Characterization of Short- and Long-Term Proteomic Response to the Fast Skeletal Myosin Inhibitor, EDG-5506, in Becker Muscular Dystrophy (BMD)

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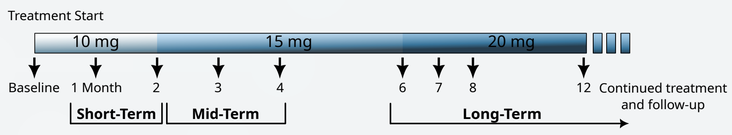
Background

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, NCT05160415) 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 I (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), mid- (3 - 4 months), and long-term (6 - 12 months) treatment.

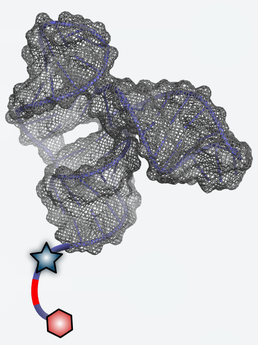
Methods

ARCH Clinical Study



12 BMD participants, 7 of whom participated in the Phase I MAD study, were enrolled and initially treated with 10 mg daily, with dose-escalation from 10 to 20 mg daily as shown. Blood draws were taken at pre-dose baseline, then at regular intervals thereafter for analysis by SOMAscan, as well as quantitation of CK activity and TNNI2 concentration by an activity assay and ELISA, respectively (1).

Analysis by SOMAscan

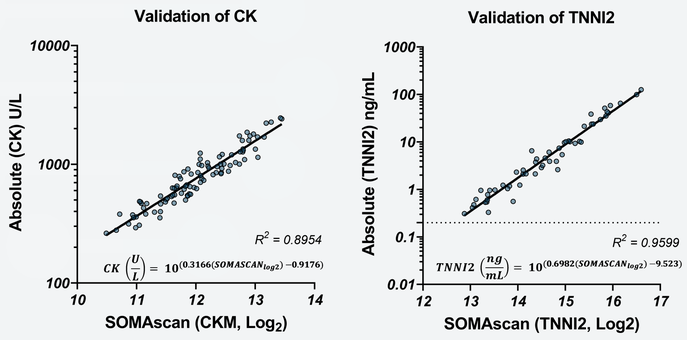


SomaScan is a multistep modified aptamer-based assay for high-throughput, sensitive, and unbiased biomarker measurement (2). Proteins in the samples are selectively bound with fluorescent aptamers, which are then measured on a chip array to yield values proportional to absolute concentrations.

In this study, SOMAscan was correlated to CK and TNNI2 to allow for direct conversion to absolute concentrations, as well as used to identify large-scale proteomic differences between short- and long-term treatment with EDG-5506, though at this time, this analysis does not differentiate effects from duration versus those from exposure.

Results

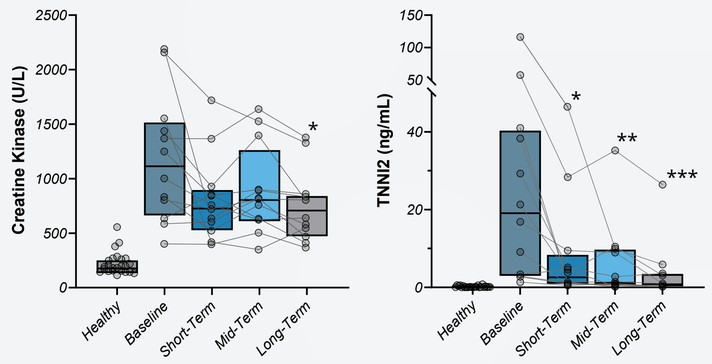
Validation of CKM and TNNI2 Somamers



We observed a strong correlation between SOMAscan and absolute measures of CK (left) and TNNI2 (right).

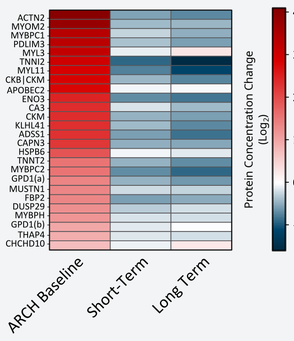
Results (cont.)

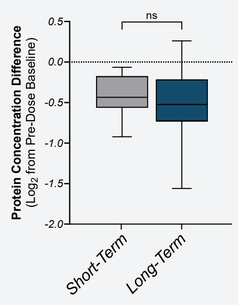
SOMAscan-Quantified CK and TNNI2 in Blood



Circulating CK and TNNI2 were significantly increased over values seen in healthy individuals at baseline and were reduced by short-term treatment. TNNI2 was reduced to nearly healthy levels by longer-term treatment timepoints. Indicated significance is for the all values at that treatment point relative to pre-dose baseline.

