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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

Nicholas Johnson, MD[1]; John Day, MD, PhD[2]; Johanna Hamel, MD[3]; Jeffrey Statland, MD[4]; S.H. Subramony, MD[5]; W. David Arnold, MD[6]; Charles Thornton, MD[3]; Matthew Wicklund, MD[7]; Payam Soltanzadeh, MD[8]; Ben Knisely[9]; Varun Goel, PhD[9]; Kelly DiTrapani, BSN[9]; Chao-Yin Chen, PhD[9]; Kristi R. Clark[9]; Alissa Peters[9]; Carrie Heusner, PhD[9]; Husam Younis, PhD[9]; Li-Jung Tai, MD, PhD[9]; Elizabeth Ackermann, PhD[9]

[1] Virginia Commonwealth University; [2]Stanford University Medical Center; [3]University of Rochester; [4]University of Kansas Medical Center; [5]University of Florida; [6]The Ohio State University; [7]University of Colorado; [8]UCLA; [9]Avidity Biosciences. All authors have met authorship criteria.

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Introduction

- DM1 is a dominantly inherited, progressive neuromuscular disease with multiple organ involvement including skeletal and cardiac muscle, the gastrointestinal system, and the central nervous system[1–3]
- DM1 is typically characterized by myotonia and muscle weakness leading to dysarthria, dysphagia, immobility, and respiratory insufficiency[1–3]
- These clinical manifestations of disease place a significant burden on patients, affecting their quality of life across multiple domains, and are associated with premature mortality[4,5]
- 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 mis-splicing of multiple downstream genes which results in multiorgan manifestations of DM1[6–8]
- There are no US Food and Drug Administration (FDA) approved disease-modifying therapies for DM1, and current medical treatment is focused on symptom management[3,9]

Mechanism of Action

- AOC 1001 is an antibody oligonucleotide conjugate (AOC) designed to lower nuclear DMPK mRNA[10,11]
- Figure 1 illustrates the structure of AOC 1001 and its three components:
  - **Antibody:** Human transferrin receptor 1 (TfR1) targeting, ef fector function-null, humanized IgG1 antibody (TfR1 mAb)[10]
  - **Non-cleavable linker**[10]
  - **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[10]
- The TfR1 mAb targets muscles for delivery of siDMPK.19 into the cytoplasm and nucleus where it mediates DMPK mRNA degradation (Figure 2)[10]

Figure 1: AOC 1001

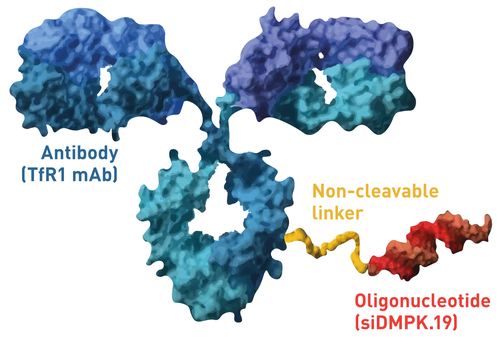
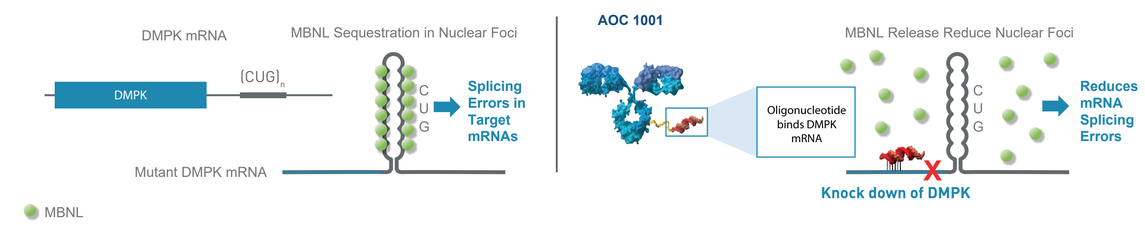


Figure 2: DM1, Caused by a Toxic Gain-of-Function mRNA, is Well Suited to an siRNA Approach



