Effects of Sevasemten on LVEF and NT proBNP in Adults with Becker Muscular Dystrophy in CANYON

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Conclusions

- Sevasemten, a specific fast skeletal muscle myosin inhibitor, exhibited a well-tolerated cardiac profile over 12 months, with no impairment of LVEF or elevation of NT-proBNP
- Relative to placebo, 12 months of sevasemten improved LVEF in specific subgroups and trended positive in all adults, in both those with preserved and decreased LVEF.
- The cardiac benefit and safety profile of sevasemten continues to be investigated in ongoing, longer-term trials.

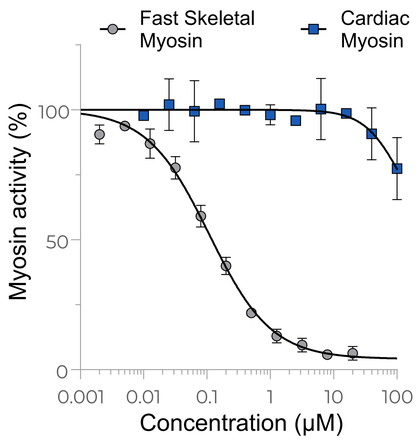
Background

Becker muscular dystrophy (BMD) is a serious, rare, neuromuscular disorder with no currently approved therapies. Beyond skeletal muscle, BMD is also accompanied by development of dilated cardiomyopathy, a major contributor of morbidity and mortality, which manifests clinically with reduced cardiac output and elevated natriuretic peptides such as NT-proBNP[1,2].

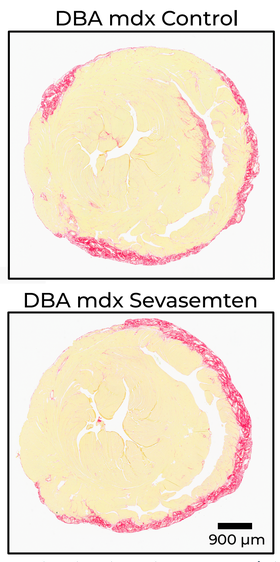
Sevasemten is an investigational, novel, oral, fast skeletal myosin inhibitor designed to protect muscle against contraction-induced damage while preserving function[3]. In human clinical trials, it has shown robust attenuation of proteomic markers of skeletal muscle injury and has been well-tolerated[4]. Sevasemten is highly selective for fast skeletal muscle myosin and does not inhibit cardiac myosin at therapeutic concentrations. Nonetheless, pre-clinical studies in DBA mdx mice suggested that sevasemten treatment resulted in trends toward reduction of cardiac fibrosis relative to untreated animals (below right), raising the potential for long-term cardiac benefit in individuals with Becker[3].

This work aimed to investigate sevasemten's cardiac effects, with respect to left ventricular ejection fraction (LVEF) and circulating NT-proBNP.

Sevasemten is > 1000-fold more selective for fast skeletal muscle over cardiac



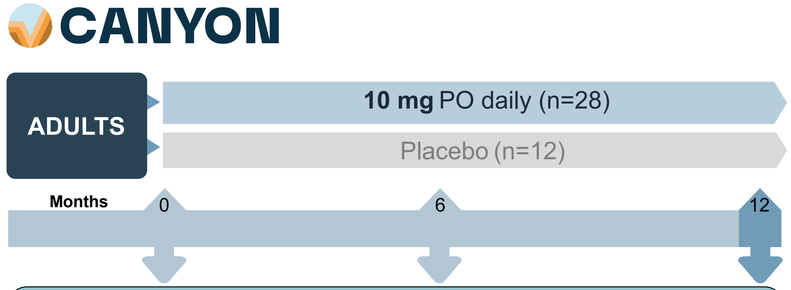
In isolated myosin activity assays, sevasemten inhibits fast skeletal myosin with much greater potency than cardiac myosin (EC_{50}: 0.1 vs >100 uM, respectively).



Sevasemten treatment was associated with decreased cardiac fibrosis in DBA-mdx mice, as indicated by picrosirius staining (red).

