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 musculoskeletal 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 3
- Clinical development of oligonucleotide therapeutics for muscle diseases has been limited due to difficulty delivering oligonucleotides into muscle.4 Avidity’s AOC platform combines the specificity of transfer receptor 1 (TfR1)-directed medicinal antibodies for muscle delivery with the potency and precision of small interfering RNA (siRNA) in reducing target RNA expression.4

Avidity’s Approach

- Avidity’s AOC platform combines the specificity of transfer receptor 1 (TfR1)-directed medicinal antibodies for muscle delivery with the potency and precision of small interfering RNA (siRNA) in reducing target RNA expression.4
- 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 TR1 antibody to generate DUXA AOC. A robust, dose-response activity was observed for 8 weeks following a single intravenous (IV) dose of DUXA AOC, with 75% or higher reduction of DUX4-regulated genes in skeletal muscle cells, which allowed selection of highly potent siRNA sequences with minimal off-target profile. The selected siDUX4.6 siRNA
- Data presented herein provide rationale and support for entering the clinic with AOC 1020 for the treatment of FSHD by the end of 2022.

Results

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

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 Wt1c3, Ivwx, Scl5as2, Sard.7

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

- The siRNA clinical candidate siDUX4.6 demonstrated activity in vivo towards the human DUX4 mRNA, measured by downregulation of DUX4-regulated mouse genes Wt1c3, Ivwx, Scl5as2, Sard.7

Conclusion

- 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

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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; TR1, transferin receptor 1