#732LBP

Post-Exercise Biomarkers of Muscle Injury are Reduced by Sevasemten, a Fast Myosin Inhibitor, in Adults with Becker Muscular Dystrophy

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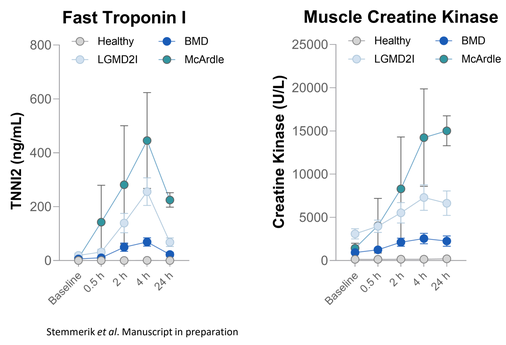
Background

Fast (Type II) skeletal muscle fibers are susceptible to injury and degeneration with activity in dystrophinopathies and other myopathies. Sevasemten is an oral, investigational agent that modulates fast skeletal muscle myosin and decreases muscle damage biomarkers while improving function in DMD disease models.

We previously showed that exercise in Becker (BMD), limb-girdle muscular dystrophy type 2I (LGMD2I/LGMDR9) and McArdle disease (McA) caused transient increases in circulating muscle injury proteins (figure below). We sought to understand whether sevasemten would alter this post-exercise muscle injury signature in BMD, LGMD2I and McA in this first placebo-controlled, single-center trial with sevasemten.



Stemmerik *et al.* Manuscript in preparation

Objectives & Methods

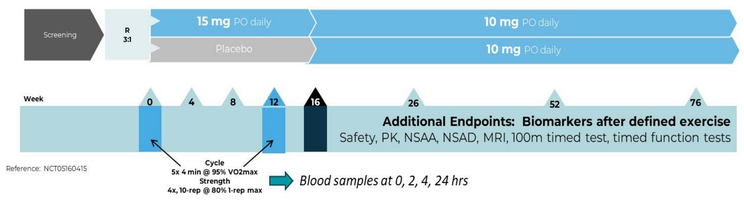
A placebo-controlled, single-center study of sevasemten effects in BMD, LGMD2I and McArdle Disease

Primary objectives:
- Assess the safety of sevasemten in adults with myopathy
- Assess effect of sevasemten treatment vs. placebo on biomarkers of muscle damage in adults w/ BMD, McArdle disease, or LGMD2I (Week 16)

Exploratory objectives:
- To assess biomarker response to an exercise challenge following 12 weeks of treatment with either sevasemten or placebo

Study Design

Schematic shown below illustrates the timing of exercise, dosing and additional function assessments in this 16-week double-blind placebo-controlled trial with an additional 9 month open-label extension phase.



Key inclusion criteria:
- Genetic diagnosis of BMD, LGMD2I or McA disease, age 18-65 (up to 75 for McA disease), and able to complete exercise protocol

Treatment:
- 15 mg sevasemten or placebo (randomized 2:1) until week 16, then 10 mg sevasemten in an open-label extension phase

Exercise challenge details:
- Quadriceps maximum repetition (1-RM) and cycle VO_{2max} measured followed by 10 min rest. Customized exercise challenge: 5x 4' cycle challenge at 95% VO_{2max} followed by 4x 10-repetitions leg exercise at 80% 1-RM

Plasma Proteomics:
- Circulating plasma proteomics measured by SomaScan 7K (V4.1, SomaLogics, Boulder CO). Conversion from SomaScan toTNNI2 concentration was performed as shown:

$$TNNI2\ \left(\frac{ng}{mL}\right) = 10^{((0.6982 * \log_2 SOMA) - 9.523)}$$

Results

Enrolled population

	BMD (n=9)	LGMD2I (n=9)	McArdle (n=3)
Mean age (yr, range)	41 (30-57)	41 (29-55)	53 (47-56)
Gender	100% M	100% M	100% F
NSAA mean (range)	21 (5-32)	14.6 (8-30)	-
NSAD mean (range)	35 (12-52)	23 (11-43)	-
10MWRT median (seconds, range)	6.0 (2.3-152.0)	11.0 (5.0-19.0)	-
4-stair climb mean (seconds, range)	4.5 (1.6 – 8.7, one unable)	11.0 (3.0 - 30.0, one unable)	2.4 (2.0 - 3.4)

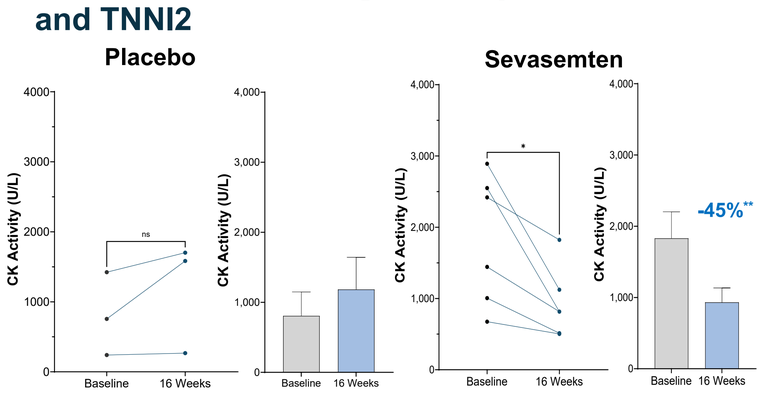
Safety & Tolerability

Treatment Emergent AE in >1	Sevasemten (n=14)	Placebo (n=7)
Dizziness	8	1
Headache	6	3
Nasopharyngitis	3	2
Influenza	1	1
Fatigue	3	1
Pyrexia	2	0
Myalgia	2	0
Nausea	2	1

