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

Barbora Malecova
Avidity Biosciences, Inc.
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 dependent\(^4\)
- 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.
FSHD is Caused by Aberrant Expression of DUX4 in Muscle

*DUX4 activates genes that are toxic to muscle cells*

**MECHANISM OF DISEASE**

1. DUX4 activates genes that are toxic to muscle cells
2. Apoptosis, immune signaling altered
3. Myogenesis inhibited

**GENETIC SIGNATURE**

- Activated by DUX4
- Shutdown by AOC 1020

**AOC, antibody-oligonucleotide conjugate.**

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

- 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

siDUX4.6
DUX4 mRNA targeted siRNA

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

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

GLP, Good Laboratory Practice; RNA-seq, RNA sequencing.
Lead siRNA Sequence siDUX4.6 Inhibits DUX4-Regulated Genes in FSHD Patient-Derived Muscle Cells

Robust downregulation of DUX4-regulated genes was observed with the lead siDUX4.6 siRNAs in FSHD donor myotubes \textit{in vitro}

FSHD Composite is a mean expression of DUX4-regulated genes KHDC1L, LEUTX, MBD3L2, ZSCAN4.

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*

- 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)

ACTA1-MCM; FLExDUX4 mouse model of FSHD\(^1\)

\(N = 5\ (*N=3; **N=4); \text{mean} \pm \text{SEM}\)

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

Study design

Day: -14

DUX4 AOC or PBS

TMX or Vehicle

Treadmill

Force

CMAP

Necropsy

N = 9-12; males; mean ± SEM

Study design

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DUX4 AOC or PBS

TMX or Vehicle

Treadmill

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N = 9-12; males; mean ± SEM

Treadmill Running

In Vivo Force

Compound Muscle Action Potential

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

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

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)

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

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)\(^1,2\) in skeletal muscle 1 month after single IV administration at therapeutically relevant doses.

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

- 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 \textit{in vitro}
  - Demonstrates efficacy \textit{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 \textit{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
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Authors

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