- Trinucleotide expansion in DMPK mRNA sequesters an RNA splicing protein MBNL (muscleblind like) in nuclear foci
- Sequestration of MBNL leads to RNA splicing errors in multiple muscle-related RNAs and induces DM1 disease manifestations
- Degradation of DMPK may allow MBNL to be released to perform its natural function to aid in splicing key mRNAs in muscle
- Potentially improves splice patterns, muscle function and reverses or stabilizes the course of DM1 disease. Splice patterns can serve as biomarkers

MARINA™ Study Objectives

The MARINA-OLE™ Phase 2 extension of the MARINA™ study is ongoing to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of multiple-doses of AOC 1001 administered intravenously to adult DM1 patients. Preliminary assessment of the MARINA™ study is on track for the last quarter of 2022

Primary Objective[11]

- **Safety and tolerability** of single and multiple doses

Secondary Objectives[11]

- **Pharmacokinetics**
- **Pharmacodynamics** (*DMPK* mRNA knockdown)
- **Spliceopathy**

Exploratory Objectives[11]

- Measures of clinical activity:
  - **Mobility**
  - **Muscle strength**
  - **Muscle function**
- Patient-reported outcomes (**PRO**)
- **Quality of life**

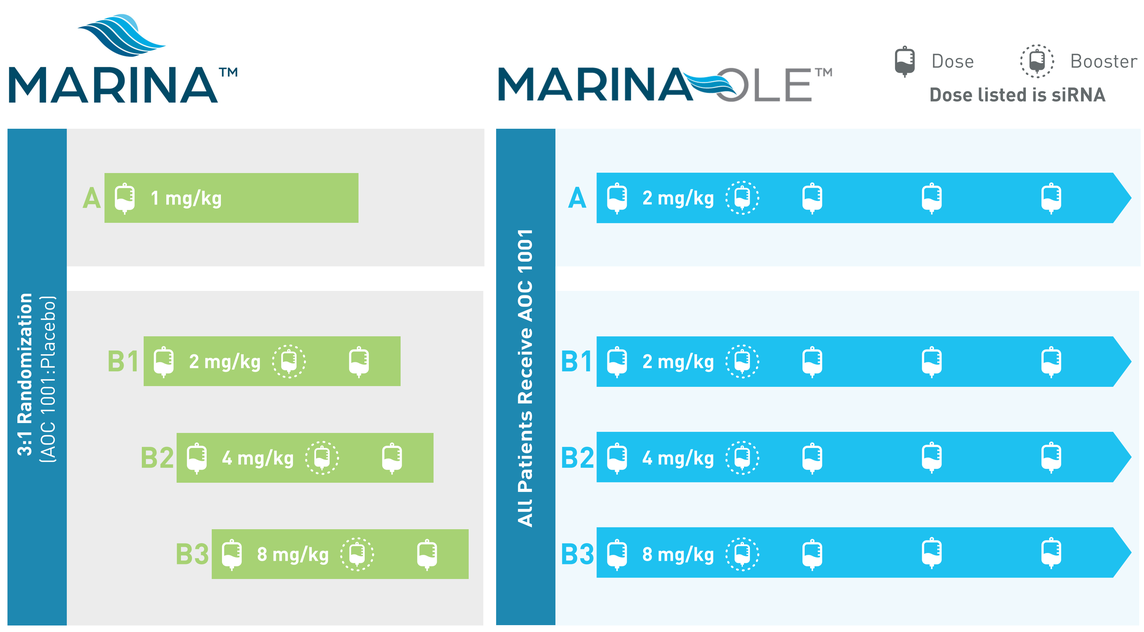
MARINA™

MARINA-OLE™

MARINA™ Study Design

- 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 (Figure 3)[11,12]
- Cohorts are initiated in a staggered fashion based on safety data review of preceding cohort(s)[11,12]
- After completing MARINA™, all patients may enroll in an open-label extension study and receive AOC1001
- Clinicaltrials.gov Identifier: NCT05027269[12]

Figure 3: MARINA™ and MARINA-OLE™ Allow for Both Short- and Long-term Data Collection to Evaluate AOC 1001*



- 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

- N = ~44 Ages 18-65
- **All patients receive AOC 1001**
- Quarterly doses - 1 booster after first 6 weeks
- 24-month treatment period

*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 closely with the FDA and the trial investigator to resolve the partial clinical hold as quickly as possible.

