Phase 1/2 Trial Evaluating AOC 1020 Safety and Pharmacokinetics in Adults with Facioscapulohumeral Muscular Dystrophy (FSHD): FORTITUDE Trial Design

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**Background**
- FSHD is one of the most common forms of muscular dystrophy affecting approximately 15,000–38,000 people in the US.
- FSHD is an autosomal dominant disease caused by abnormal expression of double homeobox 4 (DUX4), leading to a series of downstream events that result in skeletal muscle degeneration and wasting (Figure 1).1-8
  - Characterized by slowly progressive, often asymmetric skeletal muscle loss with onset often in teenage and adult years.
- Approximately 20% of patients will end up using a wheelchair.
- AOC 1020 is an antibody oligonucleotide conjugate (AOC) designed to target DUX4 messenger RNA (mRNA) for degradation and to address the underlying cause of FSHD (Figure 1B).1
- AOC 1020 has been granted fast-track and orphan designation by the U.S. FDA and orphan drug designation by the EMA for the treatment of FSHD.9

**Avidity’s Approach**
- FSHD clinical score (FCS) of 2 to 14 (inclusive, with points 0 to 14).6
- Presence or history of clinically significant illness, or abnormal test result/finding that could affect a participant’s safety or ability to comply with study procedures
- Patient-reported outcomes (PRO)
- Muscle strength (e.g., hand held dynamometry)
- Measures of clinical activity
- DUX4 siRNA optimization for the treatment of FSHD (16,000–38,000 people in the US)

**Mechanism of Action**
- Figure 2 illustrates the structure of AOC 1020 and its three components:
  1. Antibody: Humanized monoclonal antibody (hAVO1mAb) targeting DUX4 mRNA to affect delivery to skeletal muscle.1-8
  2. Non-cleavable linker: MMC maleimide linker, enhanced for stability and durability.1-8
  3. Oligonucleotide: Stabilized siRNA targeting DUX4 mRNA (siDUX4.6), engineered and stabilized to withstand lysosomal enzymes, selected for potency and specificity, and modified to diminish off-target effects.1-8

**Trial Objectives**
- **Primary Objective**: To evaluate the safety and tolerability of ascending doses of AOC 1020 in patients with FSHD
- **Secondary Objective**: Plasma pharmacokinetics and muscle concentrations
- **Key Exploratory Objectives**: Pharmacodynamics, DUX4-regulated gene expression (from muscle biopsies taken at baseline and after 4 months of treatment), measures of clinical activity, muscle strength (e.g., hand hold dynamometry), muscle composition and volume measured by magnetic resonance imaging (MRI), including MRI measures of muscle fat infiltration, muscle fat fraction, and lean muscle volume, patient-reported outcomes (PRO).

**Key Inclusion and Exclusion Criteria**
- **Inclusion Criteria**: 18 to 65 years (inclusive) of age, FSHD clinical score (FCS) of 2 to 14 (inclusive, with points 0 to 14), ambulatory and able to walk 10 meters (use of walkers or 2 canes to walk 10 meters are excluded)
- **Exclusion Criteria**: At least 1 muscle region in the leg suitable for biopsy based on the Screening MRI

**Key Exclusion Criteria**
- Diagnosed with congenital or infantile FSHD
- Body mass index (BMI) >35.0 kg/m²
- Unable to have muscle biopsy performed in the eligible muscle within 30 days of screening due to Physician discretion of the patient’s suitability
- Previous muscle biopsy within 30 days
- Presence or history of clinically significant illness, medical condition, or abnormal test result/finding that could affect a participant’s safety or ability to comply with study procedures

**References**

**DISCLOSURES**
- This poster is sponsored by Avidity Biosciences, Inc.
- Some authors are employees of Avidity Biosciences, Inc. and may have stock options or an ownership interest.