EDG-5506 is a selective inhibitor of fast skeletal muscle myosin, designed to protect against contraction-induced injury in Becker and Duchenne muscular dystrophy (BMD and DMD, respectively). In a Phase I open-label extension study (ARCH, NCT01660415) adults with BMD (N=12) were administered 10 to 20 mg EDG-5506 daily for 12 months to date.

We have previously measured short-term decreases in muscle injury biomarkers creatine kinase (CK) and fast skeletal muscle troponin 1 (TNNI2) with EDG-5506. Here, we examine changes in CK and TNNI2 with continued treatment and relationship to measures from plasma proteomics (SOMAscan). We further examine differential proteomic profiles that result from short- (1 - 2 months) and longer-term (6 months) treatment.

Results (continued)

Validation of SOMAsers for CK and TNNI2

SOMAscan and absolute measures of CK (left) and TNNI2 (right) were tightly correlated for all measured samples, enabling high-confidence quantification using SOMAscan. The dotted line indicates the LLOQ for the TNNI2 ELISA.

Biomarkers of Muscle Injury are Reduced and Stabilized Early in the Treatment

In a complete dataset generated from SOMAscan-calculated data, both CK and TNNI2 decreased significantly after short-term treatment (1 - 2 months), followed by stabilization with longer-term treatment.

Among a curated set of proteins associated with skeletal muscle injury (described in 3), the group of proteins as a whole as well as the majority of individual proteins decreased after 1 - 2 months and exhibited minimal change thereafter, even with increasing dosage. This enabled an analysis of effects due to treatment.

Proteomic Differentiation Between Long-Term and Short-Term Treatment Effects

Using SOMAscan as an unbiased screening tool, a proteomic signature of long-term treatment was selected from those proteins that exhibited significant increase or decrease at long-term (6 months) relative to short-term (1 - 2 months) and yielded 116 increased proteins and 272 decreased proteins. Clustering analysis reveals several distinct subsets with slightly different patterns of temporal changes.

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Disclaimer: EDG-5506 is an investigational drug that is not approved in any territory. The authors are employees or consultants for Edgewise Therapeutics and may hold stock and/or stock options.

References

1. SOMAscan: http://somalogic.com/somascann-platform
3. Muscle Injury Biomarkers (poster on our website)