

Targeting the Mechanism of Hypertrophic Cardiomyopathy

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Disclosures

- Dr. Semigran is a full-time employee of Edgewise Therapeutics

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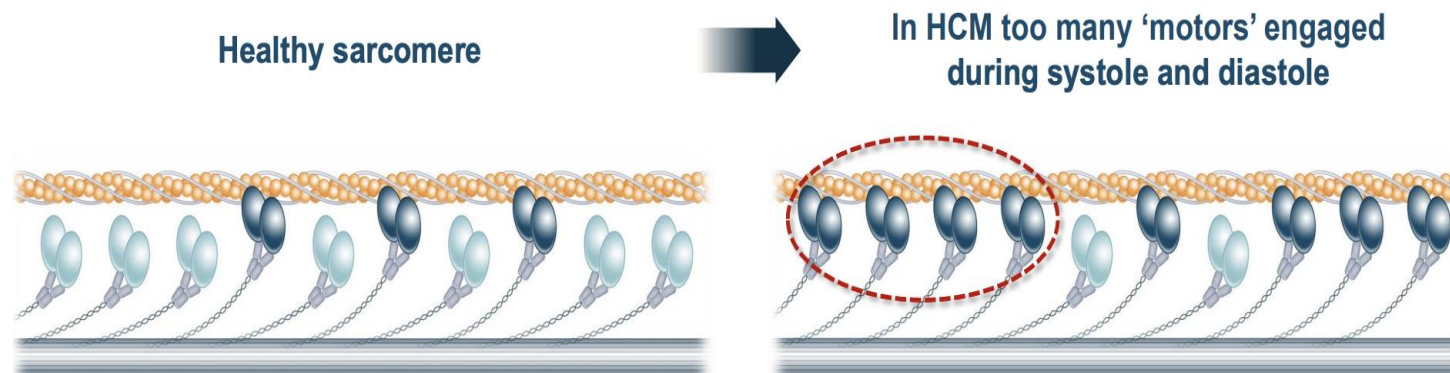
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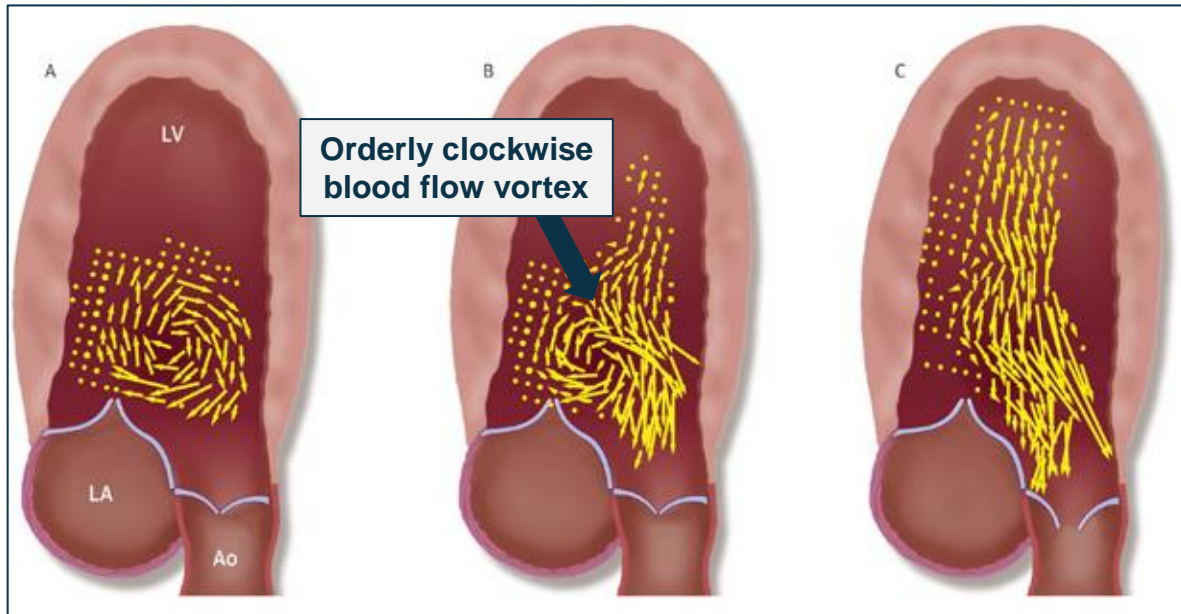
Advancing EDG-7500, a First-In-Class Sarcomere Modulator for Hypertrophic Cardiomyopathy (HCM)

