DUX4 siRNA Optimization for the Development of an Antibody-Oligonucleotide Conjugate (AOC™) for the Treatment of Facioscapulohumeral Muscular Dystrophy (FSHD)

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FSHD is Often Diagnosed in Young Adults with Few Treatment Options

There are no approved therapeutics for FSHD

AFFECTS

~16,000 - 38,000

PEOPLE IN THE US\textsuperscript{1,2}

0

APPROVED THERAPIES\textsuperscript{3}

- Facioscapulohumeral Dystrophy (FSHD)
- One of the most common forms of muscular dystrophy\textsuperscript{1}
- Autosomal dominant disease caused by abnormal expression of double homeobox 4 (DUX4)\textsuperscript{4,5}
- Characterized by progressive, asymmetric skeletal muscle loss with onset often in teenage and adult years\textsuperscript{6}
- About 20% of patients will end up using a wheelchair\textsuperscript{6}

FSHD is Caused by Aberrant Expression of DUX4 in Muscle

*DUX4 activates genes that are toxic to muscle cells*

**MECHANISM OF DISEASE**


**THERAPEUTIC APPROACH**

1. Apoptosis, immune signaling altered
2. Myogenesis inhibited
3. Genetic Signature Activated by DUX4
4. Genetic Signature Shutdown by AOC 1020

1. AOC 1020
2. DUX4

Apoptosis, immune signaling altered
Myogenesis inhibited
AOC 1020 FSHD Development Candidate is Designed to be a Potent and Specific Inhibitor of DUX4 Expression

- Antibody directed to human transferrin receptor 1 (TfR1)
- Non-cleavable linker designed to facilitate siRNA delivery to muscle
- Stabilized siRNA targeting DUX4 mRNA (siDUX4.6)
Lead DUX4 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 DUX4 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
- 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

ACTA1-MCM; FLExDUX4 mouse model of FSHD
N = 5 (*N=3); mean ± SEM
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
AOC 1020 is On-Track to be in the Clinic by the End of 2022

- siDUX4.6 was selected as the clinical candidate siRNA targeting DUX4, having an activity across variety of FSHD patient derived muscle cells, with a sub-nanomolar potency *in vitro*
- siDUX4.6 shows no concerning seed-mediated off-target profile in human muscle cells
- siDUX4.6 demonstrated potent, specific inhibition of DUX4 regulated genes in an FSHD mouse model for 8 weeks after single systemic dose
- AOC 1020 is well-tolerated in cynomolgus monkey preclinical studies at all doses and dose frequencies tested
- 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
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