Study Design of AOC 1001-CS1, a 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

Data previously presented at the 2022 Muscular Dystrophy Association Clinical & Scientific Conference

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 a Progressive Neuromuscular Disease with Multisystem Involvement[1,2]

Cardiac Arrhythmias

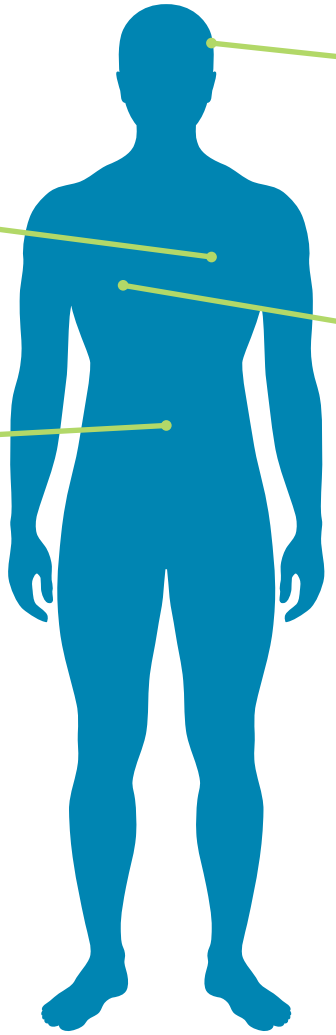
- Increase with age and weakness
- Progressive heart block, prolonged QRS and PR interval

Gastrointestinal Symptoms

- Abdominal pain, constipation, diarrhea
- Dysphagia

Endocrine Abnormalities

- Glucose intolerance, thyroid dysfunction, testosterone deficiency



Cognition Impaired

- Executive function and visual spatial processing deficits
- Global cognitive dysfunction
- Avoidant personality disorder

Respiratory

- Respiratory failure
- Anesthesia risks

Prominent Daytime Sleepiness and Fatigue

- Combination of OSA and central hypoventilation

Increased Risk of Neoplasms

DM1, myotonic dystrophy type 1; ECG, electrocardiogram; OSA, obstructive sleep apnea.

1. LoRusso S, et al. *Neurotherapeutics.* 2018;15(14):872–84; 2. Ashizawa T, et al. *Neurol Clin Pract.* 2018;8(6):507–20.

The International END-DM1 Study will Help Establish Biomarkers and Clinical Endpoints Needed to Support DM1 Clinical Trial Design

- Current natural history study for the Myotonic Dystrophy Clinical Research Network (DMCRN)
- Enrolling 700 participants
- Observation period: 24 months
- Characterizing endpoints, patient-reported outcomes, and patient populations to support design and recruitment of interventional trials

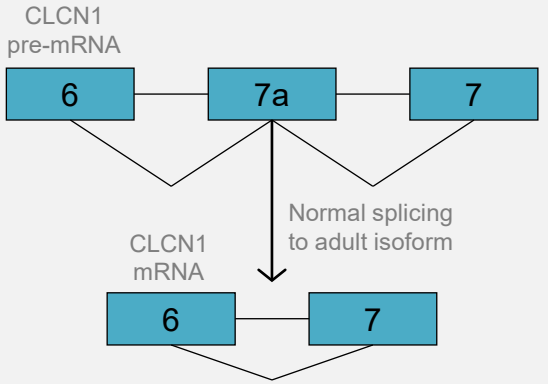
END-DM1, Establishing Biomarkers and Clinical Endpoints in Myotonic Dystrophy Type 1. ClinicalTrials.gov. NCT03981575 (END-DM1). [Last accessed March 2022].

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

Normal Conditions[1-3]

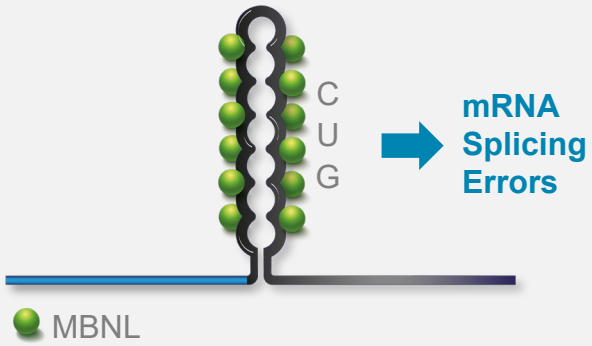
DMPK mRNA

CLCN1 pre-mRNA Splicing



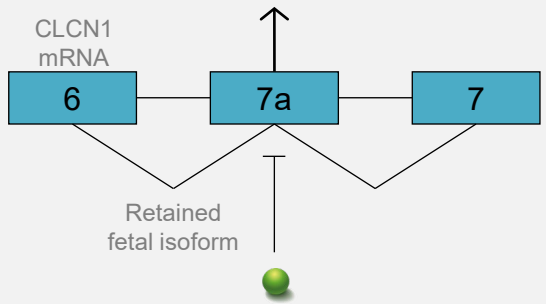
Mechanism of Disease[1-3]