- Edgewise Therapeutics' robust discovery platform is yielding novel compounds targeting important unmet needs of patients suffering from inherited disorders of cardiac and skeletal muscle.
- EDG-7500 is first-in-class oral, cardiac-selective, sarcomere modulator for HCM designed to slow myocardial contraction velocity and improve impaired relaxation, hallmarks of patients with either obstructive or nonobstructive pathophysiology.
- Preclinical data of EDG-7500 support beneficial activity in models of both obstructive and non-obstructive HCM with minimal changes in overall LV systolic performance.



LVOT Obstruction in oHCM Patients Results from Abnormalities in Early Systolic LV Blood Flow & Mitral Leaflet Structure

Normal Flow in Control Patient

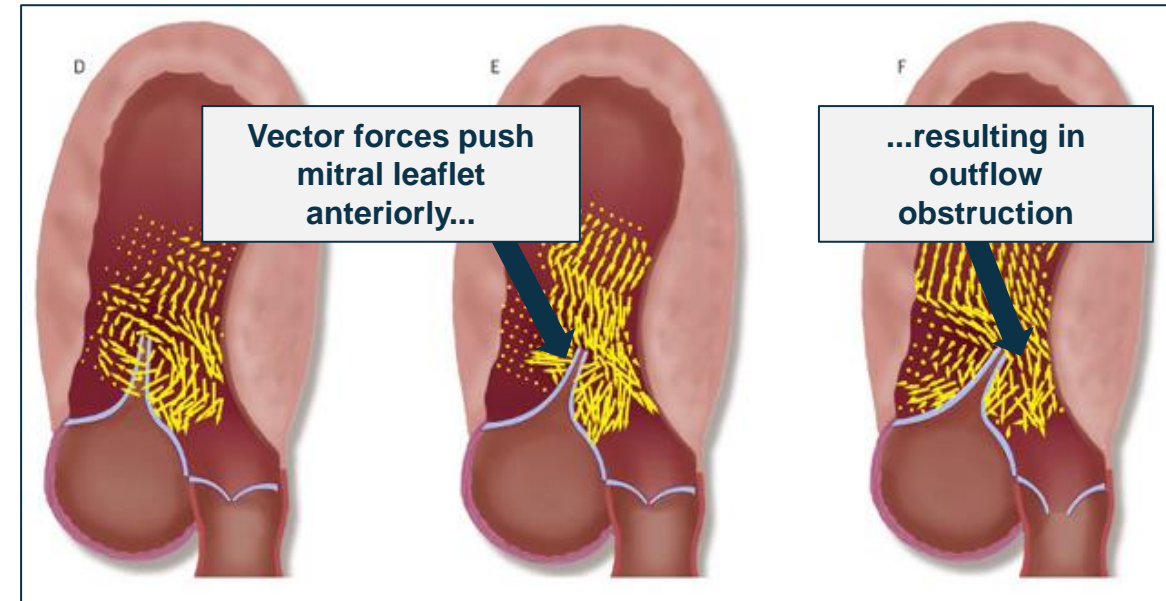


Early Isovolumic Contraction

Late Isovolumic Contraction

Early Ejection

