AOC 1020: An Antibody Oligonucleotide Conjugate (AOC) in Development for the Treatment of FSHD

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FSHD: Resulting in Lifelong, Progressive Loss of Muscle Function

AFFECTS

~16,000 - 38,000

PEOPLE IN THE US[1,2]

0

APPROVED THERAPIES[3]

- One of the most common forms of muscular dystrophy[1]
- Rare, hereditary, progressive muscle-weakening condition that causes significant pain, fatigue, and disability[1,4]
- Onset often in teenage and adult years[4]
- Steady loss of independence and ability to care for oneself[4]
- 20% of patients become wheelchair dedpendent[4]
- Autosomal dominant – multiple genes can be affected[5,6]
- Caused by aberrant double homeobox 4 (DUX4) gene expression[5,6]

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. Tawil R and Van Der Maarel SM. *Muscle Nerve.* 2006;34(1):1–15; 5. Lemmers RJLF, et al. *Science.* 2010;329(5999):1650–1653; 6. Snider L, et al. *PLoS Genet*. 2010;6(10):e1001181.

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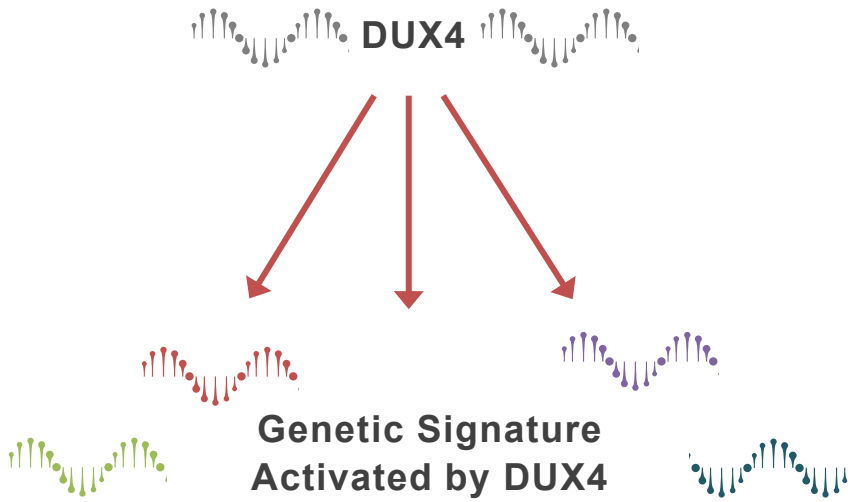
FSHD is Caused by Aberrant Expression of DUX4 in Muscle

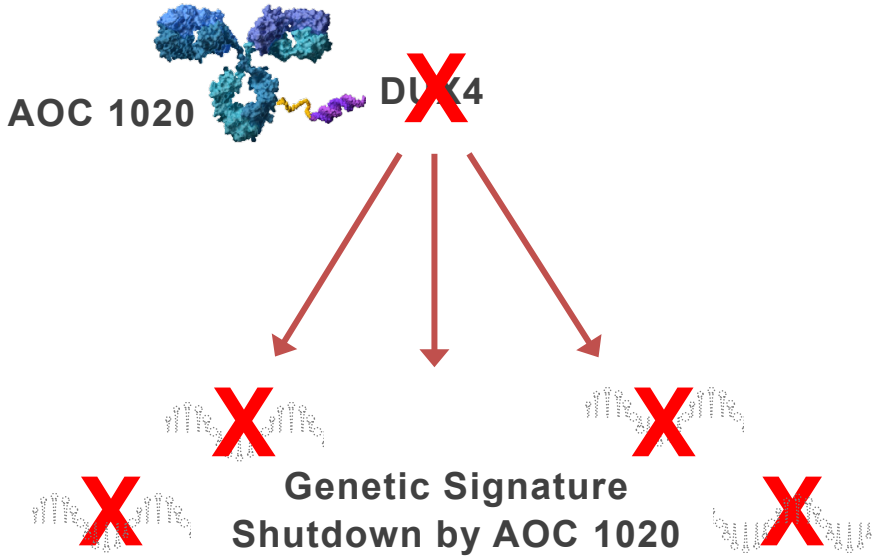
DUX4 activates genes that are toxic to muscle cells

