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Comparison of short- and long-term proteomic response to the fast skeletal myosin inhibitor, sevasemten (EDG-5506), in Becker muscular dystrophy (BMD)

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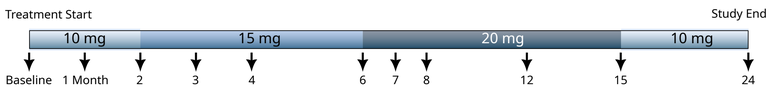
Background

Sevasemten (EDG-5506) is an investigational selective inhibitor of fast skeletal muscle myosin, designed to protect skeletal muscle from contraction-induced injury in Becker and Duchenne muscular dystrophy. In a Phase 1b open-label study (ARCH, NCT05160415), adults with BMD (N=12) were administered 10-20 mg of sevasemten daily for up to 24 months. We previously observed rapid reductions in muscle injury biomarkers, including muscle-type creatine kinase (CKM) and fast skeletal Troponin I (TNNI2), which were maintained through 12 months. Here, we used Somascan proteomic analysis to assess changes in muscle injury biomarkers and muscle fiber type-specific proteins with continued treatment up to 24 months. We also characterize the plasma proteomic changes characteristic of chronic sevasemten administration.

Methods

ARCH



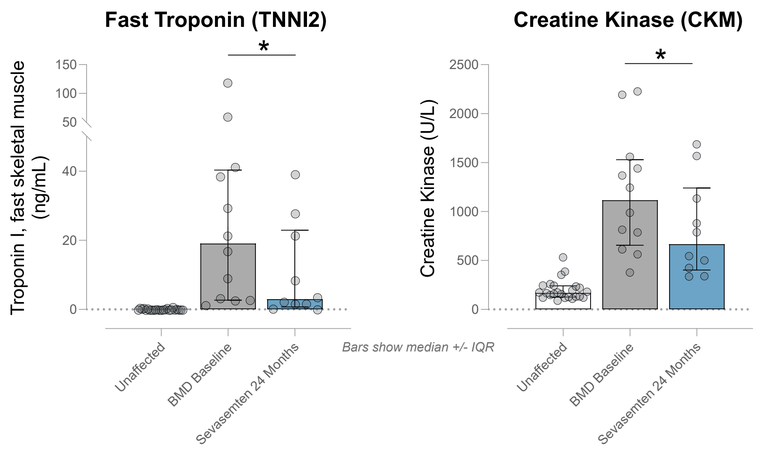
12 BMD participants, 7 of whom participated in the Phase I MAD study, were enrolled and initially treated with sevasemten at 10 mg daily, with dose-escalation from 10 to 20 mg daily as shown, returning to 10 mg daily at 15 months. Blood draws were taken at pre-dose baseline, then at regular intervals thereafter for analysis by SOMAscan (1).

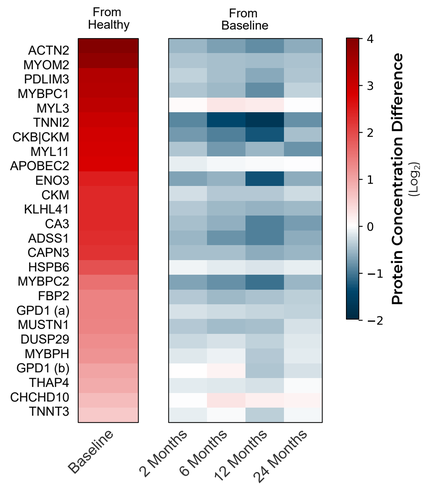
Data Analysis

SOMAscan values for CKM and TNNI2 were converted to absolute measures by extrapolation against clinically-qualified assays. Contraction-induced injury proteins were previously identified (2) and fibertype-specific protein sets were taken from published results (3). Protein response profiles were identified by performing unsupervised clustering of protein values over time with proteins that were identified as significantly different from baseline at short (1 - 3 months), mid (6 - 12 months), or long (18 - 24 months) treatment durations. Pathway enrichment analysis was performed using the Reactome database (4). The BMD-associated inflammatory proteome was selected by applying a partial-least-squares discriminant analysis (PLS-DA) to all proteins in the "Immune System" pathway family in the Reactome database to identify the set of inflammatory proteins that best differentiates BMD plasma from samples from healthy adults.

