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

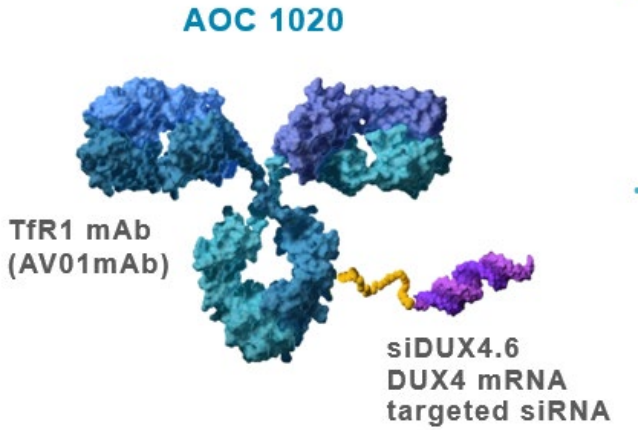
FSHD AFFECTS

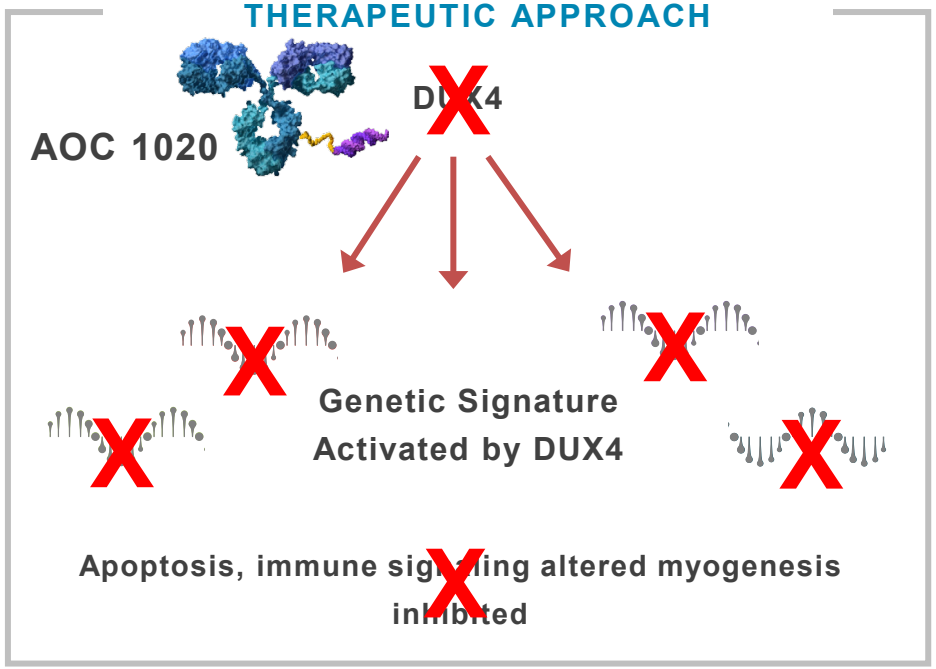
~16,000 - 38,000

PEOPLE IN THE US[1,2]

0

APPROVED THERAPIES[3]