MECHANISM OF DISEASE[1-3]



Apoptosis, immune signaling altered
myogenesis inhibited

THERAPEUTIC APPROACH



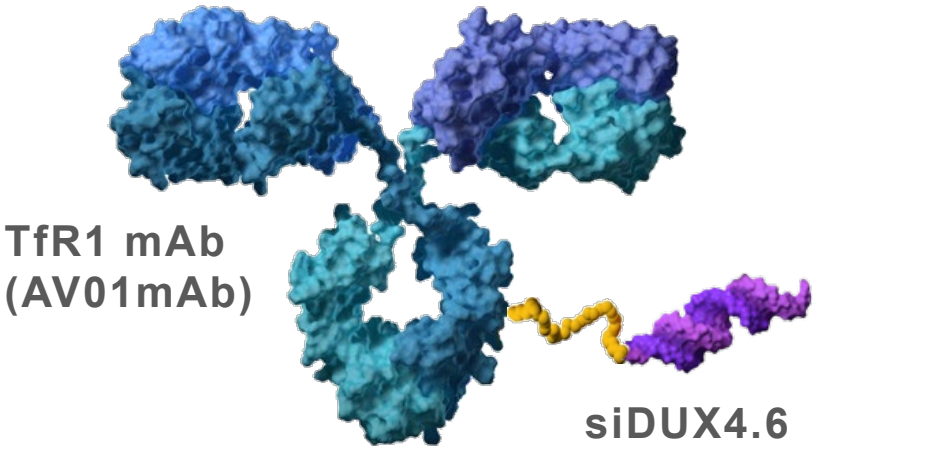
Apoptosis, immune signaling altered
myogenesis inhibited

AOC, anitbody-oligonucleotide conjugate.

1. Lemmers RJLF, et al. *Science*. 2010;329(5999):1650–1653; 2. Snider L, et al. *PLoS Genet*. 2010;6(10):e1001181;
3. Yao et al. *Hum Mol Genet*. 2014;23(20):5342-52.

Avidity's AOC 1020 Targets DUX4 mRNA for Degradation and Eliminates the Cause of FSHD

AOC 1020 - ANTIBODY OLIGONUCLEOTIDE CONJUGATE

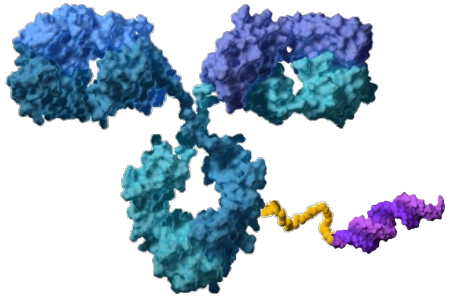


- AOCs represent a new class of therapeutics allowing delivery of oligonucleotides to target tissues
- Avidity's AOCs combine proven technologies of monoclonal antibodies and oligonucleotides
  - Specificity of targeting
  - Potency & precision of oligonucleotides
  - Targets tissues with potent and durable agents
- We optimized each of component of AOCs and engineered the molecules to maximize activity, durability, and safety
  - **TfR1 mAb:** monoclonal antibody directed to human transferrin receptor 1 (TfR1), optimized through engineering to be effector function null, epitope selection for optimal activity, highly efficient delivery to muscle
  - **Linker:** non-cleavable, enhanced for safety and durability, optimized ratio of oligonucleotides to antibodies
  - **siDUX4.6:** DUX4 mRNA targeting siRNA; engineered and stabilized to withstand lysosomal enzymes, selected for potency and specificity and modified to diminish off-target effects

mRNA, messenger RNA; RNA, ribonucleic acid; siRNA, small interfering RNA; TfR1, transferin receptor 1.