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)

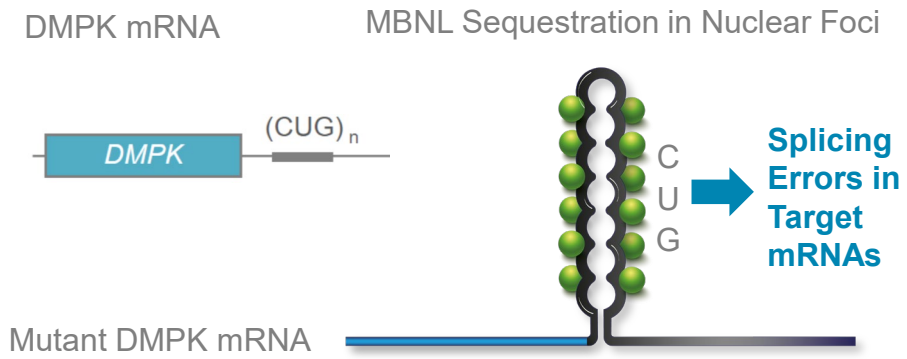


DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; MBNL, muscleblind like; mRNA, messenger ribonucleic acid.

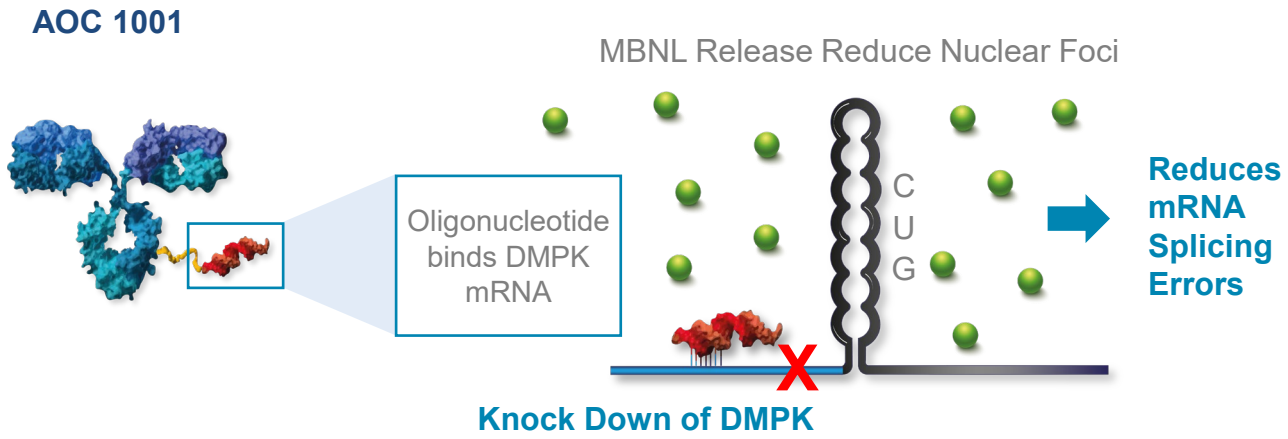
1. Brook JD, et al. *Cell.* 1992;68(4):799–808; 2. Lin X, et al. *Hum Mol Genet.* 2006;15(13):2087–97; 3. Lee JE, Cooper TA. *Biochem Soc Trans*. 2009;37(Pt 6):1281–6.