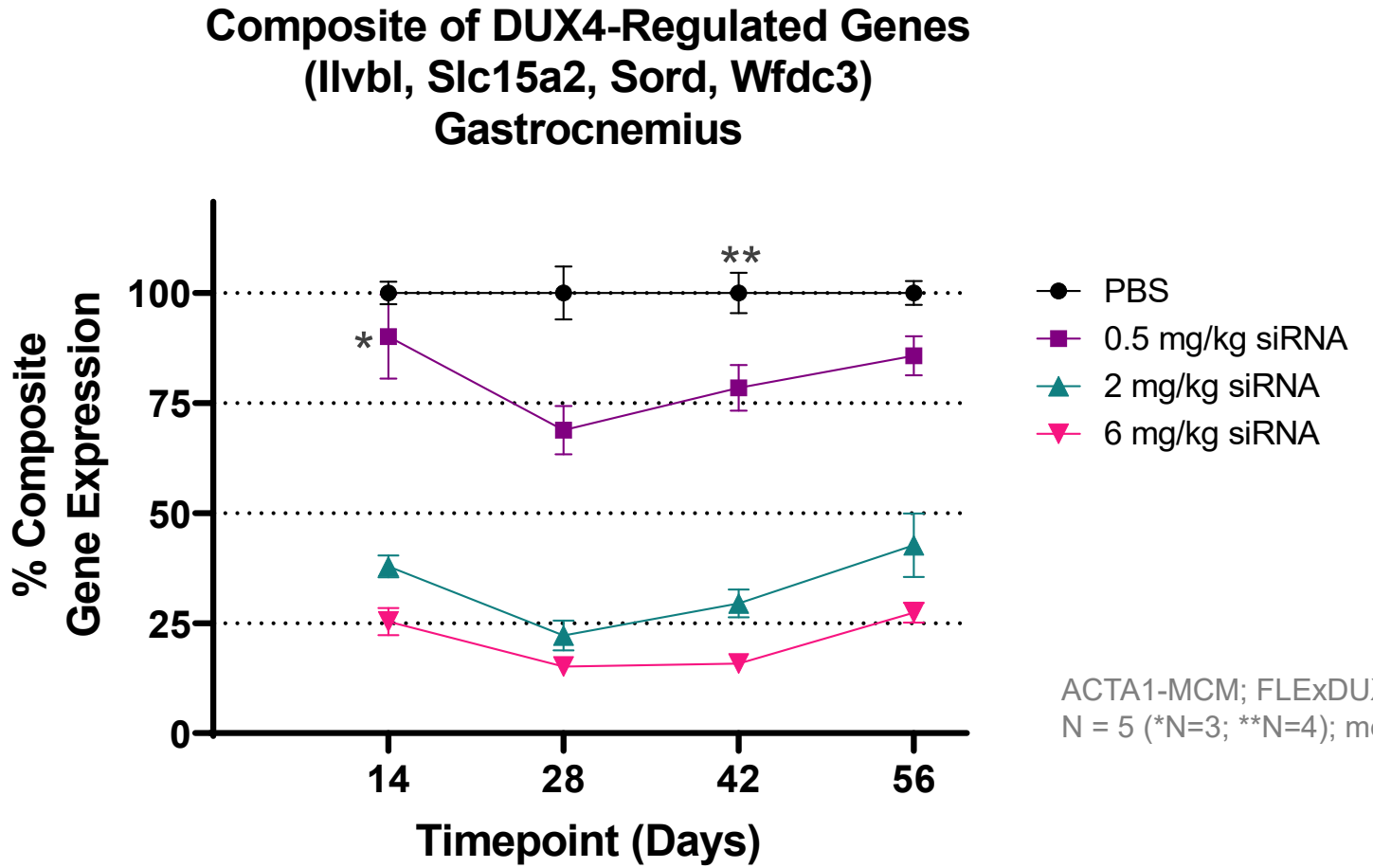
- **Antibody:** Human transferrin receptor 1 (TfR1) targeting, effector function-null, humanized IgG1 antibody (hAVO1mAb) to affect delivery to skeletal muscle
- **Non-cleavable linker:** MCC maleimide linker, enhanced for safety and durability
- **Oligonucleotide:** Stabilized siRNA targeting DUX4 mRNA (siDUX4.6); engineered and stabilized to withstand lysosomal enzymes, selected for potency and specificity, and modified to diminish off-target effects

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

1. Deenen JCW, et al. *Neurology*. 2014;83(12):1056-1059; 2. US Census Bureau. Quick Facts. https://www.census.gov/quickfacts/fact/table/US/ [Last Accessed February 2022]; 3. Cohen J, et al. *Trends Mol Med.* 2021;27(2):123-137; 4. Lemmers RJLF, et al. *Science.* 2010;329(5999):1650–1653; 5. Snider L, et al. *PLoS Genet*. 2010;6(10):e1001181; 6. Yao et al. *Hum Mol Genet*. 2014;23(20):5342-52.