Preclinical Development of AOC 1020 as a Potent and Specific Inhibitor of DUX4 Expression

AOC 1020



Transferrin receptor 1 mAb

Screen DUX4 siRNAs in FSHD donor cells using gene signature

Off-target analysis by RNA-seq

Select potent siRNAs with minimal off-target profile

Target candidate profile met

Evaluate in FSHD mouse model & GLP studies

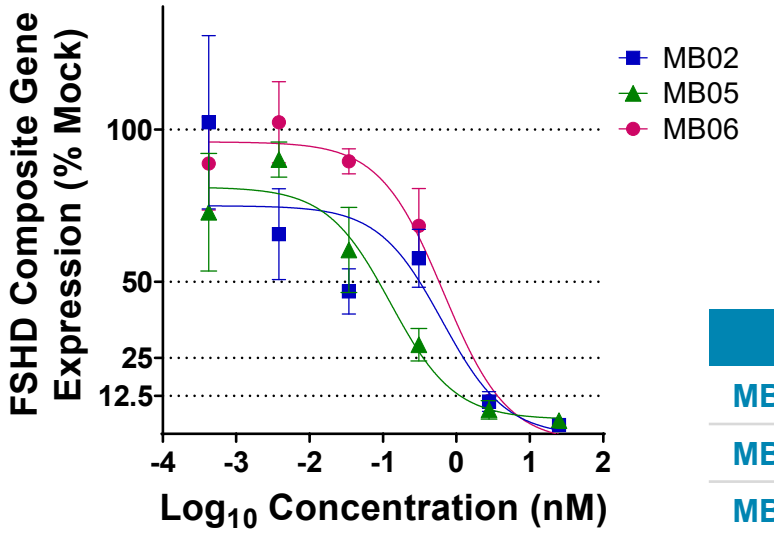
COMPLETED

COMPLETED/ ONGOING

GLP, Good Laboratory Practice; RNA-seq, RNA sequencing.

Lead siRNA Sequence siDUX4.6 Inhibits DUX4-Regulated Genes in FSHD Patient-Derived Muscle Cells

Sub-Nanomolar Potency of the siDUX4.6 Sequence *In Vitro* in FSHD Primary Patient-Derived Myotubes



N=4; mean ± SEM

	IC_{50} (nM)	E_{max} (%)
MB02	0.639	100
MB05	0.127	95
MB06	0.665	100

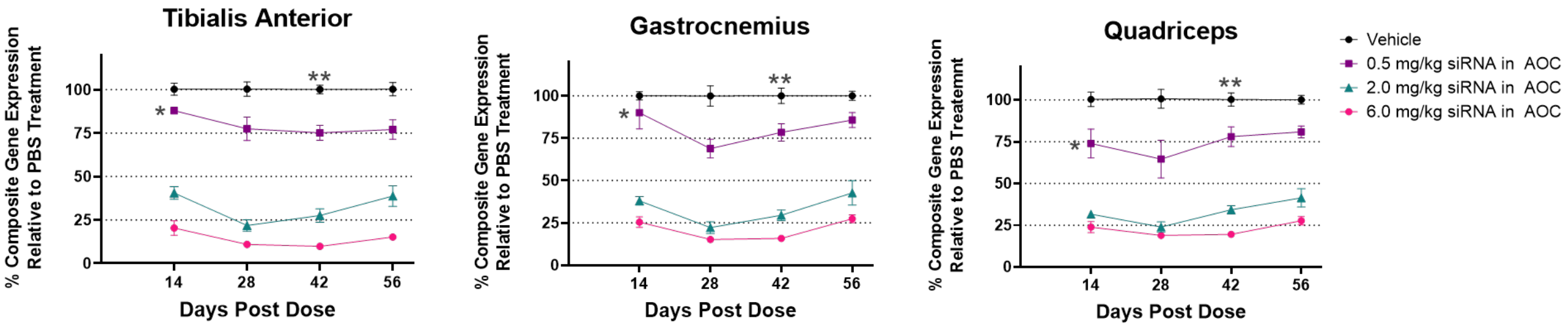
3 FSHD patients' cells

- Robust downregulation of DUX4-regulated genes was observed with the lead siDUX4.6 siRNAs in FSHD donor myotubes *in vitro*
- FSHD Composite is a mean expression of DUX4-regulated genes KHDC1L, LEUTX, MBD3L2, ZSCAN4[1]

