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

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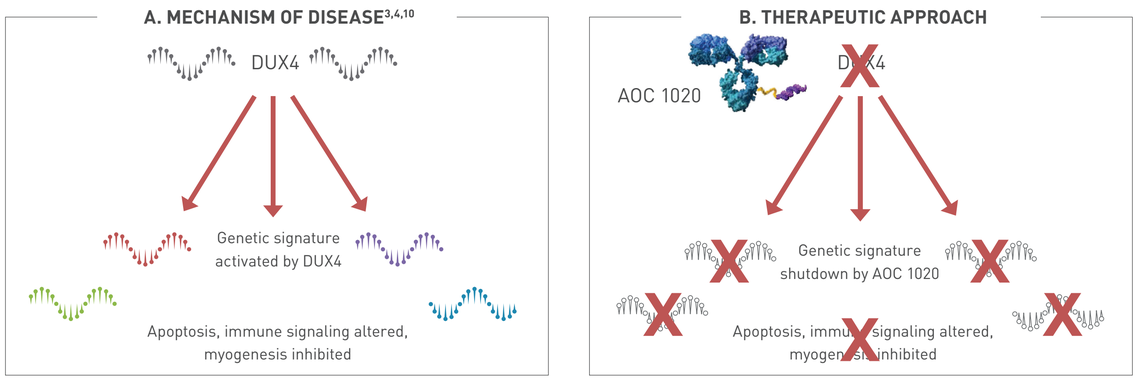
Background

- Facioscapulohumeral dystrophy (FSHD) is one of the most common forms of muscular dystrophy affecting approximately 16,000–38,000 people in the US[1,2]
- 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 variable, progressive, often asymmetric skeletal muscle loss with onset often in teenage and adult years[5]
  - Approximately 20% of patients will end up using a wheelchair[5]
- There are no US Food and Drug Administration (FDA) approved therapies for FSHD
- Current medical treatment is focused on symptom management[6]
- 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 FSHD[9]

Avidity's Approach

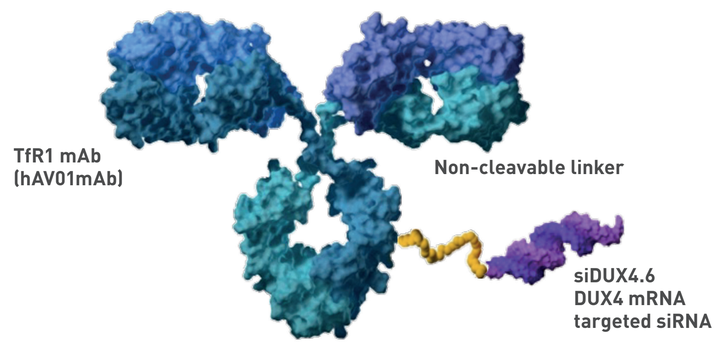
Figure 1. FSHD is caused by aberrant expression of DUX4 in muscle



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 muscle[7,8]
  2. **Non-cleavable linker:** MCC maleimide linker, enhanced for safety and durability[7,8]
  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[7,8]

Figure 2. AOC 1020: An antibody oligonucleotide conjugate targeting DUX4 mRNA for degradation



Trial Objectives and Endpoints

FORTITUDE™ Objectives and Endpoints

Primary Objective

- Evaluate safety and tolerability of AOC 1020

Secondary Objective

- Evaluate PK (plasma/muscle) of AOC 1020

Key Exploratory Objectives

- Evaluate effects of AOC 1020 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

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
- PROs to assess upper body function, quality of life, sleep, pain, anxiety, depression, and fatigue