Results

Long-term sevasemten treatment maintains acute reductions in muscle injury proteins

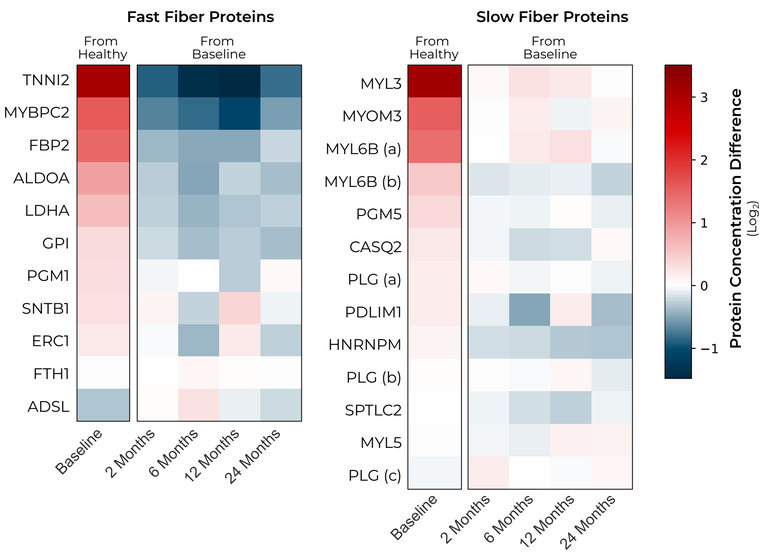




Short-term sevasemten has been shown to reduce TNNI2 and CKM, as well as a broader panel of proteins associated with contraction-induced injury (left), all of which are elevated in BMD subjects relative to healthy individuals. The low circulating levels of muscle injury proteins reached after short-term therapy were maintained at low levels for 2 years with extended sevasemten treatment.

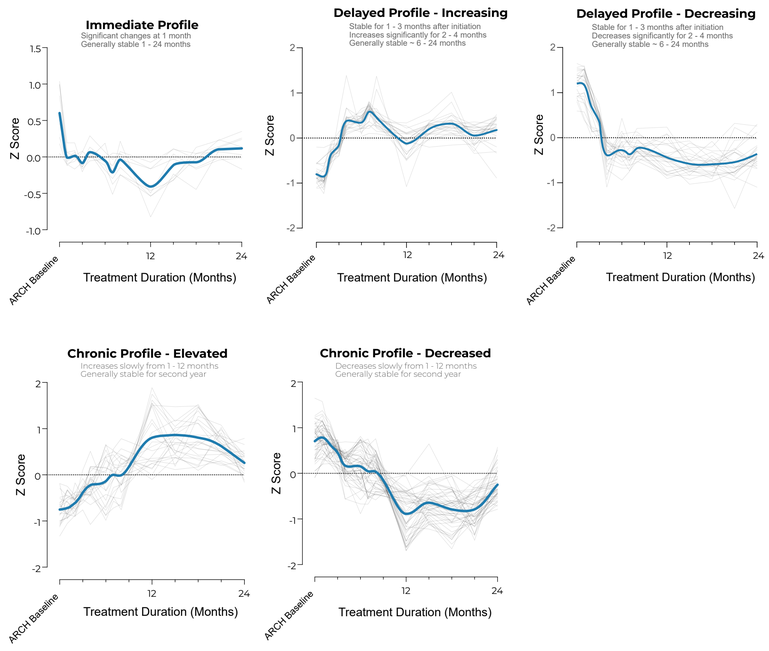
Results

Sevasemten is selective for fast muscle fibers



Proteins indicative of fast Type IIa/x fibers and slow Type I fibers (selected from Ref 3) were generally increased in circulation prior to dosing relative to healthy individuals. However, only fast fiber proteins were robustly reduced from baseline by sevasemten treatment at both short-term and long-term treatment times.

Identification of distinct biomarker response profiles after initiation of sevasemten

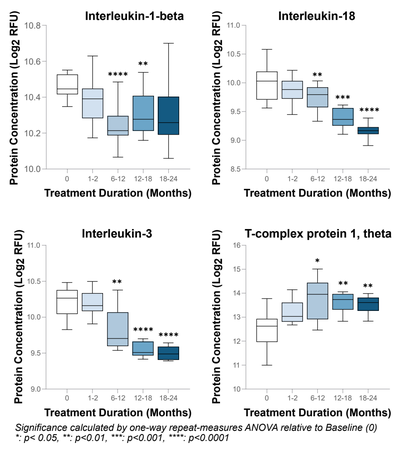


Predominant Pathways and Processes	
Immediate Profile	Muscle contraction and structure
Delayed Profile	Interleukin signaling, cell-cell communication
Chronic Profile	Signaling in the immune system (TLR, cytokine/IL, G-CSF), TGF-β signaling, neutrophil degranulation

Unbiased profiling of overall post-treatment protein responses identified five major profiles for sevasemten-responsive proteins in circulation. Individual protein profiles, plotted by Z-score vs treatment duration, are shown as grey lines and mean profile is indicated in blue. Major hallmarks and pathways for each profile are indicated.

Extended sevasemten treatment results in widespread changes to immune and inflammatory pathways and proteins

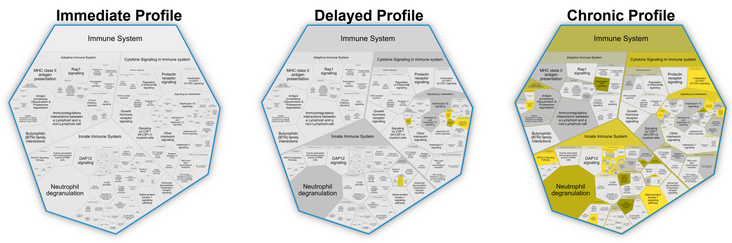
While proteins that exhibit significant change from baseline at early treatment timepoints are associated only with muscle contraction and structure, those that respond only after longer durations of sevasemten therapy tend to be strongly associated with immune and inflammatory processes.