1. Yao et al. *Hum Mol Genet*. 2014;23(20):5342-52.

siDUX4.6 Shows Potent Inhibition of DUX4-Regulated Genes in Transgenic Mouse Model of FSHD for 8 Weeks

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



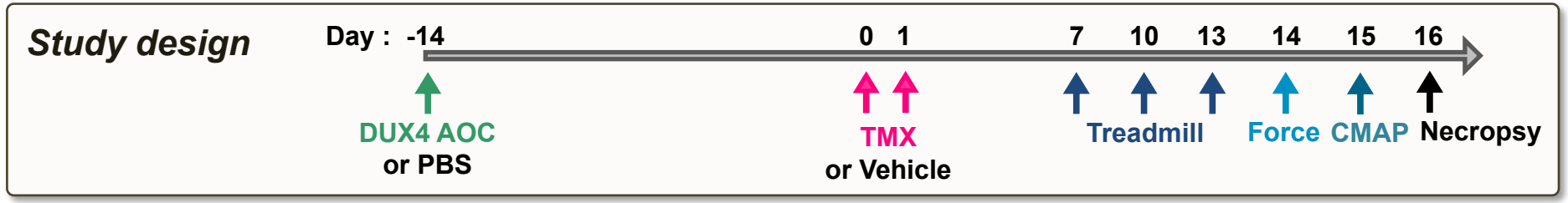
ACTA1-MCM; FLExDUX4 mouse model of FSHD[1]
N = 5 (*N=3; **N=4); mean ± SEM

- The siRNA clinical candidate siDUX4.6 demonstrated activity *in vivo* towards the human DUX4 mRNA, measured by downregulation of DUX4-regulated mouse genes Wfdc3, Ilvbl, Slc15a2, Sord[1,2].
- Demonstrated ~75% inhibition of DUX4 responsive genes following IV administration of 6 mg/kg dose (siRNA in mTfR1-siDUX4.6 AOC)

IV, intravenous.

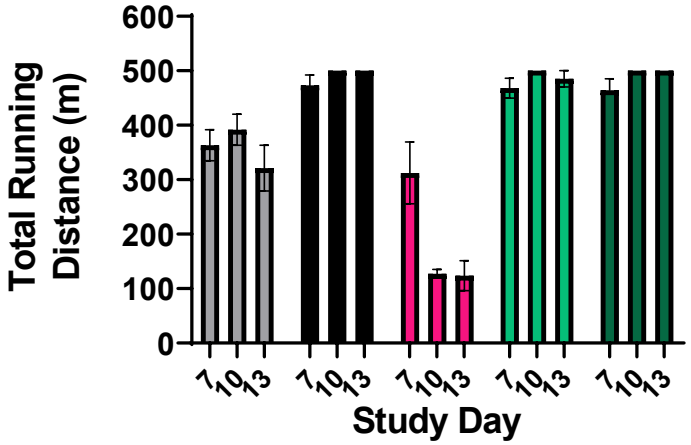
1. Jones T and Jones PL. *PLoS One*. 2018;13(2):e0192657; 2.Whiddon JL, et al. *Nat Genet*. 2017;49(6): 935–940.

Single IV Treatment with DUX4 AOC Prevents Disease Phenotype Development in Tamoxifen-Induced FSHD Mouse Model[1]