For LGMD2I, 1 patient withdrawal due to fatigue. One SAE (unrelated), cerebral infarction.

Results (Continued)

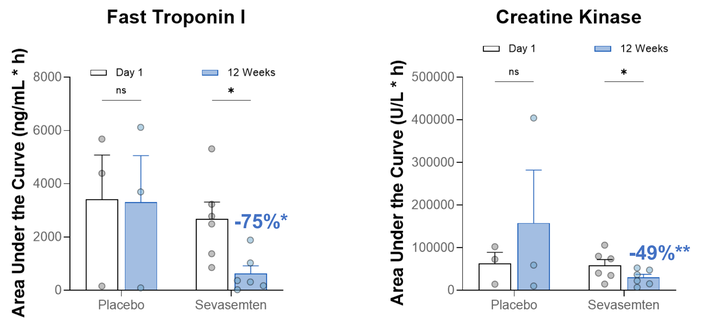
BMD: Sevasemten significantly reduced CK and TNNI2



Primary endpoint: CK change from baseline after 16 weeks sevasemten vs. placebo in BMD

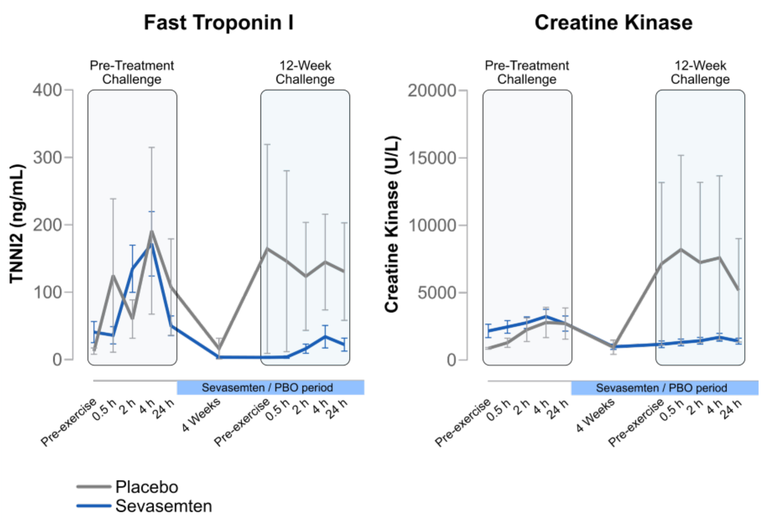
With sevasemten, CK was significantly decreased compared to baseline (**p<0.01) and compared to placebo (*p<0.05) during a period of normal activity.
At 12 weeks, with sevasemten, fast muscle troponin I (TNNI2) was significantly decreased by 89% compared to baseline (p<0.01) and compared to placebo (p<0.05) during a period of normal activity.

BMD: Sevasemten significantly reduced TNNI2 and CK over 24 hours post-exercise

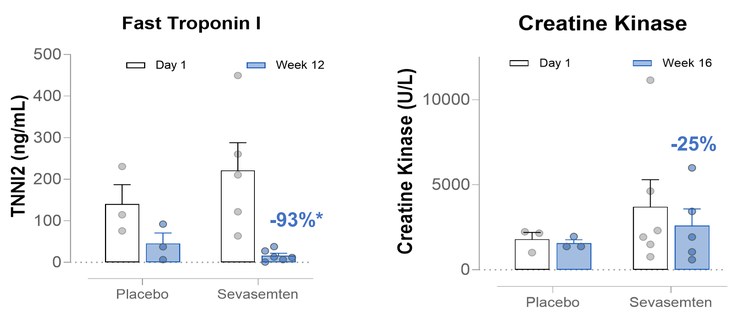


With sevasemten, TNNI2 was decreased in the 24 hours after exercise compared to baseline (*p<0.05) and compared to placebo (p=0.07).

With sevasemten, CK was significantly decreased in the 24 hours after exercise compared to baseline (**p<0.001).



