WMS LSVP.08

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

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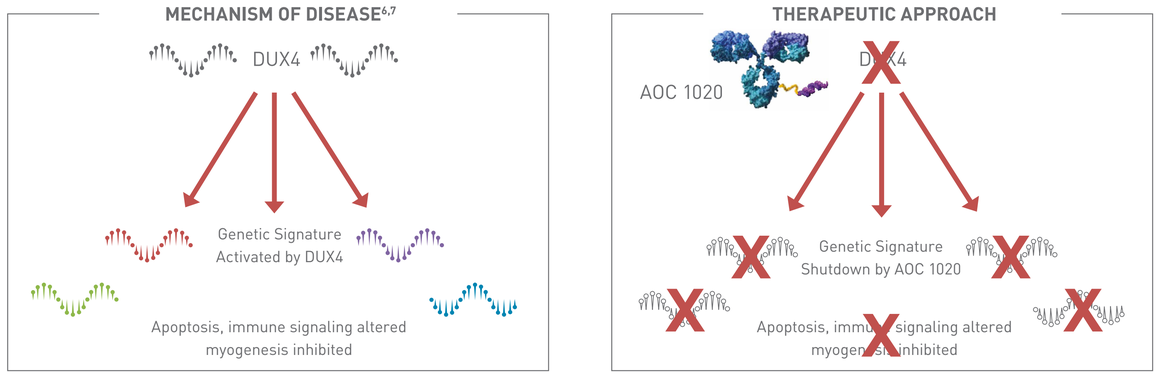
Background

- Facioscapulohumeral dystrophy (FSHD) is a rare genetic muscular disorder, usually presenting with slow-progressing and asymmetric muscle weakness.[1]
- The cause of FSHD is aberrant expression of the transcription factor DUX4 in skeletal muscle, leading to a series of downstream events that result in skeletal muscle degeneration and wasting. Strategies aimed at reducing DUX4 expression in the skeletal muscle of FSHD patients are promising therapeutic approaches.[2-4]
- Clinical development of oligonucleotide therapeutics for muscle diseases has been limited due to difficulty delivering oligonucleotides into muscle.[5] Avidity's AOC™ platform combines the specificity of transferrin receptor 1 (TfR1)-directed monoclonal antibodies for muscle delivery with the potency and precision of small interfering RNA (siRNA) in reducing target RNA expression.
- Avidity has conducted a comprehensive *in vitro* screening of a DUX4 siRNA library in a variety of FSHD patient-derived muscle cells, which allowed selection of highly potent siRNA sequences with minimal off-target profile. The selected siDUX4.6 siRNA was conjugated to the murine TfR1 antibody to generate DUX4 AOC. A robust, dose-responsive activity was observed for 8 weeks following a single intravenous (IV) dose of DUX4 AOC, with 75% or higher reduction of DUX4-regulated genes in skeletal muscle of the ACTA1-MCM; FLExDUX4 mouse model of FSHD.
- Data presented herein provide rationale and support for entering the clinic with AOC 1020 for the treatment of FSHD by the end of 2022.

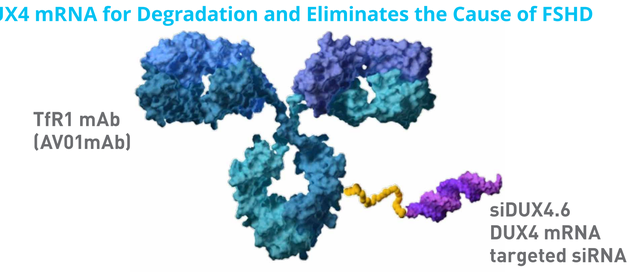
Avidity's Approach

FSHD is Caused by Aberrant Expression of DUX4 in Muscle

DUX4 activates genes that are toxic to muscle cells



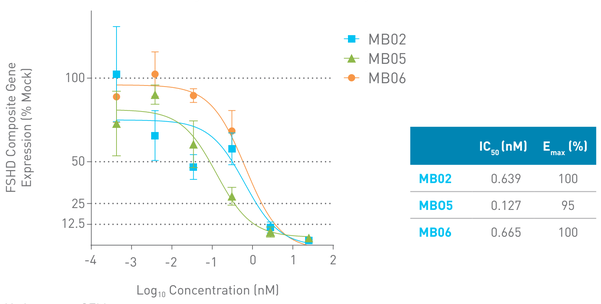
Avidity's AOC 1020 Targets DUX4 mRNA for Degradation and Eliminates the Cause of FSHD



Results

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

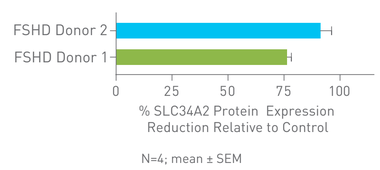
Sub-Nanomolar Potency of the siDUX4.6 Sequence *In Vitro* in FSHD Primary Patient-Derived Myotubes



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

N=4; mean ± SEM

siDUX4.6 Sequence Inhibits SLC34A2 Protein Expression in FSHD Donor Myotubes

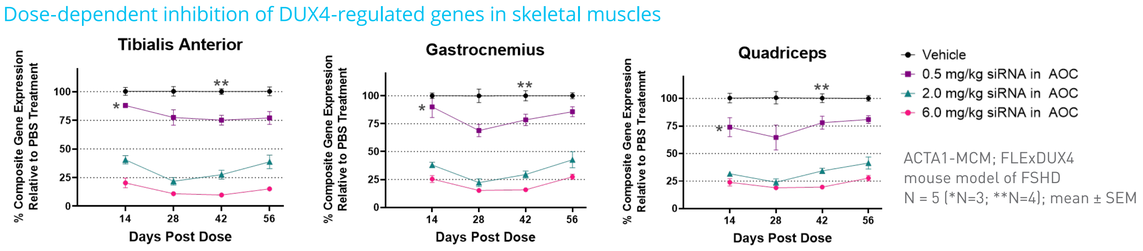


N=4; mean ± SEM

- Robust reduction 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[8]