Methods

CANYON



The CANYON study (NCT05291091) is a Phase 2, double-blind, placebo-controlled study of sevasemten in ambulatory adults and adolescents (12 - 50 yrs) with BMD and NSAA scores between 5 and 32 and not on corticosteroids. The primary endpoint was reduction of creatine kinase.

Only adult participants were included in this post-hoc analysis to study cardiac effects of sevasemten. LVEF was assessed by centrally-read echocardiography. Plasma samples from participants were analyzed by SOMAscan 7K, with specific focus on NT-proBNP (somamer ID 7655-11).

Linear regression analysis was used to calculate longitudinal absolute changes in LVEF and NT-proBNP (log-transformed, back-transformed into % change) for adult participants across Months 0, 6, and 12. Those individuals with normal baseline LVEF (≥ 55%, n=21) and reduced baseline LVEF (< 55%, n=14) were also analyzed as specific subgroups of focus.

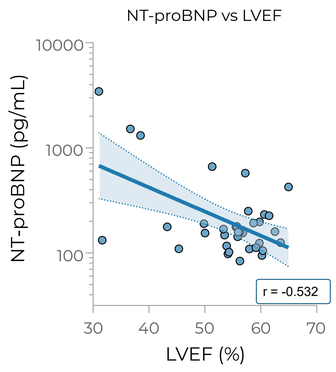
Safety

	Sevasemten (n=28) n (%)	Placebo (n=12) n (%)
Cardiovascular AEs	**3 (11%)**	**4 (33%)**
Reduced ejection fraction	0 (0%)	2 (17%)
Palpitations/flutter	2 (7%)	0 (0%)
Chest discomfort	0 (0%)	1 (8%)
Cardiomyopathy	0 (0%)	1 (8%)
LV dysfunction	1 (3.6%)	0 (0%)

Cardiac-specific adverse events (AEs) were mild, resolved during the study, and were not related to the study drug. 2/3 of sevasemten participants and 3/4 of placebo participants who experienced cardiac AEs had a medical history of cardiac disorders.

Results

Reduced baseline LVEF was associated with elevated NT-proBNP

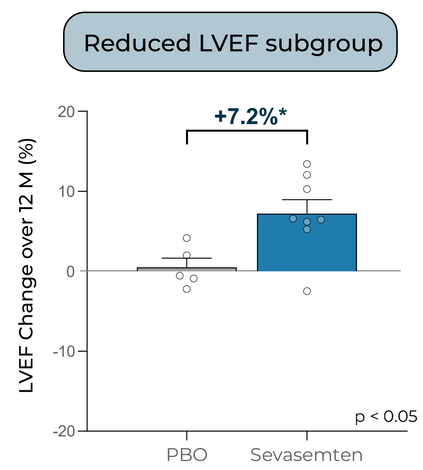


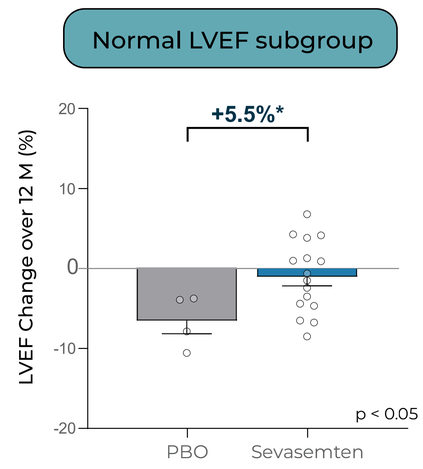
Demographics			
	Normal LVEF (≥ 55%)	Reduced LVEF (< 55%)	P-Value*
N	21	14	
Age (yrs)[a]	30.8 (26.4, 35.1)	31.4 (24.9, 37.9)	ns
NSAA[a]	21.0 (17.9, 24.1)	18.9 (13.4, 24.4)	ns
NSAD[a]	34.1 (29.9, 38.4)	31.5 (23.8, 39.2)	ns
CK (U/L)[a]	1726 (1265, 2188)	1626 (1052, 2200)	ns
NT-proBNP (pg/mL)[b]	162.5 (135.7, 194.6)	291.7 (158.2, 538.1)	p < 0.05

