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

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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]
- AOC 1001 is an investigational therapeutic designed to address the molecular pathology of DM1 by lowering levels of DMPK mRNA through an siRNA mechanism
- 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 (NCT05027269)[10–12]

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, effector 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

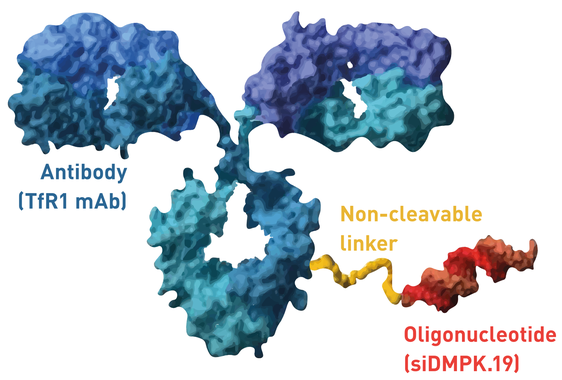
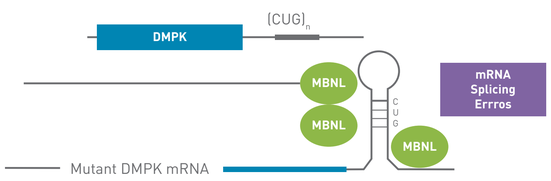


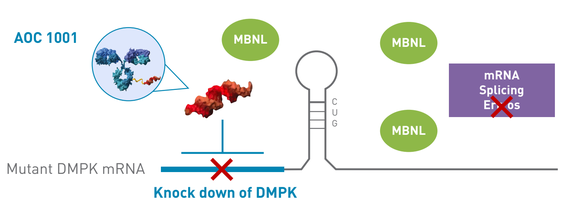
Figure 2: DM1, Caused by a Toxic Gain-of-Function mRNA, is Well Suited to an siRNA Approach

Mechanism of disease



- 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

Potential therapeutic approach



- 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 the course of DM1 disease. Splice patterns can serve as biomarkers

Objectives

Primary Objective[11]

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

Secondary Objectives[11]

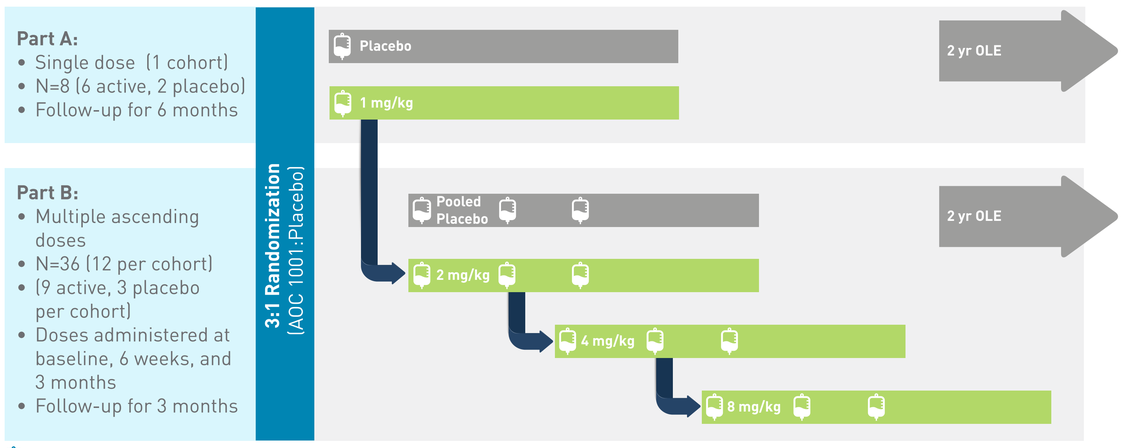
- PK profile of single and multiple doses and select major metabolites
- PD profile, including DMPK mRNA levels, from muscle biopsies
- Efficacy as measured by spliceopathy

Exploratory Objectives[11]

- Change from baseline on measures of mobility, muscle strength and patient-reported outcomes

Figure 3: 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 will be initiated in a staggered fashion based on safety data review of preceding cohort(s)[11,12]
- Clinicaltrials.gov Identifier: NCT05027269[12]



Patient population:

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

Part B key visits and assessments include:

- Biopsy at baseline and intervals throughout the study for DMPK mRNA levels and spliceopathy
- Patient reported outcome assessments collected both in-clinic (baseline, month 3 and month 6) and at home with electronic devices
- Exploratory efficacy endpoints of function and strength include myotonia, 10 meter walk run, and muscle strength assessments that are evaluated at key visits including baseline, month 3 and month 6
- After completing MARINA, participants who are eligible may enroll in an open-label extension study where all participants receive AOC 1001

Key Inclusion and Exclusion Criteria

Key Inclusion Criteria[11,12]	Key Exclusion Criteria[11,12]
• Males or females aged 18 to 65 years	• Diabetes not adequately controlled
• Genetic diagnosis of DM1 with DMPK CTG repeat length ≥100	• BMI >35 kg/m^2
• Clinician-assessed signs of DM1	• Uncontrolled hypertension (BP >160/100 mm Hg)
• Ability to walk independently for at least 10 meters at screening	• 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 medication within 14 days of Day 1

Map of Trial Sites[12]

- This map illustrates the study sites where the study is currently being conducted[12]
- Participating academic sites in the US include those from DMCRN and END-DM1[13]

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.

[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].