Systolic Anterior Motion in HCM

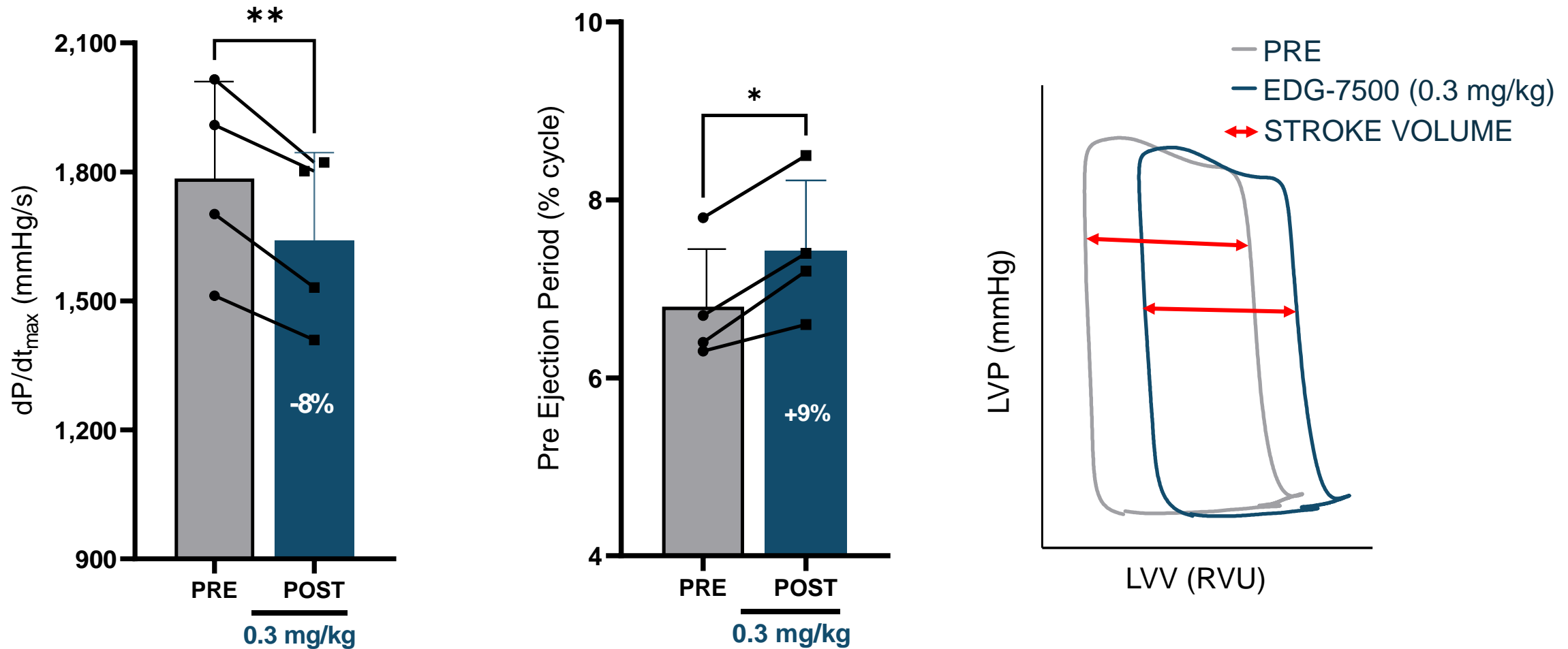


Early Isovolumic Contraction

Late Isovolumic Contraction

Early Ejection

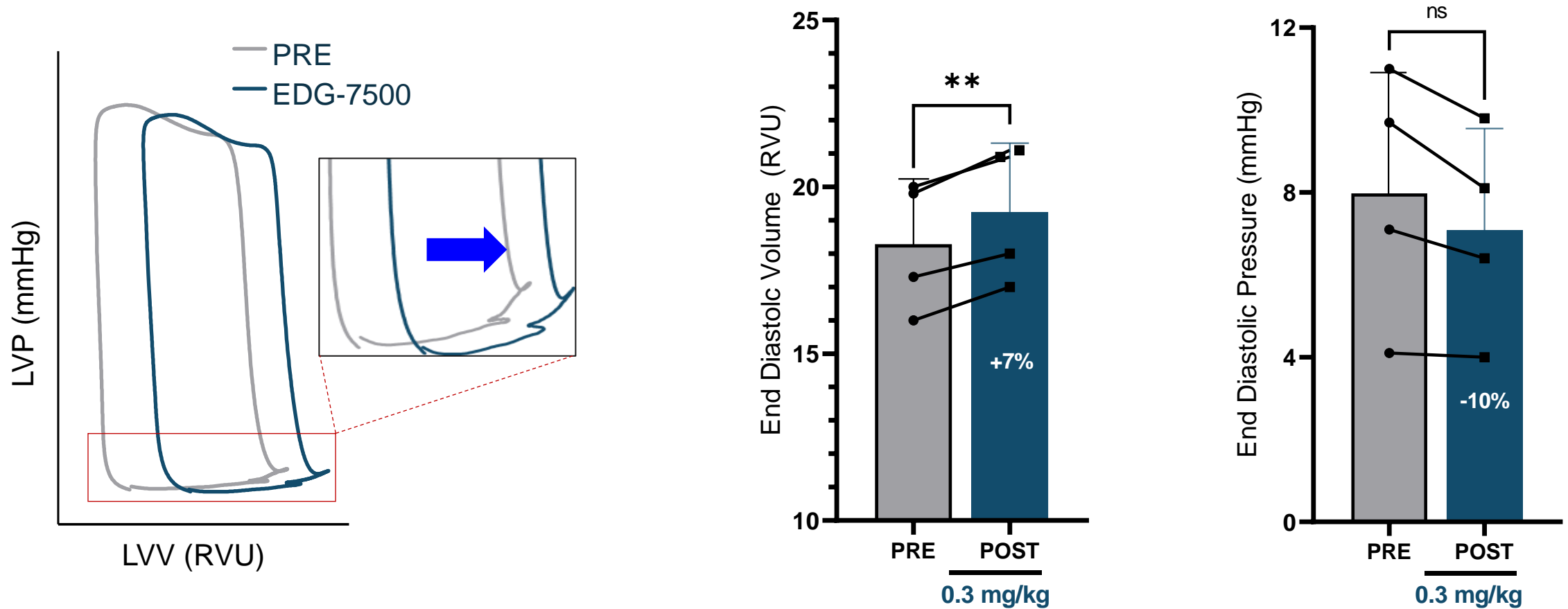
Systolic Function: EDG-7500 Reduces the Rate of Pressure Development during Isovolumic Contraction and Prolongs Pre Ejection Period; Stroke Volume is Preserved



Healthy Dogs (n=4). Measurements made after iv EDG-7500 administration.

