Improved Plasma Signature of Contraction-Induced Muscle Injury with Sevasemten in Becker Muscular Dystrophy in the CANYON Phase 2 Trial

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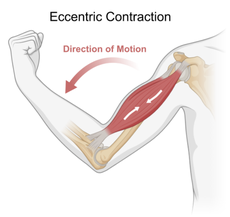
Background

Sevasemten is an investigational selective inhibitor of fast skeletal muscle myosin (1) in development for treatment of Becker muscular dystrophy (BMD). Results from an open-label study (ARCH) with sevasemten demonstrated sustained lowering of circulating biomarkers associated with muscle injury, such as creatine kinase (CK), fast skeletal troponin I (TNNI2), and myoglobin (Mb), over a 2-year period. The CANYON Phase 2 clinical trial (NCT05291091) was a randomized, double-blind, placebo-controlled study evaluating the efficacy of sevasemten versus placebo in subjects with BMD over a period of 1 year.

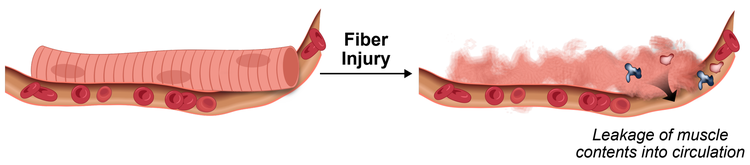
Our objective in this analysis was study how sevasemten treatment affected a broader proteomic description of skeletal muscle injury relative to placebo adminstration

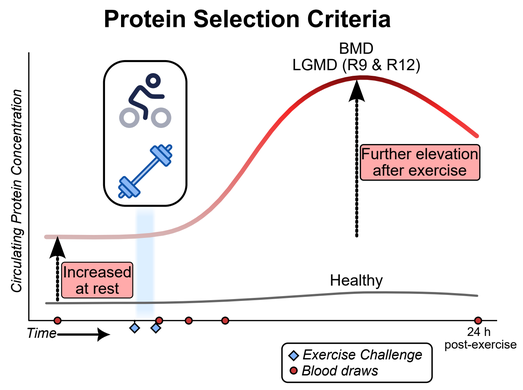
Methods

Definition of Muscle Injury Proteins



Muscle tissue may be injured by contraction, particularly if the muscle is unaccustomed to the contractile forces and duration or the muscle is lengthened during the contraction process (eccentric contraction). This is exacerbated in BMD due to lack of fully functional dystrophin and contraction-induced injury is a consequence of everyday activity. Disruption of fiber integrity releases intracellular components, such as proteins, into circulation, enabling detection through proteomic assays.

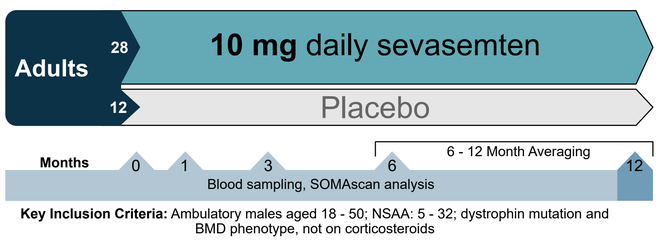




Proteins indicative of contraction-induced skeletal muscle injury were selected as those that showed both a) significant elevation over healthy in samples from three indications (BMD and limb-girdle muscular dystrophies types R9 and R12) ***at rest***; and b) further significant increase ***following exercise***.

A total of 26 somamers representing 25 unique proteins were identified to proteomically describe contraction-induced skeletal muscle injury (2).