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



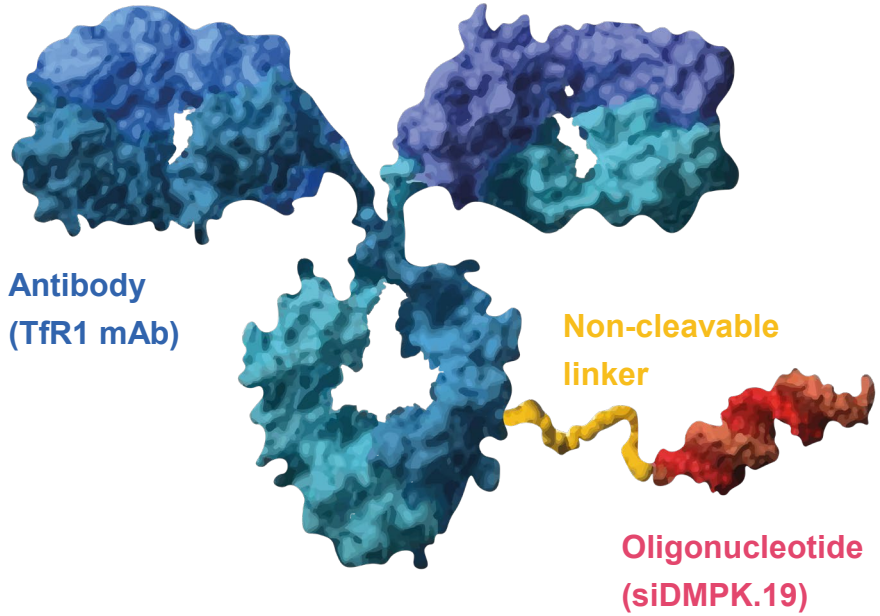
MBNL

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™ (AOC 1001-CS1) is a Randomized, Double-Blind, Placebo-Controlled, Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of AOC 1001 Administered Intravenously to Adult DM1 Patients (NCT05027269)

- **Patient population:**
  - N=44 participants (Part A and Part B)
  - Study drug administered as intravenous infusion

MARINA™

AOC, antibody oligonucleotide conjugate; CS1, clinical study 1; DM1, myotonic dystrophy type 1.

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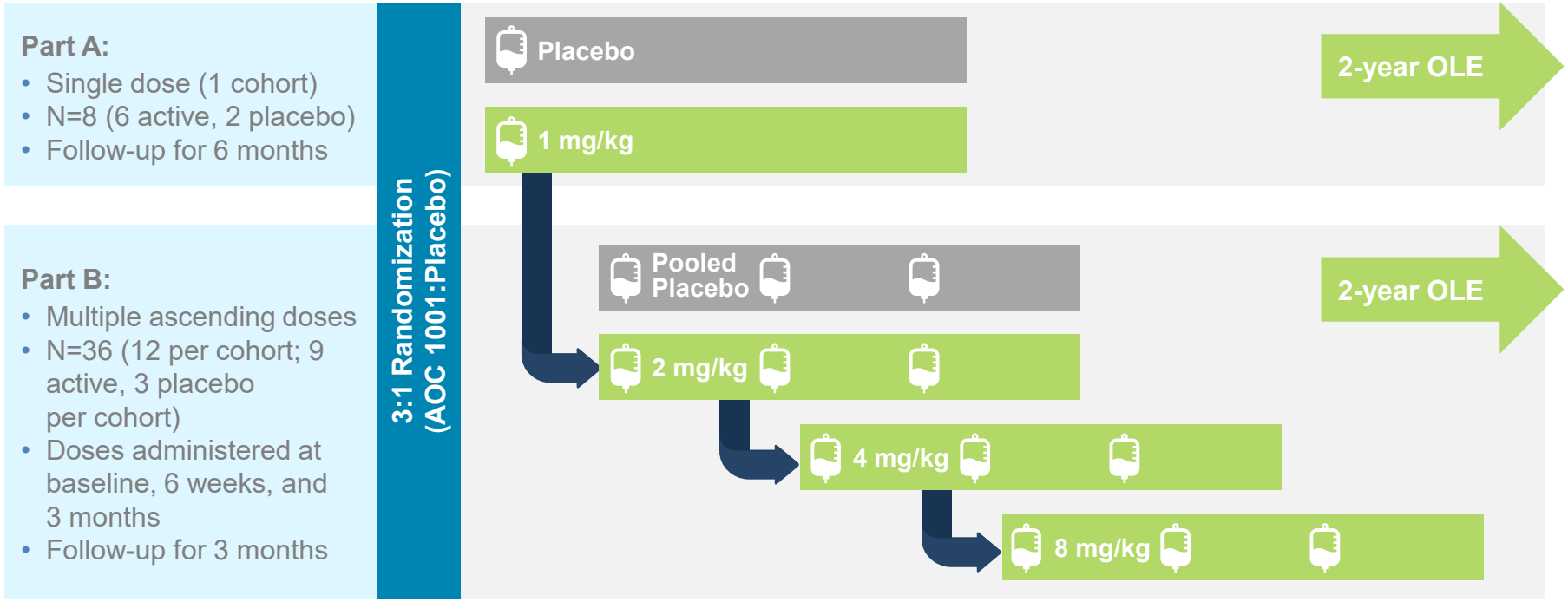
MARINA™ Study Design: Single and Multiple Doses of AOC 1001 in Adult DM1 Patients