EDG-5506 Effects on Muscle Injury Proteins

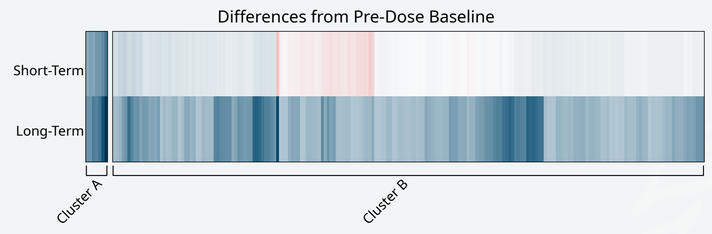


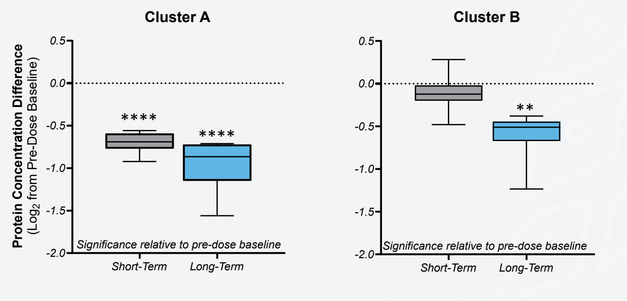


SOMAscan was used to analyze the effects of treatment on a set of proteins identified to correlate with bona-fide contraction-induced skeletal muscle injury (3). Generally, these proteins, like CK and TNNI2, were decreased from pre-dose baseline by short-term treatment and exhibited stable levels or further decreases over long-term treatments.

As a population, there was no difference in the response of muscle injury proteins with short-term and long-term treatment, suggesting that muscle effects of treatment are maximized by 10 mg treatment for 1 - 2 months.

Proteomics of Long-Term EDG-5506 Treatment





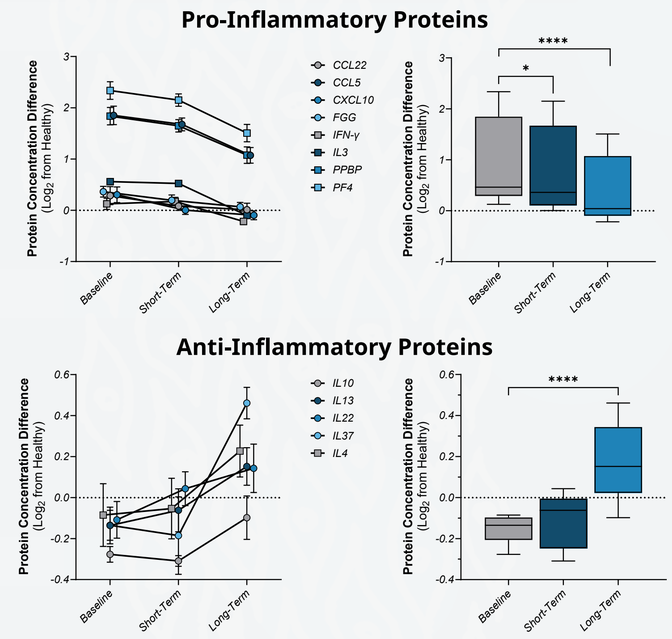
Pathway Enrichment	P-Value
Skeletal Muscle Contraction	****

Selected Pathways Enriched in Cluster	P-Value
Platelet Degranulation	****
Interleukins and Chemokines	****
Neutrophil Degranulation	****
Immune System	***

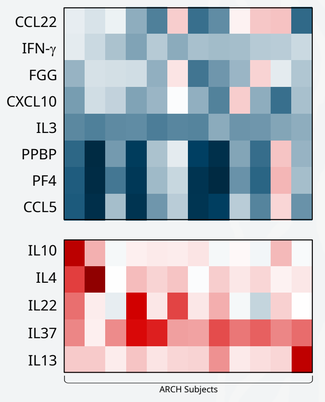
Proteins that are decreased by treatment and differentiate long-term treatment from short-term treatment exhibit two distinct clusters of changes. Cluster A is significantly decreased from pre-treatment baseline after both short- and long-term treatment and is characterized by several skeletal muscle proteins. Conversely, proteins in Cluster B are only responsive after longer periods of EDG-5506 treatments. These proteins primarily represent immune and inflammatory pathways.

Results (cont.)

Favorable Shift in Inflammatory Biomarkers with Long-Term Treatment



Pro- and Anti-Inflammatory proteins identified through references (4) and (5)



We observed a favorable shift in the inflammatory profile of study participants after long-term EDG-5506 treatment. Several pro-inflammatory cytokines and chemokines were very significantly reduced after 6 - 12 months (top), while several anti-inflammatory interleukins were increased after long-term treatment (bottom). The observed protein concentration changes after 6 - 12 months were consistent across study participants (left).

Conclusions

SOMAscan values were strongly correlated to absolute measurements of CK and TNNI2.

CK, TNNI2, and a broader set of muscle injury proteins were elevated at pre-dose baseline and decreased soon after initiation of treatment, remaining markedly decreased with long-term treatment.

The short-term proteomics of EDG-5506 treament were dominated by skeletal muscle proteins that reflect muscle damage. Additionally, long-term treatment exhibited a consistent shift in proteins associated with inflammation, wherein pro-inflammatory factors were reduced while anti-inflammatory cytokines were increased. Although this study varied both dose and duration, these proteins may be expected to require longer timespans to see significant change and may reflect trends towards normalization of muscle upon sustained reduction of muscle damage.

In summary, proteomic profiles of treatment with EDG-5506 showed a rapid and sustained decrease in markers of muscle injury with a longer-term change in the inflammatory milieu. Overall, the proteomic profile of EDG-5506 was shifted toward that of healthy individuals.

References

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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.

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