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

Amy Halseth[1], Elizabeth Ackermann[1], Teresa Brandt[1], Chao–Yin Chen[1], Mark Stahl[1], Kelly DiTrapani[1], Steve Hughes[1], Rabi Tawil[2], Jeffrey Statland[3]

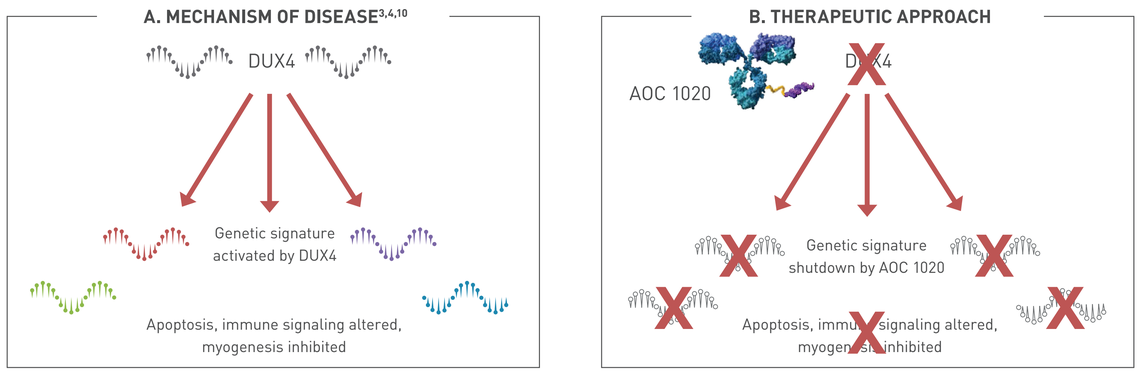
[1]Avidity Biosciences, [2]University of Rochester Medical Center, [3]University of Kansas Medical Center

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 slowly 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

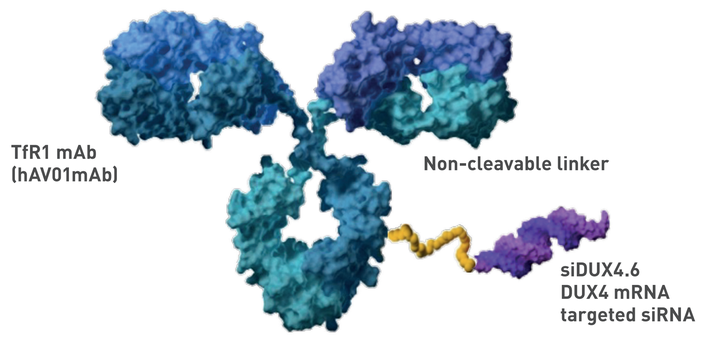
Figure 1. FSHD is caused by aberrant expression of DUX4 in muscle



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 (hAV01mAb) 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

FORTITUDE™

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)

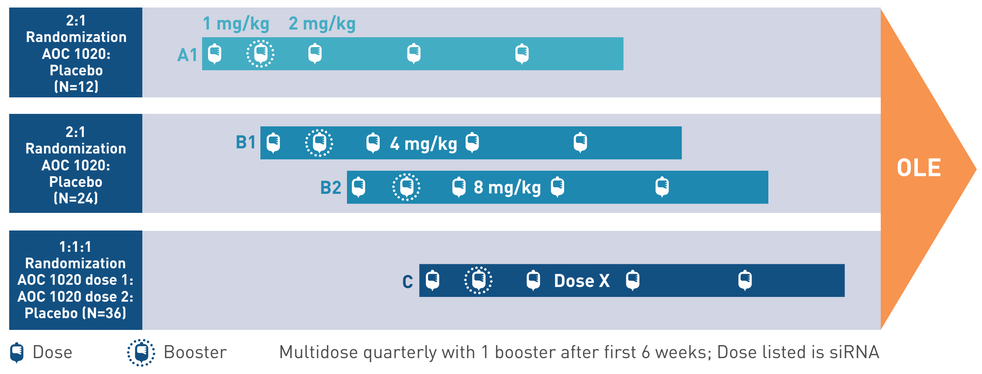
Abbreviations

AOC, antibody oligonucleotide conjugate; BMI, body mass index; DUX4, double homeobox 4; FCS, FSHD clinical score; FDA, Food and Drug Administration; EMA, European Medicines Agency; FSHD, facioscapulohumeral dystrophy; hAV01mAb, humanized IgG1 monoclonal antibody; 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.

