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.
- DM1 is typically characterized by myotonia and muscle weakness leading to dysarthria, dysphagia, immobility, and respiratory insufficiency.
- 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.
- 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 multimorbid manifestations of DM1.
- There are no US Food and Drug Administration (FDA) approved disease-modifying therapies for DM1, and current medical treatment is focused on symptom management.
- 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 2 clinical study (NCT05027269).

Mechanism of Action

- AOC 1001 is an antibody oligonucleotide conjugate (AOC) designed to lower nuclear DMPK mRNA levels.
- Figure 1 illustrates the structure of AOC 1001 and its three components:
  - Antibody: Human transferrin receptor 1 (TR1) targeting, effector function-null, humanized IgG1 antibody (TR1 mAb)
  - Non-clearable linker
  - Oligonucleotide: Double-stranded siRNA oligonucleotide (siDMPK.19) complementary to a sequence in the 3’ untranslated region (exon 15) of both wild-type and mutant human DMPK mRNA
- The TR1 mAb targets muscle cells for delivery of siDMPK.19 into the cytoplasm and nucleus where it mediates DMPK mRNA degradation (Figure 2).

Objective

- Safety and tolerability of single and multiple ascending doses of AOC 1001 in adults with DM1 in a Phases 1 and 2 clinical study (NCT05027269).

Key Inclusion and Exclusion Criteria

- Key Inclusion Criteria:
  - Mexican or females aged 18 to 65 years
  - Genetic diagnosis of DM1 with DMPK CTG repeat length ≥100
  - Clinician-ascertained signs of DM1
  - Ability to walk independently for at least 10 meters at screening
- Key Exclusion Criteria:
  - Diabetes not adequately controlled
  - BMI ≥35 kg/m²
  - Uncontrolled hypertension (BP >160/100 mm Hg)
  - Congenital DM1
  - History of skeletal anterior TAI biopsy within 3 months of Day 1 or planning to undergo TA biopsy during study period
  - Recent treatment with an investigational drug
  - Treatment with anti-myotonic medication within 16 days of Day 1

Map of Trial Sites

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