 12 weeks following the third dose at 2 mg/kg

vHOT, video hand opening time.

Delivering on the Platform and Impacting Disease Mechanism

- DM1 is an underrecognized, progressive, and often fatal neuromuscular disease with a high unmet need and no approved therapies
- Data presented provide an early mid-point look at MARINA 6 weeks post 1 or 2 doses of AOC 1001
  - Baseline demographics are generally well matched between cohorts
  - Generally favorable safety and tolerability profile
- AOC 1001 has demonstrated successful delivery of siRNA to muscle and meaningful DMPK reduction in 100% of treated participants
- Splicing improvements demonstrated AOC 1001 activity in the nucleus
  - 31% improvement in key muscle-specific panel
- AOC 1001 showed early signs of myotonia improvement just weeks after dosing with the two lowest doses in the trial

Authors and Acknowledgements

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University of Kansas Medical Center: Jeffrey Statland, MD

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