1. Approach: DUX4 as Molecular Target

Transcriptional reprogramming
More than 400 genes are upregulated by DUX4 expression compared to healthy muscle
Chromosome 4q35
Healthy: 11 to 100 D4Z4 repeat arrays = Represses DUX4 locus
FSHD1: 1 to 9 D4Z4 repeat arrays (contraction) = Loss of repression of DUX4 locus
FSHD2: DUX4 expression due to mutations in epigenetic control genes.

2. Primary Objective

Identification of a panel of DUX4-regulated gene transcripts to measure DUX4 activity in skeletal muscle needle biopsies from FSHD1 patients over 4-8 weeks

3. Study Design: MRI-guided Skeletal Muscle Biopsy

- 17 subjects were enrolled and 16 completed the SRA-002-2018 study. The mean (SD) age was 49 (13) and 70% were males with a mean severity score of 3.

5. Methodology to identify DUX-4 regulated gene transcript subset

- A biopsy characterization assay is robust and showed good repeatability (ICC ~0.5) in the preparatory biomarker study in FSHD.

6. Feasibility and Validation of Real Time qPCR by Fluidigm

- DUX4 regulated gene transcript expression values and composite score (Delta-CT) and changes from baseline by visit – descriptive statistics by qPCR

7. DUX4-regulated Gene Subset Analysis presented as individual genes and composite

- Data summarized by 2 methods: Individual genes using logarithmic transformation of normalized counts (log (FPKM)). Mean Composite score combines all 6 genes into a single DUX4 Score. Composite score is the Mean C of 6 genes CCNA1; KDHC1L1; MBID3L2; PRAMEF6; ZSCAN4 normalized to 3 reference genes HBD; CDKN1B; TPB

8. Summary

- DUX4-regulated gene transcripts may provide a pharmacodynamic biomarker endpoint of DUX4 activity to measure treatment effect for the root cause of FSHD in losmapimod therapeutic clinical trials.

9. Conclusion

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