EDG-7500 (EDG-002), A FIRST-IN-CLASS TARGETED SARCOMERE REGULATOR THAT PRESERVES INTRINSIC MYOSIN-MOTOR FUNCTION, NORMALIZES SYSTOLIC FUNCTION AND ELIMINATES LVOT OBSTRUCTION IN CATS WITH HYPERTROPHIC CARDIOMYOPATHY

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BACKGROUND

- Hypertrophic Cardiomyopathy (HCM) is a myocardial disease characterized by LV hypertrophy, systolic hyperactivity, and diastolic dysfunction that can result in LV outflow tract (LVOT) obstruction. HCM is recognized as a sarcomeric disease because it is caused by mutations in genes that encode for sarcomeric proteins such as beta-myosin heavy chain and myosin-binding protein C. In patients with or without known genetic mutations, excess sarcomere activity is present.
- EDG-7500 is a sarcomere regulator designed to preserve myosin function and potentially offer salutary effects in HCM while minimizing impact on systolic function. Here, this hypothesis was tested in a translationally relevant cat model of obstructive HCM (oHCM)†‡.

†Stern et al. Plos One, 2016; ‡Sharpe et al., Sci Rep., 2023

METHODS

- ***In vitro:*** The effects of EDG-7500 were evaluated biochemically in actin-activated myosin-S1, as well as biomechanically on LV skinned fibers.
- ***In vivo (IV)***: Seven cats (A31P MYBPC3 mutants , mean 4.8 ± SD 0.4 kg) with HCM were studied; *LVOT obstruction was established with dobutamine* (10-20 µg/kg/min IV) in 6/7 cats (1/7 existing). Echocardiographic exams were performed before and after acute EDG-7500 IV administration (0.3 - 4 mg/kg); in addition, 3 cats received vehicle to serve as controls.

IV Study Schema: Dose-escalation in A31P MYBPC3 oHMC cats

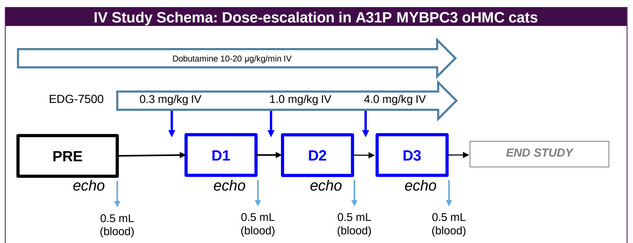


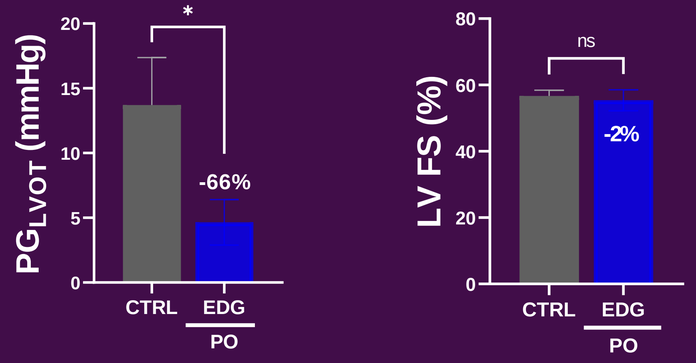
Figure 1: *Dose-escalation experimental design used to evaluate the acute effects of EDG-7500 (IV) in cats with oHCM. A subset of animals received vehicle (VEH) instead of EDG-7500.*

- ***In vivo (PO)***: Seven cats (A31P MYBPC3 mutants, 5.2 ± 0.5 kg) with HCM received either placebo (VEH) or EDG-7500 as a single-dose capsule (regardless of weight), in a blinded fashion following a cross-over/Latin Square design. Echocardiographic exams under sedation were done before (baseline) and after (+6 and +48hrs) each dosing; in addition, post-dose (at +6hr), dynamic LVOT obstruction was studied during a dobutamine challenge (+15 µg/kg/min IV). *All cats successfully completed the studies and recovered post-dose.*

CONCLUSION

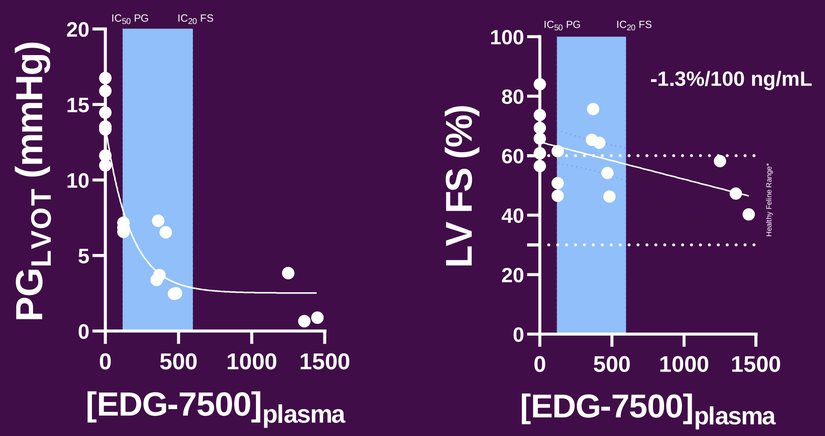
- EDG-7500, is a targeted sarcomere regulator **designed to preserve cardiac myosin activity**
- EDG-7500 improved systolic function and **eliminated LVOT obstruction** in a model of oHCM, while being **tolerated over a wide range of exposures**.
- This novel profile could be valuable for the treatment of patients with HCM.

