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, Steve Hughes1, Rabi Tawil2, Jeffrey Statland3

1Avidity Biosciences, University of Rochester Medical Center, 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.
- 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)1-4.
- One characteristic by variable, progressive, often asymmetric, skeletal muscle loss with onset often in adolescence and adult years1.
- Approximately 25% of patients will end up using a wheelchair5.
- There are no US Food and Drug Administration (FDA) approved therapies for FSHD.
- Current medical treatment is focused on symptom management.

AOC 1020 is a non-cleavable linker (NCL) designed to target DUX4 messenger RNA (mRNA) for degradation and to address the underlying cause of FSHD (Figure 1B).1
- AOC 1020 has been reported to treat and arrest progression by the U.S. FDA and orphan drug designation by the EMA for the treatment of FSHD.

Avidity’s Approach

Mechanism of Action
- Figure 2 illustrates the structure of AOC 1020 and its three components:
  1. Antibody: Human transmembrane TIR1 targeting, effector function-null, humanized IgG1 antibody (hAVO1mAb) to effect delivery to skeletal muscle5.
  3. Dipeptidylglycine: 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 effects7.

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

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.
- DUX4-regulated gene panel.

Key Exploratory Clinical Endpoints
- Reachable Workspace (RWS).
- Functional/mobility endpoints.
- Time up and go, 10-meter walk/run, time to ascend/descend 4 stairs.
- Strength measurements.
- Hand-held dynamometry.
- PDQ to assess upper body function, quality of life, sleep, pain, anxiety, depression, and fatigue.

Key Inclusion and Exclusion Criteria

Key Inclusion 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 or more canes to walk 10 meters are excluded).
- Meet 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.
- Some authors are employees of Avidity Biosciences, Inc. and may have stock options or an ownership interest.
- Clinicaltrials.gov identifier: NCT05747924

Figure 3. FORTITUDE™ trial design

Key Exclusion Criteria
- Body mass index (BMI) <19.3 kg/m².
- 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 lesion that results in finding that could affect a participant’s safety or ability to comply with study procedures.

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

References

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