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
- The trial will last 12 months and participants in each part will 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 employs both single and multiple dosing cohorts

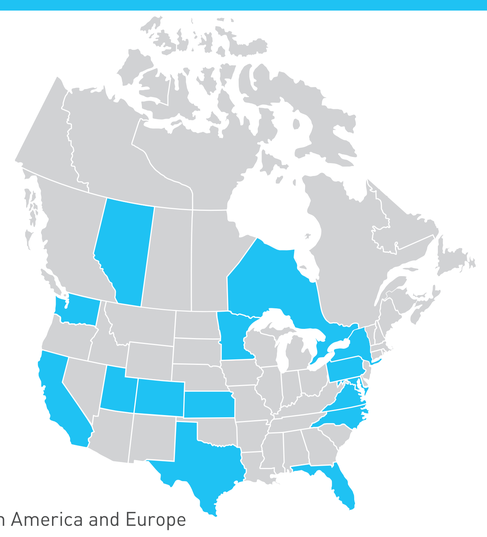


Key Inclusion and Exclusion Criteria

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)
• At least 1 muscle region in the leg suitable for biopsy based on the Screening MRI
	• Diagnosed with congenital or infantile FSHD
	• Body mass index (BMI) >35.0 kg/m^2
	• 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
	  – Plans to undergo a non-study muscle biopsy
	• Clinically significant laboratory abnormalities
	• Congenital or infantile FSHD
	• 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

References

1. Deenen JCW, et al. *Neurology*. 2014;83(12):1056–59.
2. US Census Bureau. Quick Facts. July 1 2022. https://www.census.gov/quickfacts/fact/table/US/ [Last Accessed March 2023].
3. Lemmers RJLF, et al. *Science.* 2010;329(5999):1650–53.
4. Snider L, et al. *PLoS Genet*. 2010;6(10):e1001181.
5. Tawil R and Van Der Maarel SM. *Muscle Nerve*. 2006;34(1):1–15.
6. Cohen J, et al. *Trends Mol Med*. 2021;27(2):123–37.
7. Malecova B, et al. AOC 1020: An Antibody Oligonucleotide Conjugate (AOC) in Development for the Treatment of FSHD. Oral presentation at the 29th Annual FSHD Society International Research Congress, Orlando, FL, June 6–17 2022.
8. Malecova B, et al. DUX4 siRNA Optimization for the Development of an Antibody-Oligonucleotide Conjugate (AOC™) for the Treatment of Facioscapulohumeral Muscular Dystrophy (FSHD). Oral presentation at the 2022 Muscular Dystrophy Association Clinical & Scientific Conference, Nashville, TN, March 13–16 2022.
9. Avidity Biosciences, Inc. Avidity Biosciences Reports Fourth Quarter and Year-End 2022 Financial Results and Recent Highlights. February 28 2023. https://aviditybiosciences.investorroom.com/2023-02-28-Avidity-Biosciences-Reports-Fourth-Quarter-and-Year-End-2022-Financial-Results-and-Recent-Highlights. [Last accessed March 2023].
10. Yao, et al. *Hum Mol Genet*. 2014;23(20):5342–52.
11. Clinicaltrials.gov. NCT05747924 [FORTITUDE]. https://clinicaltrials.gov/ct2/show/NCT05747924 [Last accessed March 2023].

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.

MDA Clinical & Scientific Conference 2023 | Hilton Anatole | Dallas, TX | March 19–22, 2023