* p < 0.05; ** p < 0.01

Diastolic Function: EDG-7500 Increases Left Ventricular Compliance

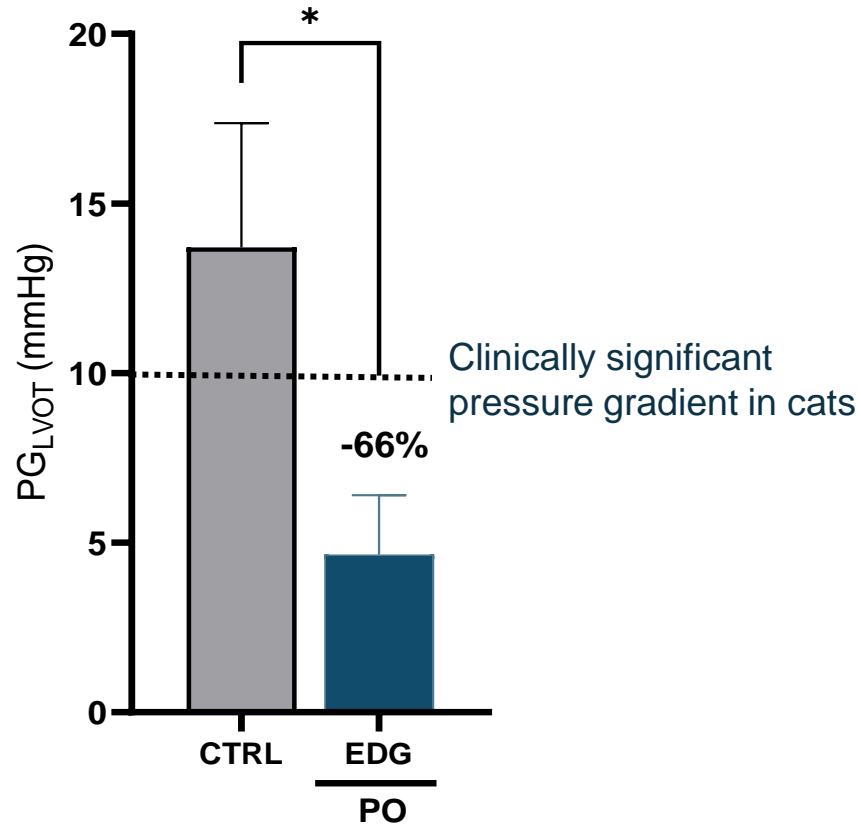


Healthy Dogs (n=4). Measurements made after iv EDG-7500 administration.

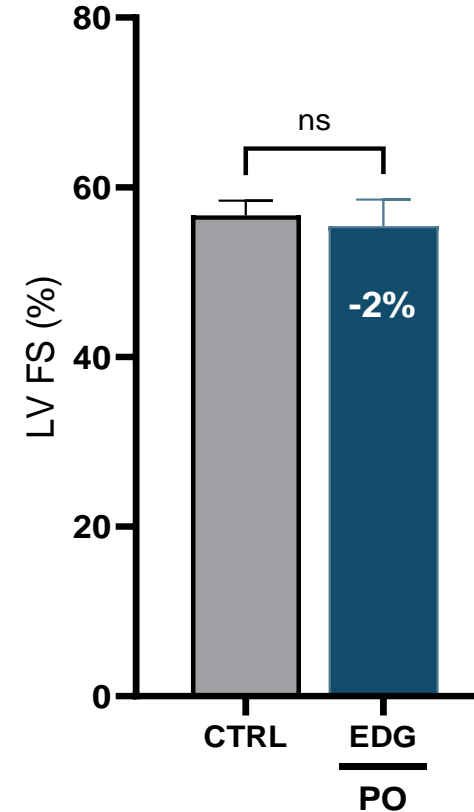
** p < 0.01

EDG-7500 Relieves LVOT Gradient Without Changing % Fractional Shortening in Cats with Genetic oHCM

EDG-7500 Driven LVOT Gradient Relief



LVFS Maintained with Oral EDG-7500 Treatment



A31P MyBP-C Mutation Cat Model of oHCM (n=6).

Measurements made after single fixed dose oral EDG-7500 administration. Plasma EDG-7500 levels 68-560 ng/mL.

* p < 0.01

Summary

- Knowledge of muscle biology and the pathophysiologic mechanisms of HCM has informed design of a small molecule that directly targets both early-systolic and diastolic myocardial function with modest effects on overall systolic performance as measured by ejection-phase indices.
- The myocardial effects of EDG-7500 have been shown to eliminate clinically significant LVOT obstruction in a cat model of oHCM over a wide range of exposures without altering %FS.
- EDG-7500 efficacy has been observed in preclinical animal models of nHCM.
- Single ascending dose human studies of the safety & tolerability of EDG-7500 have begun.
- EDG-7500's novel mechanism of action supports investigating fixed-dose regimens for treatment of patients with HCM.