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

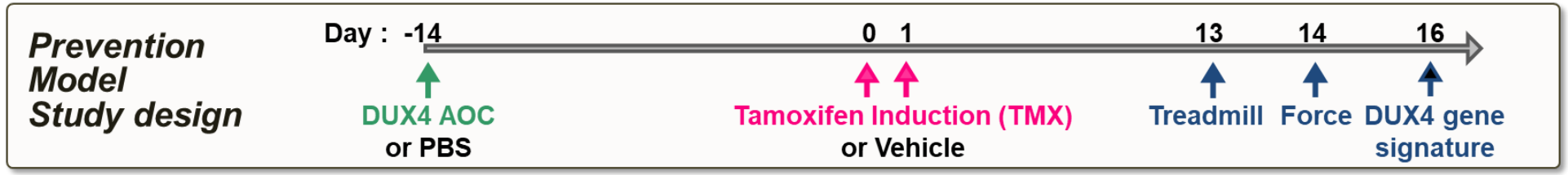
Dose-dependent inhibition of DUX4-regulated genes in skeletal muscles



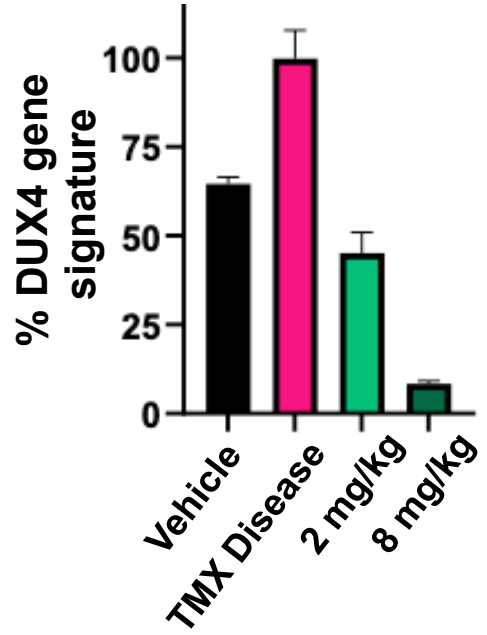
ACTA1-MCM; FLExDUX4 mouse model of FSHD
N = 5 (*N=3; **N=4); mean ± SEM

AVIDITY BIOSCIENCES

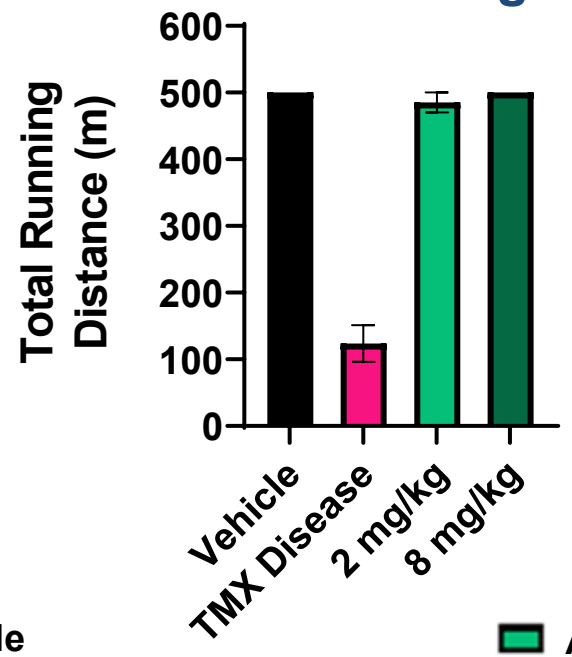
AOC 1020* Prevents Muscle Weakness Development in FSHD Mouse Model