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

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

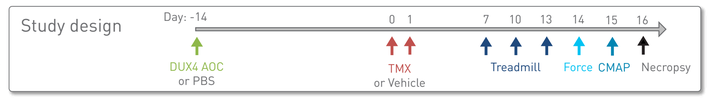


ACTA1-MCM; FLExDUX4 mouse model of FSHD
N = 5 (*N=3; **N=4); mean ± SEM

- 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.[9,10]
- Approximately a 75% reduction in DUX4 responsive genes was induced after a single systemic IV administration of 6 mg/kg of siRNA within the AOC (mTfR1-siDUX4.6)

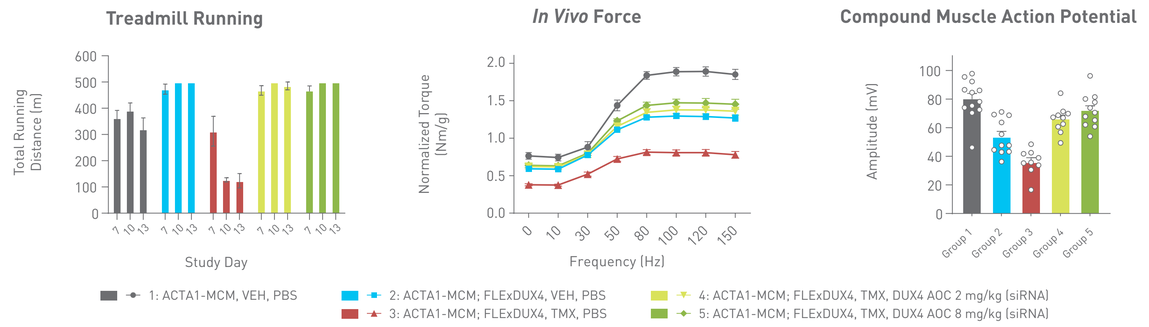
Results

Schema for results 3 & 4

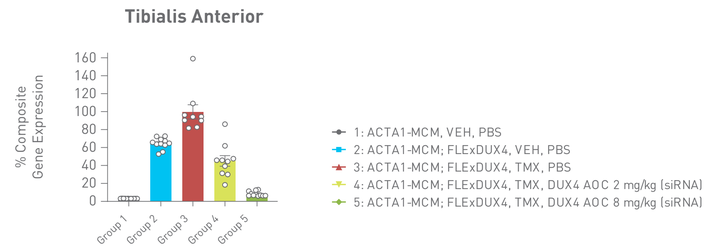


N=9-12; males; mean ± SEM

3. Single Intravenous Treatment with DUX4 AOC Prevents Disease Phenotype Development in FSHD Mouse Model

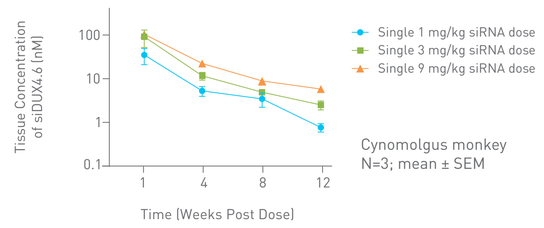


4. Single Dose of DUX4 AOC Inhibits DUX4-Regulated Gene Expression in Muscle of Tamoxifen-Induced FSHD Mouse Model



- The siRNA clinical candidate siDUX4.6 robustly inhibits expression of DUX4-regulated mouse genes (Wfdc3, Ilvbl, Slc15a2, Sord)[9,10] in skeletal muscle 1 month after single IV administration at therapeutically relevant doses.

5. 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

Conclusion

- 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 robust activity *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
- AOC 1020 is currently in GLP toxicology studies
- Avidity is planning to enter the clinic with AOC 1020 for treatment of FSHD by end of 2022

Acknowledgements

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Abbreviations and References

AOC, antibody oligonucleotide conjugate; FSHD, facioscapulohumeral dystrophy; IV, intravenous; mRNA, messenger RNA; PBS, phosphate-buffered saline; RNA, ribonucleic acid; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SEM, standard error of the mean; siRNA, small interfering RNA; TfR1, transferrin receptor 1.

[1]Tawil R, et al. *Neuromuscul Disord*. 2010;20(7):471–5; [2]Bouwmann LF, et al. *Curr Opin Neurol*. 2020;33(5):635–40; [3]Ansseau et al. *Genes*. 2017;88(3):93; [4]Le Gall et al. *J Clin Med*. 2020; 7(9):2886; [5]Roberts TC, et al. *Nat Rev Drug Discov*. 2020;19(10):673–94; [6]Lemmers RJLF, et al. *Science*. 2010;329(5999):1650–3; [7]Snider L, et al. *PLoS Genet*. 2010;6(10):e1001181; [8]Yao et al. *Hum Mol Genet*. 2014;23(20):5342-52; [9]Whiddon et al. *Nat Genet*. 2017; 49(6): 935–940; [10]Jones T and Jones PL. *PLoS One*. 2018;13(2):e0192657.