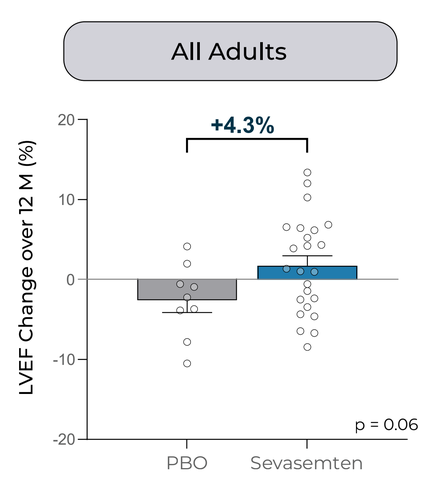
*Nominal p-values displayed. ns: not significant.
[a]Mean with 95%CI; p-values calculated using unpaired t-tests.
[b]Geometric mean with 95%CI; screening and Day 1 values were aggregated for each participant; p-value calculated using unpaired t-test on log-transformed values.

Baseline LVEF and baseline NT-proBNP were strongly correlated (left, r=0.532, p = 0.001). Subpopulations based on LVEF did not differ in age, North Star Ambulatory Function (NSAA), NSAA for Limb-Girdle muscular dystrophy (NSAD), or baseline creatine kinase. NT-proBNP was significantly elevated in reduced LVEF participants relative to normal LVEF participants.

Sevasemten treatment was associated with a positive difference in LVEF relative to placebo (PBO) in both LVEF subgroups

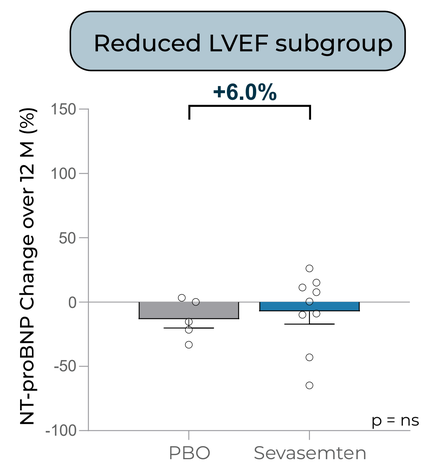


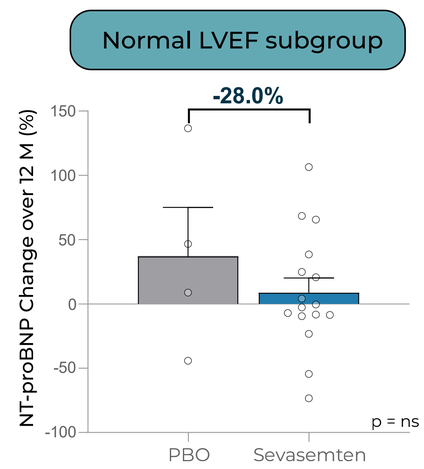


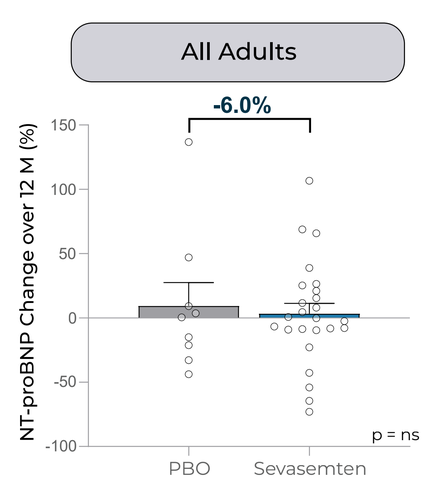


Points indicate the 12-month change estimates derived from a linear regression analysis for each participant. Error bars show mean and SEM. Nominal p-values shown calculated with an unpaired t-test.

Sevasemten treatment for 12 months had no significant effect on NT-proBNP







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References

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Disclosures

Sevasemten is an investigational agent that is not approved for use by any regulatory authority in any territory.

Ben Barthel, Roxana Donisa Dreghici, James MacDougall, Alan Russell, and Joanne Donovan are employees of and hold shares of Edgewise Therapeutics. Craig McDonald, Diana Castro, Katherine Mathews, Erik Niks, Aravindhan Veerapandiyan, Michela Guglieri, and Anne M. Connolly are consultants for Edgewise Therapeutics. All others listed are investigators in the CANYON trial.

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