Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Effects of AOC 1020 Administered Intravenously to Adult Patients with Facioscapulohumeral Muscular Dystrophy (FORTITUDE™) Trial Design

Amy Halseth1, Elizabeth Ackermann1, Teresa Brandt1, Chao-Yin Chen1, Mark Stahl1, Kelly DiTrapani1, Steve Hughes1, Rabi Tawil2, Jeffrey Statland3

1Avidity Biosciences, 2University of Rochester Medical Center, 3University of Kansas Medical Center

All authors have met the authorship criteria.

Background

- Facioscapulohumeral dystrophy (FSHD) is one of the most common forms of muscular dystrophy affecting approximately 16,000–38,000 people in the U.S.2
- 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 1A).3,4
- Characterized by slowly progressive, often asymmetric, skeletal muscle loss with onset often in teenage and adult years5
- Approximately 20% of patients with FSHD will end up using a wheelchair5
- There are no U.S. Food and Drug Administration (FDA) approved therapies for FSHD6
- Current medical treatment is focused on symptom management6
- 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)7,8
- 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 FSHD9

Sponsorship and Disclosures

This poster is sponsored by Avidity Biosciences. Some authors are or were employees of Avidity Biosciences and may have stock options or ownership interest. Data previously presented at the 2023 Muscular Dystrophy Association Clinical & Scientific Conference.

Avidity’s Approach to Treat FSHD

Figure 1. FSHD is Caused by Aberrant Expression of DUX4 in Muscle. DUX4 activates genes that are toxic to muscle cells

A. MECHANISM OF DISEASE3,4

- Apoptosis, immune signaling altered
- Myogenesis inhibited

B. THERAPEUTIC APPROACH

- Genetic signature activated by DUX4
- Genetic signature shutdown by AOC 1020

Abbreviations

AOC, antibody oligonucleotide conjugate; BMI, body mass index; DUX4, double homeobox 4; FDA, Food and Drug Administration; EMA, European Medicines Agency; FSHD, facioscapulohumeral dystrophy; mRNA, messenger RNA.

References

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Mechanism of Action

Figure 2 illustrates the structure of AOC 1020 and its three components:

1. Antibody: Human transferrin receptor 1 (TfR1) targeting, effector function-null, humanized IgG1 antibody (hAVO1mAb) to affect delivery to skeletal muscle1,2

2. Non-cleavable linker: MCC maleimide linker, enhanced for safety and durability1,2

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 effects1,2

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-held dynamometry)
    - Muscle function (e.g., reachable workspace, timed up and go test)
  - 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)

Abbreviations

AOC, antibody oligonucleotide conjugate; BMI, body mass index; DUX4, double homeobox 4; FCS, FSHD clinical score; FSHD, facioscapulohumeral dystrophy; hAVO1mAb, humanized IgG1 monoclonal antibody; MCC, XXXX; MRI, magnetic resonance imaging; mRNA, messenger RNA; OLE, open-label extension; PRO, patient-reported outcomes; siDUX4.6, stabilized small interfering RNA targeting DUX4 mRNA; siRNA, small interfering RNA; TfR1, human transferrin receptor 1.

References


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FORTITUDE™ Trial Design

- FORTITUDE™ (AOC 1020-CS1) is a randomized, placebo-controlled, double-blind, global trial designed to evaluate the safety and tolerability of AOC 1020. The trial is being conducted in three parts in patients with FSHD (Figure 3):
  - Part A: A single cohort dose titration group evaluating two lower doses
  - Part B: Two multiple ascending dose cohorts evaluating two higher doses
  - Part C: A single-cohort, parallel-group, evaluating two doses selected based on part A and B results
- The trial will last 12 months and participants in each part will receive five doses of study medication administered quarterly with one booster at 6 weeks
- Eligible participants will have the option to enroll in an open-label extension (OLE) study
- Clinicaltrials.gov identifier: NCT05747924

References

Abbreviations
AOC, antibody oligonucleotide conjugate; OLE, open-label extension.
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Key Inclusion and Exclusion Criteria

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<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
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<tr>
<td>• 18 to 65 years of age (inclusive)</td>
<td>• Diagnosed with congenital or infantile FSHD</td>
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<tr>
<td>• Genetic diagnosis of FSHD1 or FSHD2</td>
<td>• Body mass index (BMI) &gt;35.0 kg/m²</td>
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<tr>
<td>• FSHD clinical score (FCS) of 2 to 14 (inclusive, with points from upper and lower body)</td>
<td>• Unable to have muscle biopsy performed (in the eligible muscle) within 30 days of screening due to:</td>
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<tr>
<td>• Ambulatory and able to walk 10 meters (use of walkers or two canes to walk 10 meters are excluded)</td>
<td>- Physician discretion of the patient’s suitability</td>
</tr>
<tr>
<td>• At least one muscle region in the leg suitable for biopsy based on the Screening MRI</td>
<td>- Previous muscle biopsy within 30 days</td>
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<td>- Plans to undergo a non-study muscle biopsy</td>
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Abbreviations

AOC, antibody oligonucleotide conjugate; BMI, body mass index; FCS, FSHD clinical score; FSHD, facioscapulohumeral dystrophy; MRI, magnetic resonance imaging.

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