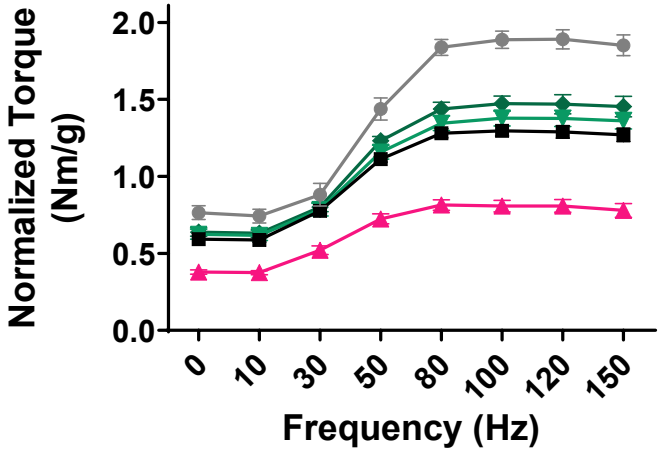
N = 9-12; males; mean ± SEM

Treadmill Running



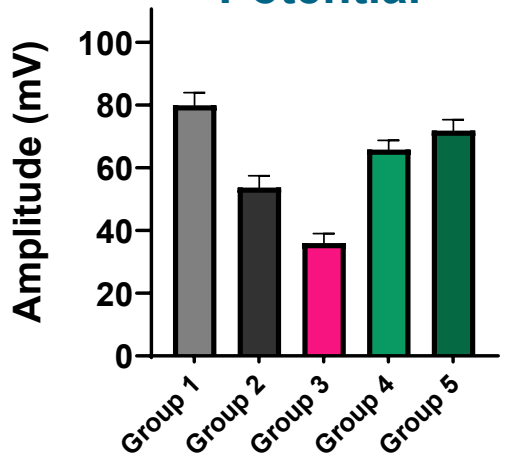
Treadmill running day 13: Adjusted $p<0.0001$ for all 3 comparisons: group 3 vs 2, group 3 vs 4, group 3 vs 5

In Vivo Force



Adjusted $p<0.0001$ for all 3 comparisons: group 3 vs 2, group 3 vs 4, group 3 vs 5

Compound Muscle Action Potential



Adjusted $p<0.01$ for group 3 vs 2; adjusted $p<0.0001$ for group 3 vs 4 and group 3 vs 5

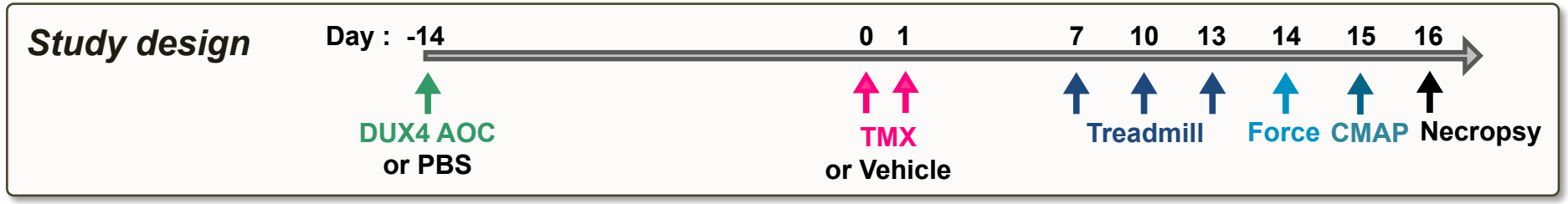
1: ACTA1-MCM, VEH, PBS
2: ACTA1-MCM; FLExDUX4, VEH, PBS
3: ACTA1-MCM; FLExDUX4, TMX, PBS
4: ACTA1-MCM; FLExDUX4, TMX, DUX4 AOC 2 mg/kg (siRNA)
5: ACTA1-MCM; FLExDUX4, TMX, DUX4 AOC 8 mg/kg (siRNA)