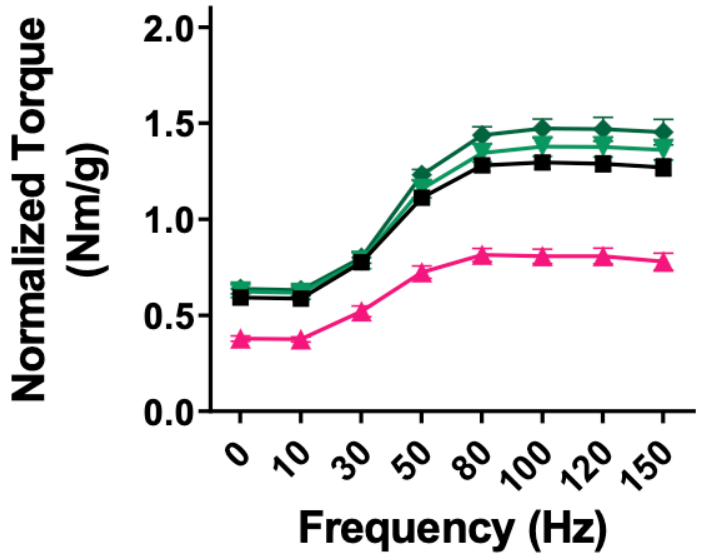
Inhibition of DUX4 genes



Treadmill Running



In Vivo Force



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

*Preclinical studies used anti-TfR1 antibody suitable for mice

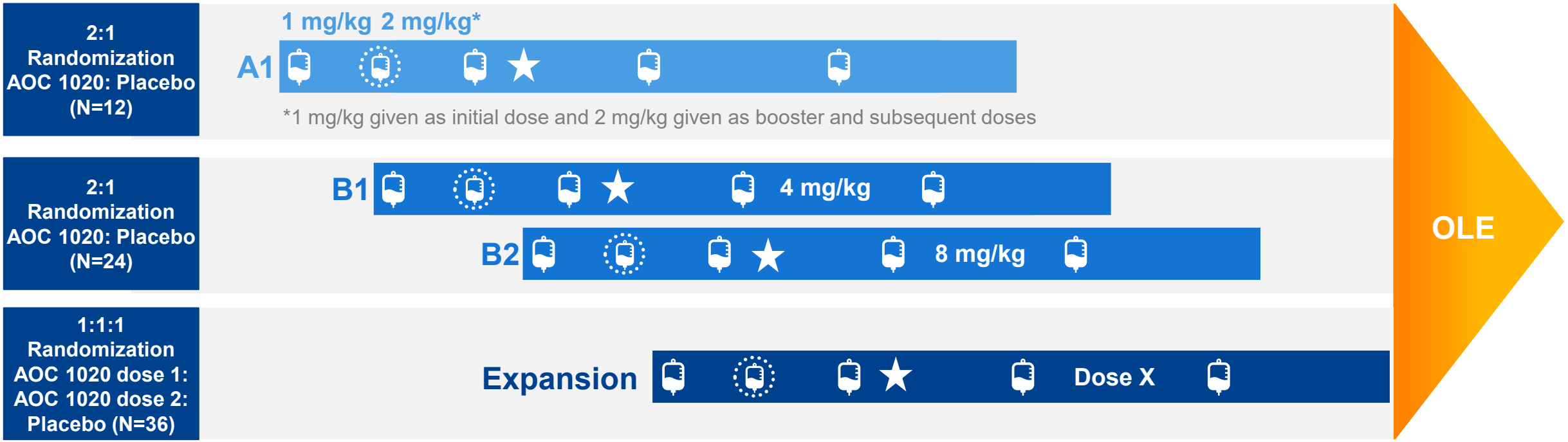
A Phase 1/2 Study of AOC 1020 in Adults with FSHD