- Cohorts will be initiated in a staggered fashion based on safety data review of preceding cohort(s)
- After completing MARINA™, participants who are eligible may enroll in an OLE study where all participants receive AOC 1001



Dose listed for all cohorts is based on siRNA weight

AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; OLE, open-label extension; siRNA, small inhibitory ribonucleic acid.

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Part B Key Visits and Assessments at Baseline, Month 3, and Month 6

MARINA™

Assessments:

- PRO[a]
- Myotonia
- 10-meter walk/run
- Muscle strength

Biopsy at baseline and intervals throughout the study for DMPK mRNA levels and spliceopathy.

[a]PRO assessments collected both in clinic (baseline, Month 3, and Month 6) and at home with electronic devices.

DMPK, DM1 protein kinase; mRNA, messenger ribonucleic acid; PRO, patient-reported outcome.

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MARINA™ Study Objectives

PRIMARY OBJECTIVE

- Safety and tolerability of single and multiple ascending doses of AOC 1001 in DM1 patients

SECONDARY OBJECTIVES

- PK profile of single and multiple doses and select major metabolites
- PD profile, including DMPK mRNA levels, from muscle biopsies
- Target pathway activity as measured by spliceopathy

EXPLORATORY OBJECTIVES

- Change from baseline on measures of mobility, muscle strength, myotonia and PROs

AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; mRNA, messenger ribonucleic acid; PD, pharmacodynamic; PK, pharmacokinetic; PRO, patient-reported outcome.

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MARINA™ Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Males or females aged from 18 to 65 years • Genetic diagnosis of DM1 with DMPK CTG repeat length ≥100 • Clinician-assessed signs of DM1 • Ability to walk independently for at least 10 meters at screening	• Diabetes not adequately controlled • BMI >35 kg/m^2 • Uncontrolled hypertension (BP >160/100 mm Hg) • Congenital DM1 • History of TA biopsy within 3 months of Day 1 or planning to undergo TA biopsies during study period • Recent treatment with an investigational drug • Treatment with anti-myotonic medication within 14 days of Day 1

BMI, body mass index; BP, blood pressure; DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; TA, tibialis anterior.

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MARINA™ Study Sites

- Participating academic sites in the US include those from DMCRN and END-DM1

Investigators:

- **Virginia Commonwealth University:** Nicholas Johnson, MD, MSCI, FAAN
- **Stanford University Medical Center:** John Day, MD, PhD
- **University of Rochester Medical Center:** Johanna Hamel, MD, PhD; Charles Thornton, MD
- **University of Kansas Medical Center:** Jeffrey Statland, MD
- **University of Florida:** SH Subramony, MD
- **Ohio State University:** W David Arnold, MD
- **University of Colorado, Denver:** Matthew Wicklund, MD
- **University of California, Los Angeles:** Payam Soltanzadeh, MD

DMCRN, Myotonic Dystrophy Clinical Research Network; END-DM1, Establishing Biomarkers and Clinical Endpoints in Myotonic Dystrophy Type 1; US, United States.

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MARINA™ Study Update

- In October 2021, a VCU Health patient was the first to receive an infusion in the MARINA™ study[1]
- The Part A single dose cohort is fully enrolled, and dosing is complete
  - No serious adverse events observed[2]
  - All adverse events were mild to moderate[2]
- The Part B multidose cohort is enrolling, and the MARINA™ study is on track for a preliminary assessment in the last quarter of 2022

Photo credit: Kevin Morley, VCU Health

VCU, Virginia Commonwealth University.
1. VCU Health News Center. 2021. https://www.vcuhealth.org/news/vcu-health-administers-first-infusion-in-milestone-study-of-myotonic-dystrophy. [Last accessed March 2022]; 2. Current as of April 5, 2022.

Authors and Acknowledgements

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Avidity would like to acknowledge the patients, families, and study staff involved in the MARINA™ trial