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 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]

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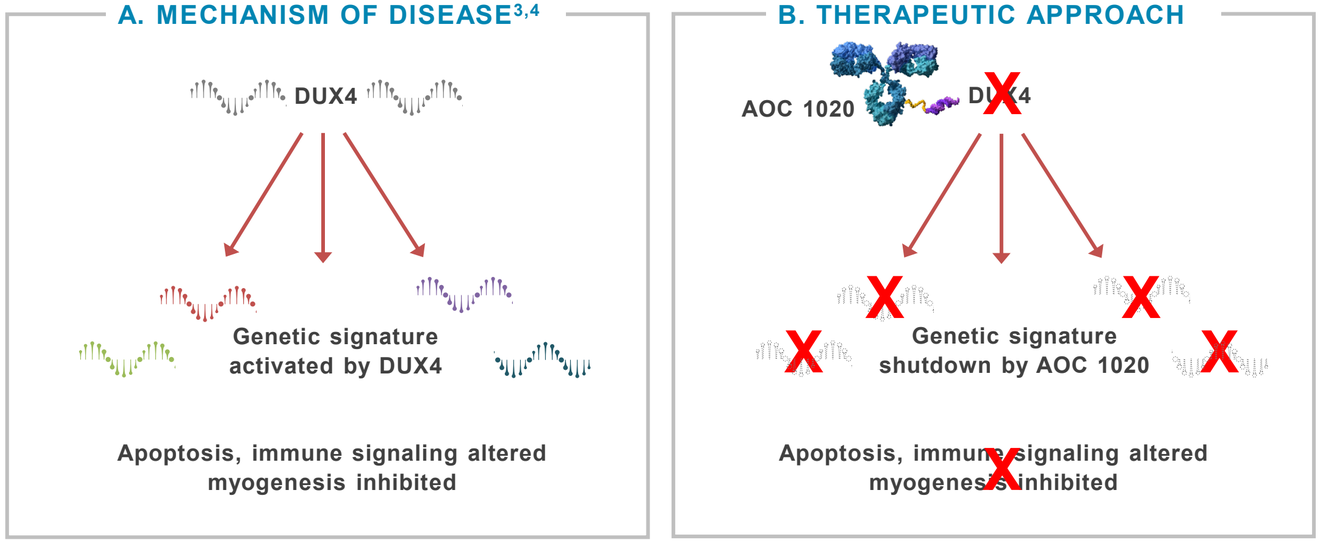
All authors have met the authorship criteria.

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.[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 with FSHD will end up using a wheelchair[5]
- There are no U.S. Food and Drug Administration (FDA) approved therapies for FSHD[6]
- 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 to Treat FSHD

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



Sponsorship and Disclosures
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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
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].

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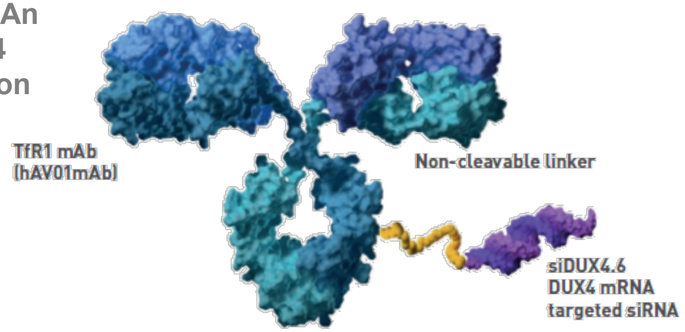
Mechanism of Action

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 muscle[1,2]
2. **Non-cleavable linker:** MCC maleimide linker, enhanced for safety and durability[1,2]
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 effects[1,2]

Figure 2. AOC 1020: An AOC 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)

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References

1. 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; 2. 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.