AVIDITY BIOSCIENCES

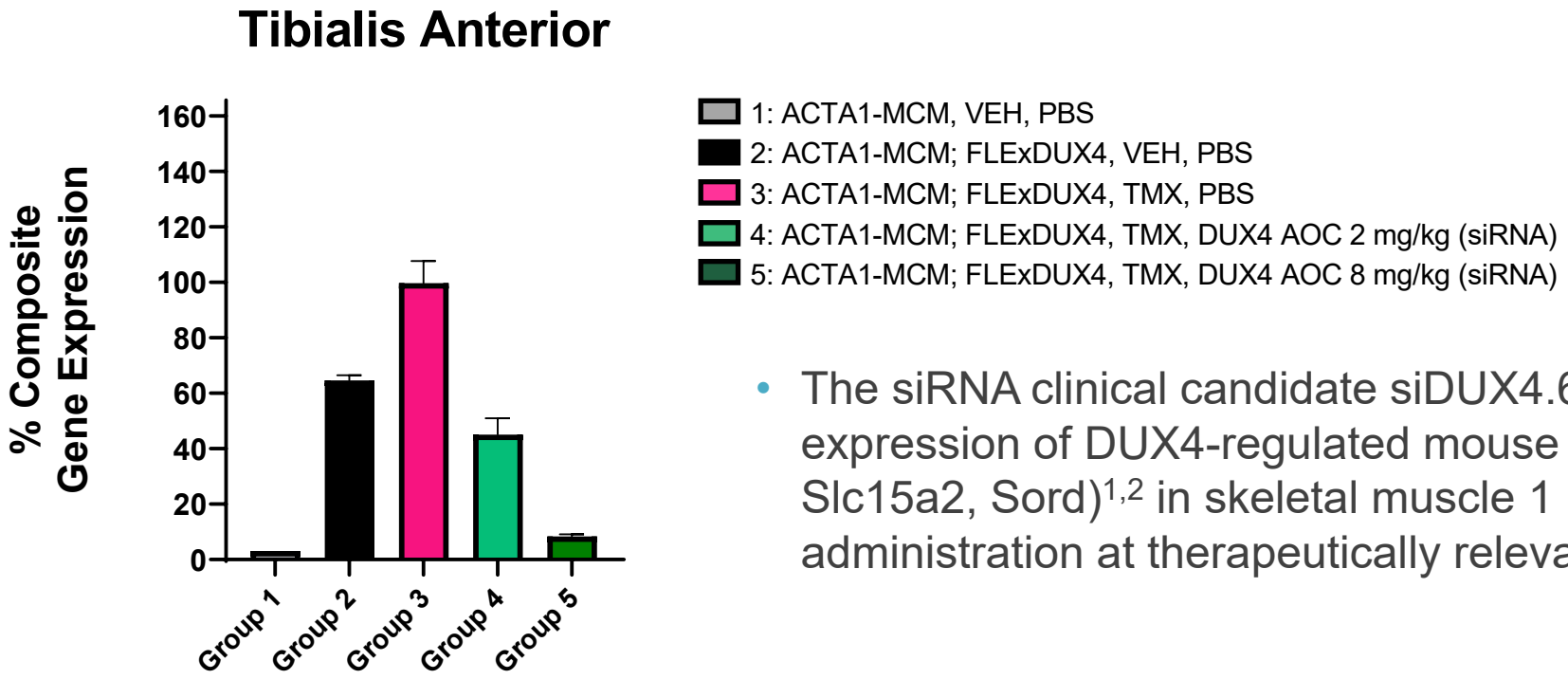
CMAP, compound muscle action potential; PBS, phosphate-buffered saline; SEM, standard error of the mean; TMX, tamoxifen; VEH, vehicle.

1. Jones TI, et al. *Skelet Muscle*. 2020;10(1):8.

Single Dose of DUX4 AOC Inhibits DUX4-Regulated Gene Expression in Muscle of Tamoxifen-Induced FSHD Mouse Model