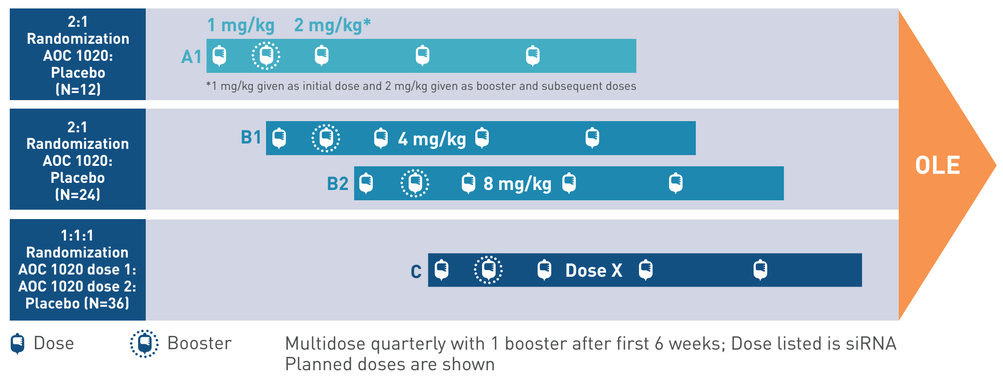
Abbreviations

AOC, antibody oligonucleotide conjugate; BMI, body mass index; DUX4, double homeobox 4; FCS, FSHD clinical score; FDA, Food and Drug Administration; EMA, European Medicines Agency; FSHD, facioscapulohumeral dystrophy; hAVO1mAb, humanized IgG1 monoclonal antibody; MRI, magnetic resonance imaging; mRNA, messenger RNA; OLE, open-label extension; PRO, patient-reported outcomes; RWS, reachable workspace; siDUX4.6, stabilized small interfering RNA targeting DUX4 mRNA; siRNA, small interfering RNA; TfR1, human transferrin receptor 1.

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 that in three parts in patients with FSHD (**Figure 3**):
  - **Part A**: A single cohort dose titration group evaluating 2 lower doses
  - **Part B:** 2 multiple ascending dose cohorts evaluating 2 higher doses
  - **Part C:** A single-cohort, parallel-group, evaluating 2 doses selected based on part A and B results
- Each participant will be followed for 12 months and receive 5 doses of study medication administered quarterly with 1 booster at 6 weeks
- Eligible participants will have the option to enroll in an open-label extension (OLE) study
- Clinicaltrials.gov identifier: NCT05747924[11]

Figure 3. FORTITUDE™ trial design

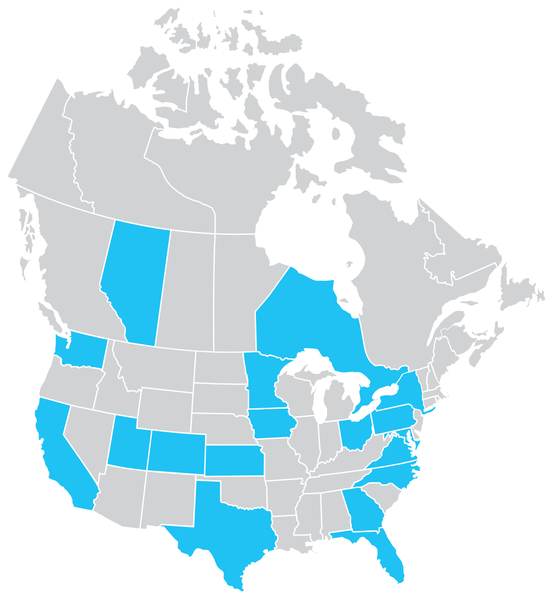


Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria

• 18 to 65 years of age (inclusive)
• Genetic diagnosis of FSHD1 or FSHD2
• FSHD clinical score (FCS) of 2 to 14 (inclusive, with points from upper and lower body)
• Ambulatory and able to walk 10 meters (use of walkers or 2 canes to walk 10 meters are excluded)
• Meets specific criteria for two upper quadrants in reachable workspace (RWS)
• At least 1 muscle region in the leg suitable for biopsy based on the Screening MRI
	• Body mass index (BMI) >35.0 kg/m^2
	• Unable to have muscle biopsy performed (in the eligible muscle) due to
	  - Physician discretion of the patient's suitability
	  - Previous muscle biopsy within 30 days
	  - Plans to undergo a non-study muscle biopsy
	• Clinically significant laboratory abnormalities
	• Any contraindication to MRI
	• 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

Map of Planned North American Sites



Additional sites are planned for North America and Europe

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DISCLOSURES

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

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