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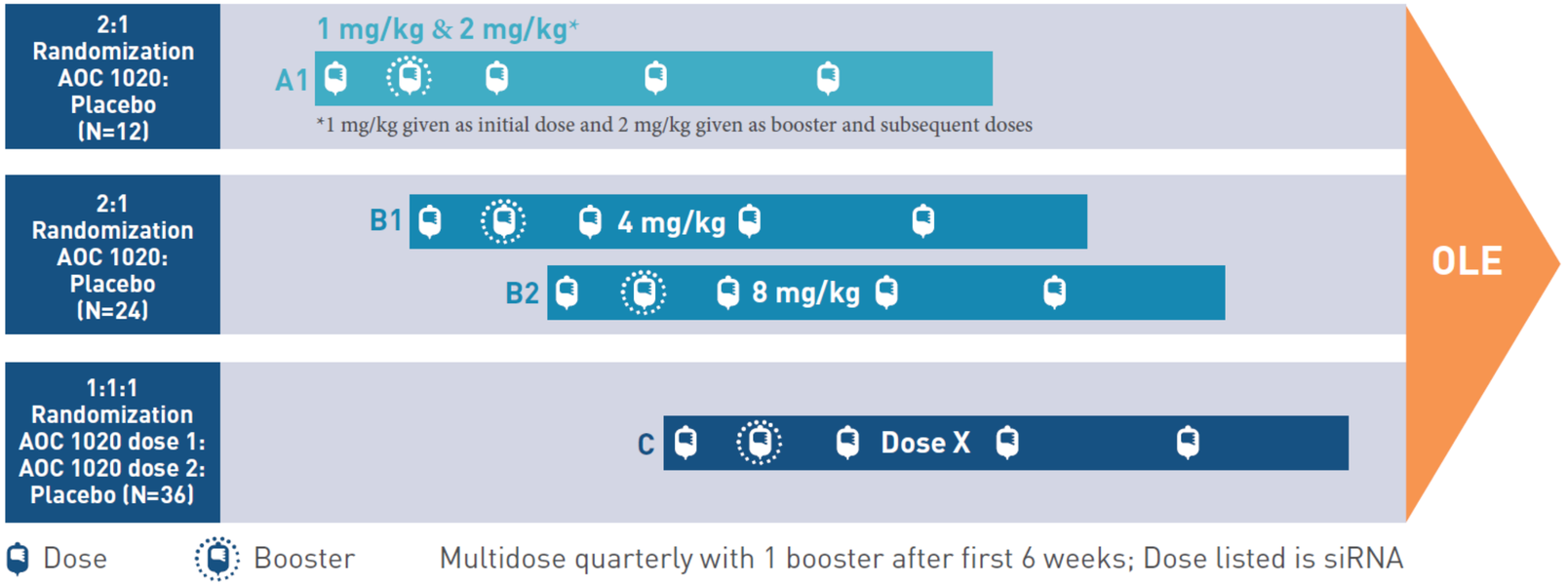
FORTITUDE™ Trial Design

- 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[1]

Figure 3. FORTITUDE™ Trial Design



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References

1. Clinicaltrials.gov. NCT05747924 [FORTITUDE]. https://clinicaltrials.gov/ct2/show/NCT05747924 [Last accessed March 2023].

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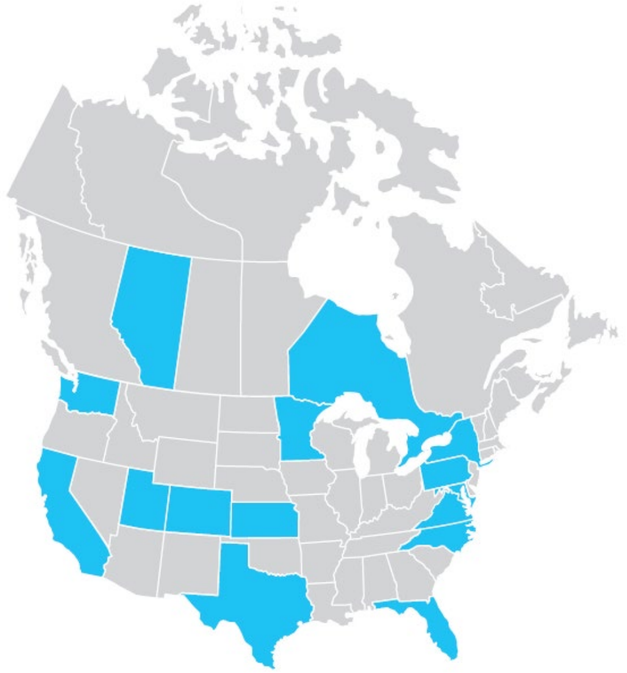
Key Inclusion and Exclusion Criteria

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 two canes to walk 10 meters are excluded) • At least one 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 • 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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