In a fixed oral dose study in cats with HCM, EDG-7500 alleviated LVOT gradient with minimal changes in FS



In vivo (PO): Fixed single oral doses resulted in mean ± SEM exposures of 208 ± 37 ng/mL, ranging from 68 to 560 ng/mL. EDG-7500 reduced PG (peak gradient) at rest (14 ± 4 mmHg vs. 5 ± 2 mmHg, -66 ± 13%,) ($P < 0.05$) with negligible changes in FS (57 ± 2% vs. 55 ± 3%, -2 ± 6%,); EDG-7500 reduced the incidence of LVOT obstruction (43% vs. 7%). Similar effects were also noted under a dobutamine challenge (PG: -40 ± 12%, LVOTo: 89% vs. 43%)

EDG-7500 shows a shallow exposure-response in FS, remaining in the normal range over greater than 12x exposure range



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Poster Number: 1066-13
Presented at the American College of Cardiology (ACC)
72nd Annual Scientific Sessions I New Orleans, LA I March4-6, 2023

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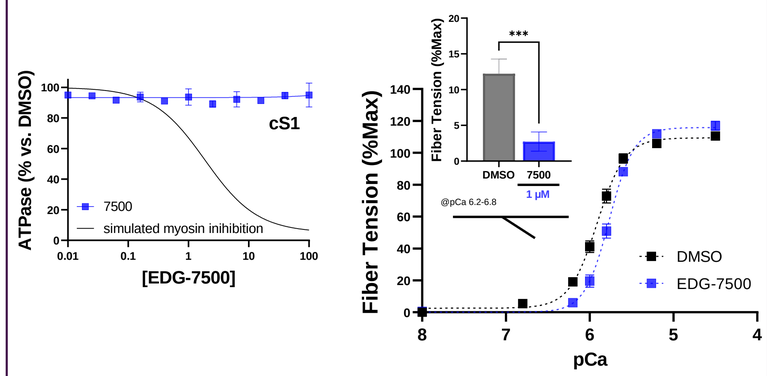
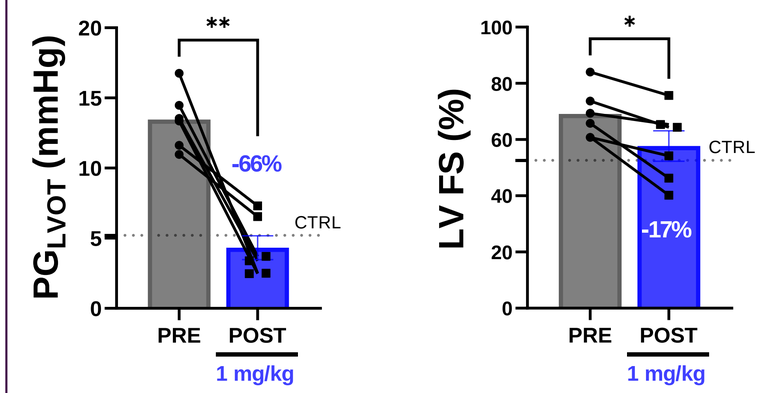
EDG-7500 preserves cardiac myosin-S1 enzymatic activity, but attenuates force generation



In vitro: EDG-7500 preserved the enzymatic activity of myosin-S1 with blunted (desensitizing) tension generation.

EDG-7500 improves indices of systolic function and alleviates LVOT gradient, even under dobutamine stress



In vivo (IV): all cats had hyperdynamic contraction and LVOT obstruction. EDG-7500 blunted hyperdynamic contraction and reduced PG (@1 mg/kg, FS: 67 ± 4% vs. 58 ± 5%, PG: 13.8 ± 0.8 mmHg vs. 4.3 ± 0.9 mmHg; all $P<0.05$), eliminating LVOT obstruction; EDG-7500 exposures @ 1 mg/kg ranged between 351 to 484 ng/mL, data above.
Data in center bottom panel: PG reductions were noted at exposures with negligible effects in FS; EDG-7500 exposures (124 to 1450 ng/mL) and showed a shallow FS exposure-response (-1.3%/100 ng/mL). *Fox PR et al., Circulation, 1995

DISCLOSURE INFORMATION

EDG-7500 is a nonclinical stage investigational compound that is not approved in any territory. SL, MD, MM, JT, NH, SS, AR, and ME are employees of Edgewise Therapeutics, CDR is a consultant and all the foregoing hold stock or stock options.