LGMD2I: TNNI2 and CK trended down with sevasemten

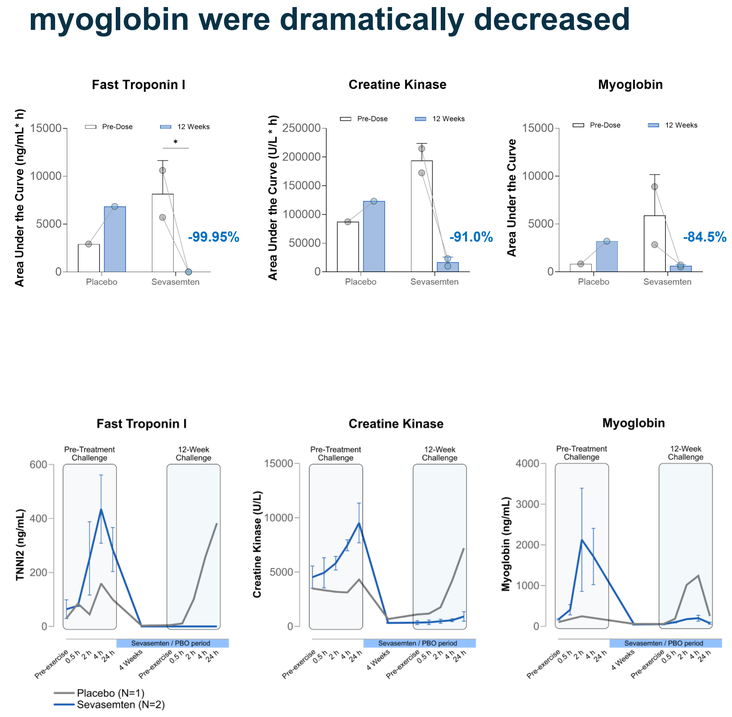


With sevasemten, TNNI2 was decreased 93% relative to baseline (p<0.05) during a period of normal activity.
With sevasemten, CK trended down compared to baseline during a period of normal activity (p=NS).

No difference was observed between placebo and sevasemten with respect to post-exercise AUC at 12 weeks relative to baseline.

Results (Continued)

McA: With sevasemten, CK, TNNI2 and myoglobin were dramatically decreased



After 16 weeks of Sevasemten, CK and myoglobin were in the normal range, and TNNI2 was decreased by >99% during a period of normal activity.

With sevasemten, CK, TNNI2 and myoglobin were all substantially decreased in the 24 hours after exercise compared to baseline or placebo. These data are limited by n=3 participants.

Sevasemten did not affect exercise capacity or strength in BMD, LGMD2I or McA

		Pre-Dose			Week 12			Change from Pre-Dose Means (%)		
		1-RM (kg)	VO2Max (mL*kg*min-1)	Max Work (J*s)	1-RM (kg)	VO2Max (mL*kg*min-1)	Max Work (J*s)	1-RM (kg)	VO2Max (mL*kg*min-1)	Max Work (J*s)
BMD	Active	22.8 +/- 31	20.6 +/- 6.8	68 +/- 53.9	19.3 +/- 24.7	21.8 +/- 7	65.3 +/- 52.7	-15.7%	6.2%	-3.9%
	Placebo	59.3 +/- 53	27.9 +/- 9.4	148 +/- 106	61.2 +/- 52.1	28.1 +/- 10.3	143.3 +/- 83.7	3.2%	0.7%	-3.2%
LGMDR9	Active	16 +/- 18.6	18.7 +/- 8.9	49.5 +/- 46	19.9 +/- 23.3	15.9 +/- 3.3	55.2 +/- 49	24.5%	-15.0%	11.5%
	Placebo	4.8 +/- 0.4	15.1 +/- 0.8	28.7 +/- 1.2	4.8 +/- 0.3	16.7 +/- 1.6	28.7 +/- 1.2	1.4%	10.1%	0.0%
McArdle	Active	59 +/- 1.4	23.5 +/- 3	90 +/- 0	55.5 +/- 7.8	26.4 +/- 3.5	100 +/- 14.1	-5.9%	12.4%	11.1%
	Placebo	45	17.1	69	50	18.4	76	11.1%	7.6%	10.1%

Conclusions

- In BMD, sevasemten decreased CK and TNNI2 significantly compared to placebo during a period of normal activity.
- In BMD, 12 weeks of treatment resulted in significant reductions in the post-exercise increases in multiple biomarkers of muscle injury, including CK and TNNI2.
- In LGMD, exercise at baseline appeared to decrease CK and TNNI2, making assessment of compound effects challenging 12 weeks later.
- In McA, 12 weeks of treatment normalized post-exercise biomarkers of muscle damage, including CK, TNNI2 and myoglobin.
- Sevasemten did not significantly alter exercise capacity or strength in BMD, LGMD2I or McA.
- Sevasemten was generally well tolerated in BMD, LGMD and McA.

The results from this study are supportive of a protective mechanism for sevasemten with the potential to protect muscle at doses that do not compromise strength or exercise capacity. The robust response in McA supports further exploration of sevasemten in this indication.

Changes in CK are the primary endpoint for the CANYON placebo-controlled study of sevasemten in BMD (N=40, NCT05291091), and results are expected in Q4 2024.

Disclaimers
For all graphs, errors bars indicate the SEM.
Sevasemten (EDG-5506) is an investigational agent that is not approved for use by any regulatory authority in any territory. AR, JD, BB, and JM are employees or consultants for Edgewise Therapeutics and may hold stock and/or stock options.
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