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 tract, and the central nervous system [1]. DM1 is typically characterized by myotonia and muscle weakness leading to dysarthria, dysphagia, immobility, and respiratory insufficiency [2]. 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 [3]. 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 multigene manifestations of DM1 [4]. There are no US Food and Drug Administration (FDA) approved disease-modifying therapies for DM1, and current medical treatment is focused on symptom management [5].

Mechanism of Action

AOC 1001 is an antibody oligonucleotide conjugate (AOC) designed to lower nuclear DMPK mRNA [6,7]. Figure 1 illustrates the structure of AOC 1001 and its three components:

- Antibody: Human transferrin receptor 1 (TfR1) targeting, of factor function-null, humanized IgG1 antibody (TfR1 mAb)
- Non-clearable 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 DMPK mRNA

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, leading to nuclear foci
- Sequestration of MBNL leads to RNA splicing errors in multiple muscle-related RNAs and induces DM1 disease manifestations

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

- Degradation of MBNL 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 histones to the course of DM1 disease
- Splice patterns can serve as biomarkers

MARINA™ Study Design

Primary Objective

- Safety and tolerability of single and multiple doses

Secondary Objectives

- Pharmacokinetics
- Pharmacodynamics (DMPK mRNA knockdown)
- Splicopathy

Exploratory Objectives

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

Key Inclusion and Exclusion Criteria

**MARINA™**

- Males or females aged 18 to 65 years
- Genomic diagnosis of DM1 with DMPK CTG repeat length ≥2000
- Clinician-assessed signs of DM1
- Ability to walk independently for at least 10 meters at screening

**MARINA-OLE™**

- Completion of MARINA™ study with satisfactory compliance

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**MARINA™** Key Exclusion Criteria

- **Key Exclusion Criteria**
  - Diabetes not adequately controlled
  - BMI ≥35 kg/m²
  - 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 medication within 14 days of Day 1

**MARINA-OLE™**

- Completion of MARINA™ study with satisfactory compliance and no significant tolerability issues
- New 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

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, muscleblind-like protein; NCT, National Clinical Trial; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic; QM, every three months; QM, every six months; TA, tibialis anterior; TfR1, transferrin receptor 1; US, United States; VCU, Virginia Commonwealth University.