Key Inclusion and Exclusion Criteria

MARINA™

Key Inclusion Criteria[11,12]

- Males or females aged 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

Key Exclusion Criteria[11,12]

- Diabetes not adequately controlled
- BMI >35 kg/m^2
- Uncontrolled hypertension (BP >160/100 mm Hg)
- Congenital DM1
- History of tibialis anterior (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 medicwation within 14 days of Day 1

MARINA-OLE™

- Completion of MARINA™ study with satisfactory compliance and no significant tolerability issues
- Any new conditions or worsening of existing conditions that in the opinion of the investigator or sponsor would make the participant unsuitable for the study or could interfere with participation or completion of the study

MARINA™ Update

- US Food and Drug Administration (FDA) has placed a partial clinical hold on new participant enrollment in the Phase 1/2 MARINA™ clinical trial of AOC 1001 in adults with myotonic dystrophy type 1 (DM1). The partial clinical hold is in response to a serious adverse event reported in a single participant in the 4mg/kg cohort of the MARINA study
- 38 participants are currently enrolled in the MARINA and MARINA open label extension (MARINA-OLE™) trials
- All current participants, whether they are on AOC 1001 or placebo, may continue in their current dosing cohort and roll over into the MARINA-OLE where they will receive AOC 1001 as planned
- For more information visit: https://aviditybiosciences.investorroom.com/2022-09-27-Avidity-Biosciences-Announces-FDA-Partial-Clinical-Hold-on-New-Participant-Enrollment-in-Phase-1-2-MARINA-TM-Trial

AOC, antibody oligonucleotide conjugate; BMI, body mass index; BP, blood pressure; DM1, myotonic dystrophy type 1; DMCRN, Myotonic Dystrophy Clinical Research Network; DMPK, DM1 protein kinase; END-DM1, Establishing Biomarkers and Clinical Endpoints in Myotonic Dystrophy Type 1; MBNL, muscle blind-like protein; NCT, National Clinical Trial; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic; Q3M, every three months; Q6M, every six months; TA, tibialis anterior; TfR1, transferrin receptor 1; US, United States; VCU, Virginia Commonwealth University.

1. Udd B and Krahe R. *Lancet Neurol.* 2012;11(10):891–905; 2. Gourdon G and Meola G. *Front Cell Neurosci.* 2017;11:101; 3. LoRusso S, et al. *Neurotherapeutics.* 2018;15(4):872–84; 4. Hagerman KA, et al. *Muscle Nerve.* 2019;59(4):457–464; 5. Landfeldt E, et al. *J Neurol.* 2019;266(4):998–1006; 6. Brook JD, et al. *Cell.* 1992;68(4):799-808; 7. Lin X, et al. *Hum Mol Genet.* 2006;15(13):2087-97; 8. Lee JE and Cooper TA. *Biochem Soc Trans.* 2009; 37(PT 6):1281-6; 9. Ashizawa T, et al. *Neurol Clin Pract.* 2018;8(6):507–20; 10. Avidity Biosciences, Inc. Investigator's Brochure. 2021. 1.14.4.1. Edition 2.0; 11. Avidity Biosciences, Inc. AOC 1001-CS1 Protocol. 2021. Version 2.0; 12. Clinicaltrials.gov. NCT05027269 (MARINA). https://clinicaltrials.gov/ct2/show/NCT05027269 [Last accessed January 2022]; 13. Avidity Biosciences, Inc. Corporate Presentation. December 2021. https://aviditybiosciences.investorroom.com/download/December+2021+Avidity+Corporate+Presentation+FINAL.pdf [Last accessed January 2022]; 14. Avidity Biosciences, Inc. News Update. November 2021. https://aviditybiosciences.investorroom.com/2021-11-04-Avidity-Announces-First-Person-Dosed-with-an-Antibody-Oligonucleotide-Conjugate-AOC-TM [Last accessed January 2022]; 15. 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].