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

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Abstract:

FSHD is a rare genetic disorder that affects skeletal muscles, often leading to progressive muscle weakness. Treatment options are limited and disease progression is not fully understood. Avidity Biosciences is developing AOC 1020, an antibody oligonucleotide conjugate targeted to DUX4, a transcription factor dysregulated in FSHD patients. AOC 1020 demonstrated potent in vitro and in vivo activity, reducing DUX4-regulated genes and improving muscle function in preclinical models.

Background:

- Facioscapulohumeral dystrophy (FSHD) is a rare genetic muscular disorder, usually presenting with slow-progressing and asymmetric muscle weakness.
- 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 response 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.

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 AOC 1020 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; siRNA, small interfering RNA; TfR1, transferrin receptor 1.