Phase 1/2 Trial Evaluating AOC 1020 in Adults with FSHD: FORTITUDE™ Trial Design
Amy Halseth, PhD, Avidity Biosciences, Inc.
AOC 1020: An AOC Targeting DUX4 mRNA for Degradation

FSHD AFFECTS
~16,000 - 38,000
PEOPLE IN THE US¹,²

0 APPROVED THERAPIES³

THERAPEUTIC APPROACH

AOC 1020

¬ Antibody: Human transferrin receptor 1 (TfrR1) targeting, effector function-null, humanized IgG1 antibody (hAV01mAb) to affect delivery to skeletal muscle

¬ Non-cleavable linker: MCC maleimide linker, enhanced for safety and durability

¬ 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

AOC, an antibody-oligonucleotide conjugate; DUX4, double homeobox 4; FSHD, facioscapulohumeral dystrophy; US, United States.

**siDUX4.6 Shows Potent Inhibition of DUX4 Regulated Genes in Transgenic DUX4 Mouse Model of FSHD**

*Dose-dependent inhibition of DUX4-regulated genes in skeletal muscles*

Composite of DUX4-Regulated Genes
(Ilvbl, Slc15a2, Sord, Wfdc3)
Gastrocnemius

<table>
<thead>
<tr>
<th>% Composite Gene Expression</th>
<th>Timepoint (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>90</td>
<td>28</td>
</tr>
<tr>
<td>80</td>
<td>42</td>
</tr>
<tr>
<td>70</td>
<td>56</td>
</tr>
</tbody>
</table>

- **PBS**
- 0.5 mg/kg siRNA
- 2 mg/kg siRNA
- 6 mg/kg siRNA

ACTA1-MCM; FLExDUX4 mouse model of FSHD
N = 5 (*N=3; **N=4); mean ± SEM
AOC 1020* Prevents Muscle Weakness Development in FSHD Mouse Model

**Inhibition of DUX4 genes**

- **% DUX4 gene signature**
  - Vehicle
  - TMX Disease 2 mg/kg
  - TMX Disease 8 mg/kg

**Treadmill Running**

- **Total Running Distance (m)**
  - Vehicle
  - TMX Disease 2 mg/kg
  - TMX Disease 8 mg/kg

**In Vivo Force**

- **Normalized Torque (N/m/g)**
  - Vehicle
  - TMX Induced Disease
  - AOC; 2 mg/kg
  - AOC; 8 mg/kg

Additional AOC 1020 preclinical data were presented during the FSHD IRC 2023 poster session.

*Preclinical studies used anti-TfR1 antibody suitable for mice.*
A Phase 1/2 Study of AOC 1020 in Adults with FSHD
Clinicaltrials.gov identifier: NCT05747924
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.

**Trial Design**

**A1**
- 2:1 Randomization
- AOC 1020: Placebo (N=12)
- 1 mg/kg 2 mg/kg
- *1 mg/kg given as initial dose and 2 mg/kg given as booster and subsequent doses

**B1 & B2**
- 2:1 Randomization
- AOC 1020: Placebo (N=24)
- 4 mg/kg
- 8 mg/kg

**Expansion**
- 1:1:1 Randomization
- AOC 1020 dose 1: AOC 1020 dose 2: Placebo (N=36)
- Dose X

**OLE**

- Multidose quarterly with 1 booster after first 6 weeks; Dose listed is siRNA

- Follow-up of up to 12 months
- All participants will also receive biopsies at baseline


*One month after 3rd dose
Objectives and Endpoints

Primary Objective: Evaluate safety, tolerability
Secondary Objective: Evaluate PK (plasma/muscle) of AOC 1020
Key Exploratory Objectives: Evaluate effects on PD biomarkers and clinical endpoints (12 months)

Key Biomarker Endpoints
- MRI (total muscle volume, muscle fat fraction, muscle fat infiltration)
- DUX-4 regulated gene panel
- Circulating biomarkers

Key Exploratory Clinical Endpoints
- Reachable Workspace (RWS)
- Functional/mobility endpoints: Timed Up and Go, 10-meter walk/run, Time to ascend/descend 4 stairs
- Strength measurements (hand-held dynamometry & manual muscle testing)
- PROs to assess upper body function, quality of life, sleep, pain, anxiety, depression, and fatigue
- Clinical severity scores
<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 18 to 65 years of age (inclusive)</td>
<td>• Body mass index (BMI) &gt;35.0 kg/m²</td>
</tr>
<tr>
<td>• Genetic diagnosis of FSHD1 or FSHD2</td>
<td>- Previous muscle biopsy in study defined muscle group within 30 days of screening</td>
</tr>
<tr>
<td>• FSHD clinical score (FCS) of 2 to 14 (inclusive, with points from upper and lower body)</td>
<td>- Plans to undergo a non-study muscle biopsy</td>
</tr>
<tr>
<td>• Ambulatory and able to walk 10 meters (use of walkers or two canes to walk 10 meters are excluded)</td>
<td>• Clinically significant laboratory abnormalities</td>
</tr>
<tr>
<td>• Meets specific criteria for two upper quadrants in Reachable Workspace (RWS)</td>
<td>• Any contraindication to MRI</td>
</tr>
<tr>
<td>• At least one muscle region in the leg suitable for biopsy as assessed at the Screening MRI</td>
<td>• Clinically significant illness, medical condition, or abnormal test result that could affect a participant’s safety or ability to comply with study procedures</td>
</tr>
</tbody>
</table>
Additional sites are planned for North America and Europe
Summary and Conclusions

- AOC 1020 was designed to target the underlying cause of FSHD in muscle.
- Preclinical studies of AOC 1020 established inhibition of the DUX4 gene and prevention of muscle weakness development in an FSHD mouse model.
- We are now initiating the Phase 1/2 FORTITUDE™ study of AOC 1020 in adults with FSHD.
  - Primary Objective: Safety & Tolerability.
  - Exploratory objectives around muscle strength, function, and composition.
  - Trial sites are planned in the North America and Europe.
  - Continued collaboration between patients, caregivers, pharmaceutical companies, and the scientific community will be key to advance potential treatments for FSHD.
Thank You

- To access this, and other research conducted by the Avidity team, please use the QR code below or go to www.aviditybiosciences.com/platform/publications/
Backup slides
FSHD Mouse Model Study design

**Prevention Model Study design**

Day: -14

- DUX4 AOC or PBS

Day: 0

- Tamoxifen Induction (TMX) or Vehicle

Day: 13

- Treadmill Force

Day: 14

- DUX4 gene signature

Day: 16

- N = 9-12; males; mean ± SEM