CANYON

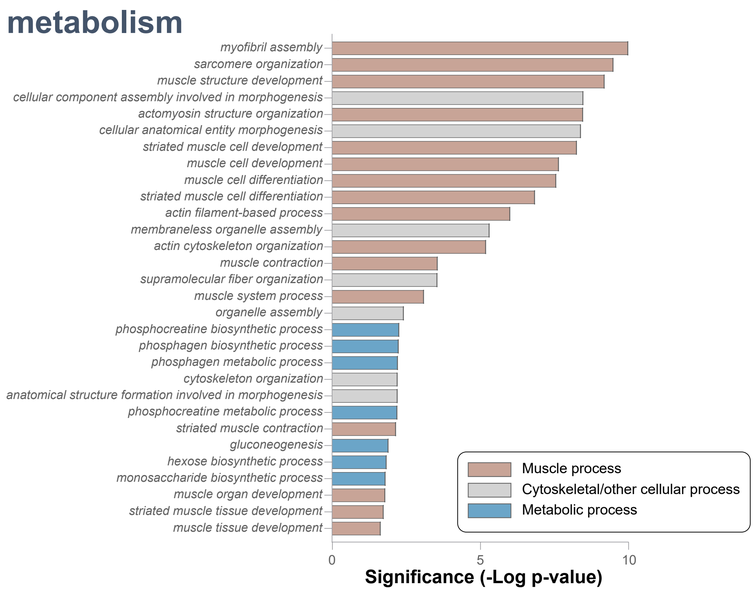


Key Inclusion Criteria: Ambulatory males aged 18 - 50; NSAA: 5 - 32; dystrophin mutation and BMD phenotype, not on corticosteroids

A total of 40 adults between 18 and 50 were enrolled in the CANYON trial to study the safety and efficacy of daily sevasemten. Blood samples were taken prior to dosing, as well as at timepoints of 1, 3, 6, and 12 months. Analysis of circulating proteins was performed using SOMAscan 7K assay, a high-throughput, unbiased assay for ~ 7000 proteins based on aptamer recognition and chip-based readout.

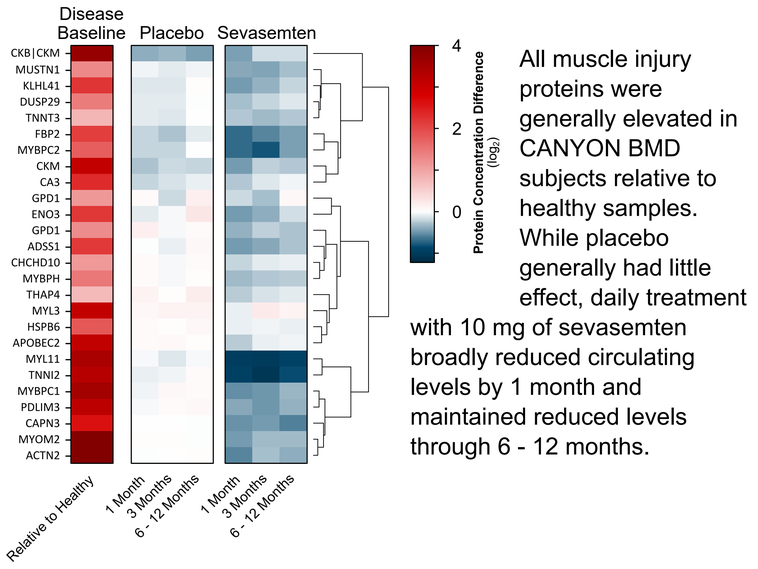
Results

Muscle injury proteins are primarily associated with muscle structure, contraction, and metabolism

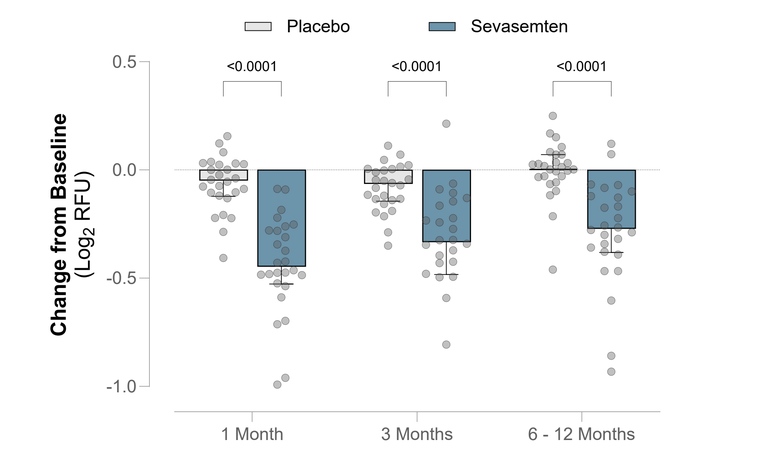


The muscle injury proteins (abbreviations below) were analyzed by gene ontology associations (3) and found to be strongly linked to biological processes involved in muscle structure and function, as well as muscle-associated metabolic pathways.