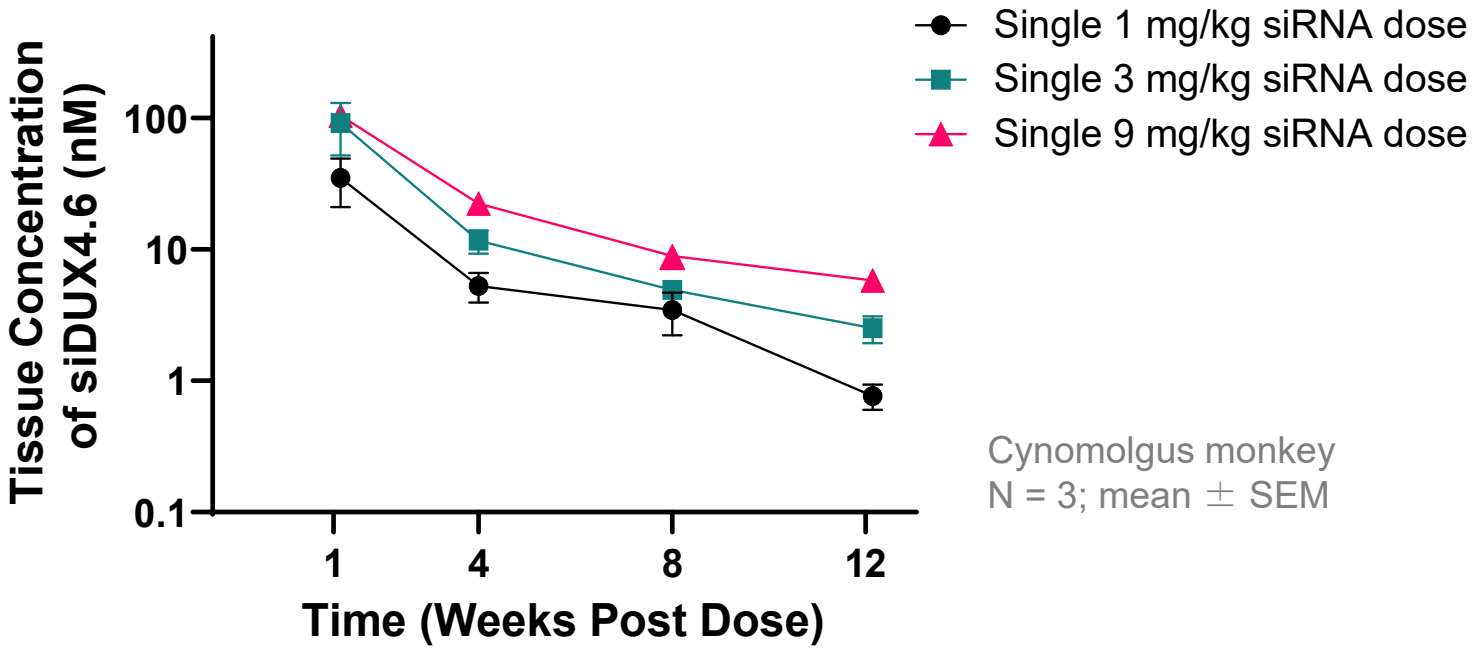
N = 9-12; males; mean ± SEM



- The siRNA clinical candidate siDUX4.6 robustly inhibits expression of DUX4-regulated mouse genes (Wfdc3, Ilvbl, Slc15a2, Sord)[1,2] in skeletal muscle 1 month after single IV administration at therapeutically relevant doses.

1. Jones T and Jones PL. *PLoS One*. 2018;13(2):e0192657; 2.Whiddon JL, et al. *Nat Genet*. 2017;49(6): 935–940.

AOC 1020 PK Results in NHP Muscle Tissue Support an Infrequent Dosing Regimen for FSHD Patients



Cynomolgus monkey
N = 3; mean ± SEM

- AOC 1020 produced dose-dependent increase in siRNA tissue exposure in skeletal muscle tissues following single systemic IV doses
- The muscle tissue concentration for siDUX4.6 in NHP at therapeutically relevant doses is above IC50 values that we typically observed for other TfR1-based AOCs
- Based on our data, we anticipate this will allow for an infrequent dose schedule in the clinic

Data Support the Evaluation of AOC 1020 in the Phase 1/2 FORTITUDE Clinical Trial

- siDUX4.6:
  - Was selected as clinical candidate siRNA targeting DUX4 mRNA, having an activity across all tested 11 FSHD patient-derived muscle cell lines, with a sub-nanomolar potency *in vitro*
  - Demonstrates efficacy *in vitro* by downregulating a panel of known DUX4-regulated genes in FSHD patient-derived myotubes
  - Demonstrates a dose-dependent activity and long duration of action (8 weeks) after single systemic IV dose *in vivo* in FSHD mouse model expressing human DUX4
  - Prevents a muscle weakness development after 2 and 8 mg/kg (siRNA within AOC) single systemic IV dose in FSHD mouse model
  - Has minimal seed-mediated off-target profile in human muscle cells
- Avidity is evaluating AOC 1020 in the Phase 1/2 FORTITUDE clinical trial in adults with FSHD

FORTITUDE™

Authors and Acknowledgements

Authors

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