Significance calculated by one-way repeat-measures ANOVA relative to Baseline (0)
**: p< 0.05, **: p<0.01, ***: p<0.001, ****: p<0.0001*

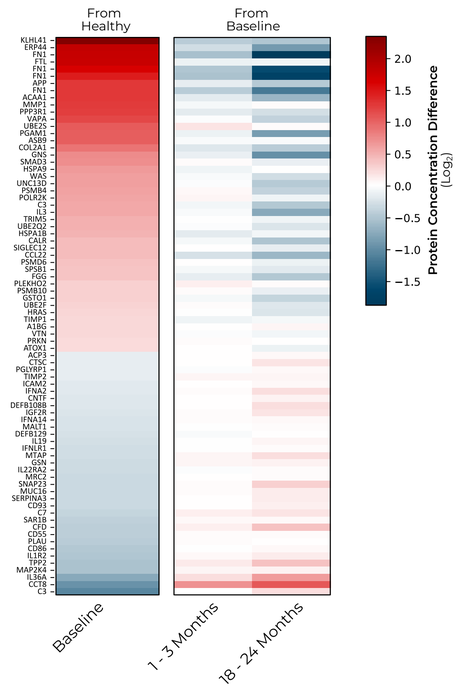
Reactome Immune System Superpathway (R-HSA-168256) Over-representation

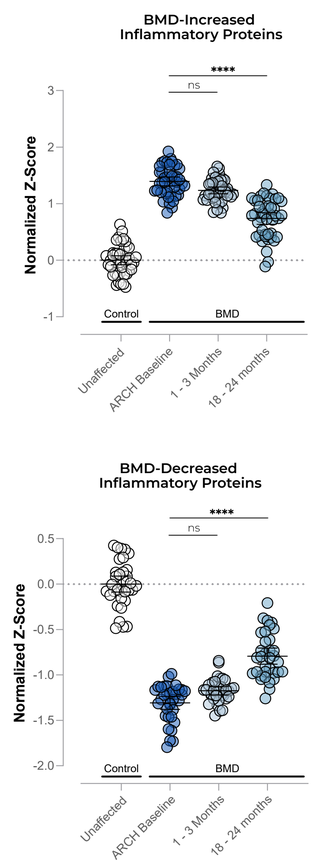
Light grey: no representation
Dark grey: insignificant over-representation
Yellow: Over-representation p<0.05; intensity correlates to significance



Results

Reversal of BMD-associated inflammatory proteome with long-term sevasemten





A baseline BMD-associated inflammatory proteome was defined by performing PLS-DA on pre-dosing samples from unaffected and BMD subjects, using the entirety of the "Immune System" Reactome superpathway (R-HSA-168256, 1442 proteins). 78 proteins were identified that resulted in correct classification a validation set of unaffected and BMD samples (training R^2=0.974, validation Q^2=0.848).

The inflammatory proteins increased in BMD at baseline were significantly reduced after 18 - 24 months of sevasemten. Conversely, those proteins decreased in BMD at baseline were signficantly increased after 18 - 24 months of sevasemten. ****: p < 0.0001 in a nonparametric Friedman test.

Conclusions

TNNI2, CKM, and a broad panel of contraction-induced muscle injury biomarkers, are quickly reduced upon initiation of sevasemten treatment. Reduced levels of these proteins were maintained for the duration of the study. Similarly, high levels of circulating proteins derived from fast muscle fibers (Type IIa/x) were reduced and stabilized by sevasemten, while proteins derived from slow Type I muscle fibers were relatively unaffected.

Five distinct response profiles for proteins that respond to sevasemten treatment were identified. Early-responding proteins were strongly associated with muscle contraction or physical structure, while those proteins that responded after extended durations of sevasemten were mapped to immune and inflammatory processes.

A 78-protein inflammatory proteomic profile was defined which correctly identified all tested samples as deriving from a BMD subject or a healthy subject. Treatment with sevasemten for 18 - 24 months resulted in a significant shift of this profile towards values that more closely resembled healthy individuals.

In summary, sevasemten exhibited rapid and durable reduction in circulating markers of muscle injury, combined with longer-term effects on inflammatory pathways, suggesting a broad proteomic shift of treated BMD subjects towards a profile associated with healthy individuals.

References

1. SOMAscan: http://somalogic.com/somascan-platform

2. https://edgewisetx.com/application/files/3616/5592/3718/New_Directions_Exercise_Poster_-_Final.pdf

3. Murgia, et al. Skeletal Muscle. 2021 Nov; 11(24):

4. Milacic M, et al. The Reactome Pathway Knowledgebase 2024. Nucleic Acids Research. 2024

The authors are grateful to all participants in the trials

Sevasemten 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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