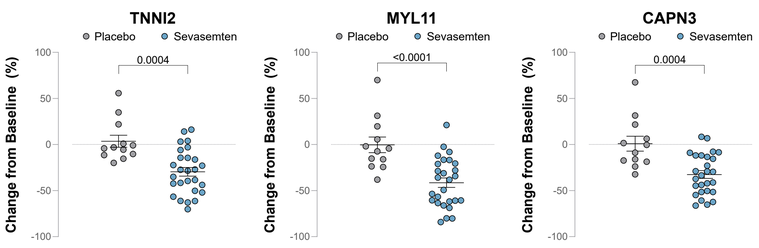
Sevasemten significantly and robustly reduced muscle injury proteins relative to placebo



All muscle injury proteins were generally elevated in CANYON BMD subjects relative to healthy samples. While placebo generally had little effect, daily treatment with 10 mg of sevasemten broadly reduced circulating levels by 1 month and maintained reduced levels through 6 - 12 months.



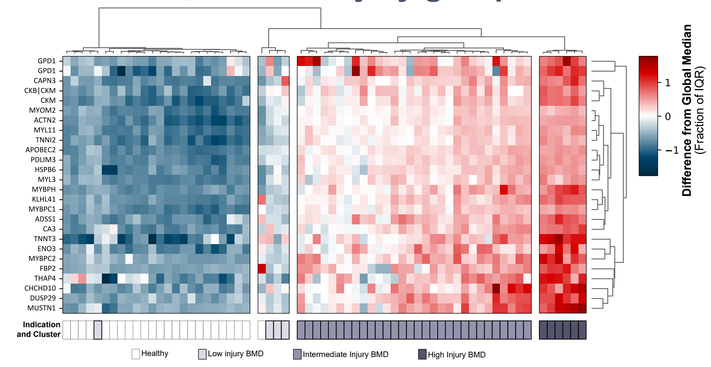
Quantification of 10 mg daily sevasemten showed that the reduction of muscle injury proteins from pre-dose baseline was highly significant relative to placebo at all timepoints ($p < 0.0001$), indicating a robust and durable muscle protective effect from sevasemten.



TNNI2, fast skeletal regulatory light chain (MYL11) and calpain-3 (CAPN3), all of which are enriched in fast skeletal muscle, were the proteins most decreased from baseline at 6 - 12 months and are all significantly reduced by sevasemten relative to placebo.

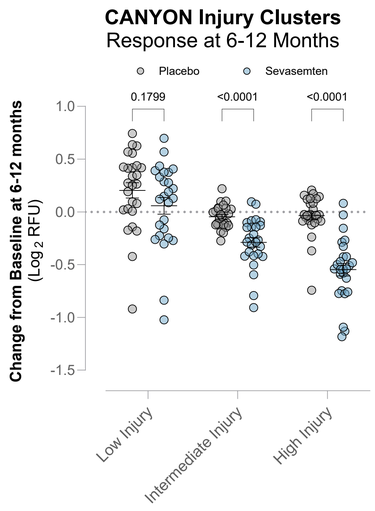
Results

CANYON subjects cluster into high, intermediate, and low injury groups at baseline



Unsupervised clustering of robust Z-scores was used to classify the BMD subjects at pre-dose baseline into high, intermediate, and low baseline injury groups, based on their difference from healthy subject samples. High-injury samples (far right cluster) exhibited the greatest elevation of muscle injury proteins over levels found in healthy samples, while low-injury subjects generally showed circulating levels very similar to those found in healthy subjects.

Response of muscle injury proteins associates with baseline injury



Sevasemten's ability to reduce and maintain muscle injury proteins at 6 - 12 months of treatment was associated with the level of injury present at baseline. For all but the lowest-injury subjects, circulating muscle protein levels were reduced significantly relative to placebo ($p < 0.0001$ for intermediate- and high-injury subjects).

Conclusions

A proteomic description of skeletal muscle injury in response to contractile stress was generated using three distinct neuromuscular disorders. The proteins were strongly associated with muscle structure, contractile function, and muscle metabolic processes.

Circulating muscle injury were significantly reduced from baseline by 1 month and maintained at significantly reduced levels for 12 months in adults treated with 10 mg daily sevasemten relative to placebo.

Sevasemten treatment for 6 - 12 months exhibited the greatest reduction in muscle injury proteins and was most differentiated from placebo in subjects with the highest levels of injury at baseline.

These results provide evidence that sevasemten protects skeletal muscles from contraction-induced myofiber injury in BMD individuals, particularly when baseline injury is profound.

References

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Sevasemten is an investigational drug that is not approved in any territory. BB, RDD, JM, JD, and AR are employees or consultants for Edgewise Therapeutics and may hold stock and/or stock options.

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