Clinicaltrials.gov identifier: NCT05747924

AVIDITY BIOSCIENCES

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



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

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

†One month after 3rd dose

FORTITUDE™ 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

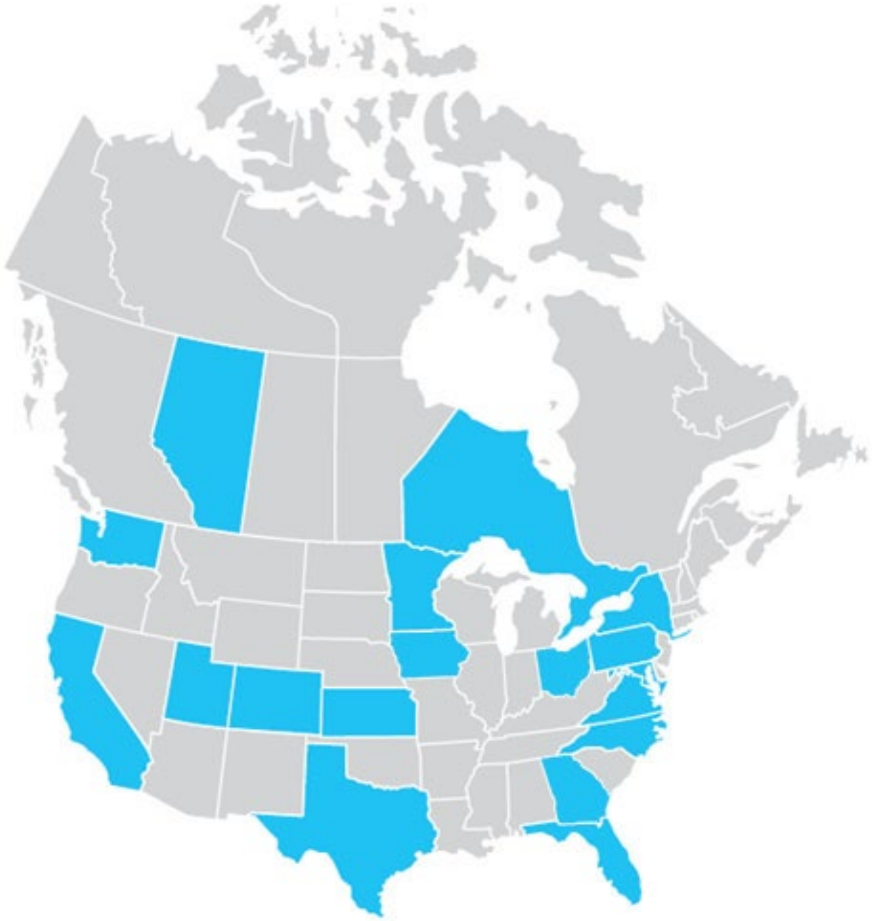
- Reachable Workspace (RWS)
- Functional/mobility endpoints: Timed Up and Go, 10-meter walk/run, Time to ascend/descend 4 stairs
- Strength measurements (hand-held dynamometry & manual muscle testing)
- PROs to assess upper body function, quality of life, sleep, pain, anxiety, depression, and fatigue
- Clinical severity scores

FORTITUDE™ 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) • Meets specific criteria for two upper quadrants in Reachable Workspace (RWS) • At least one muscle region in the leg suitable for biopsy as assessed at the Screening MRI	• Body mass index (BMI) >35.0 kg/m^2 - Previous muscle biopsy in study defined muscle group within 30 days of screening - Plans to undergo a non-study muscle biopsy • Clinically significant laboratory abnormalities • Any contraindication to MRI • Clinically significant illness, medical condition, or abnormal test result that could affect a participant's safety or ability to comply with study procedures

AVIDITY BIOSCIENCES

FORTITUDE™ Map of Planned North American Sites



Additional sites are planned for North America and Europe

AVIDITY BIOSCIENCES

Summary and Conclusions

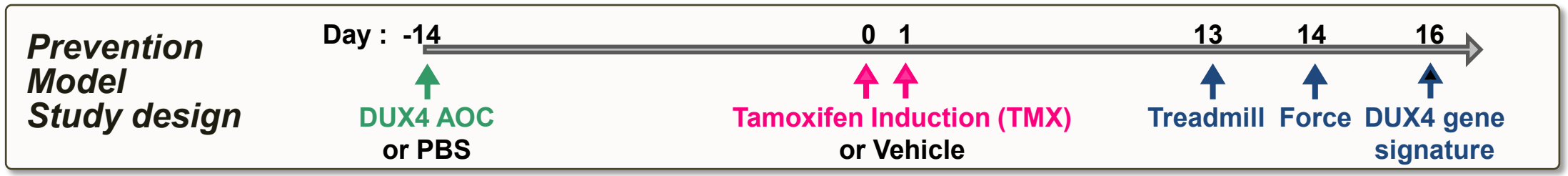
- AOC 1020 was designed to target the underlying cause of FSHD in muscle
- Preclinical studies of AOC 1020 established inhibition of the DUX4 gene and prevention of muscle weakness development in an FSHD mouse model
- We are now initiating the Phase 1/2 FORTITUDE™ study of AOC 1020 in adults with FSHD
  - 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



N = 9-12; males; mean ± SEM