Chronic administration of EDG-7500, a novel sarcomere modulator, prevents increases in cardiac mass, T1 relaxation time, and left ventricular end diastolic pressure in a Yucatan mini-pig model of genetic non-obstructive hypertrophic cardiomyopathy.

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Study Aims

To determine if EDG-7500 can prevent pathologic cardiac remodeling and disease progression in a mini-pig model of non-obstructive HCM (nHCM) caused by heterozygous *MYH7* R403Q mutation.

Background

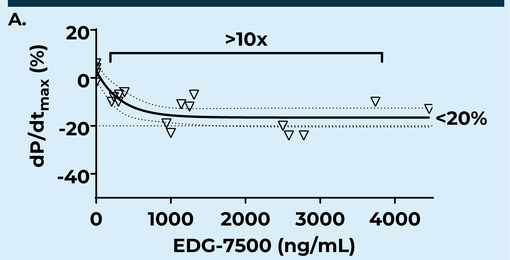


Figure 1. EDG-7500 slows the rate of contraction in a self-limiting manner while speeding relaxation. (A) EDG-7500 decreases the rate of pressure development in the LV of normal healthy dogs to a level that plateaus at 20% of baseline despite increasing exposure. **(B)** Peak mitral annular velocity during early diastolic filling (e') is increased to normal control levels in R403Q swine treated daily with EDG-7500 compared to placebo.

Results

EDG-7500 does not impair resting systolic function

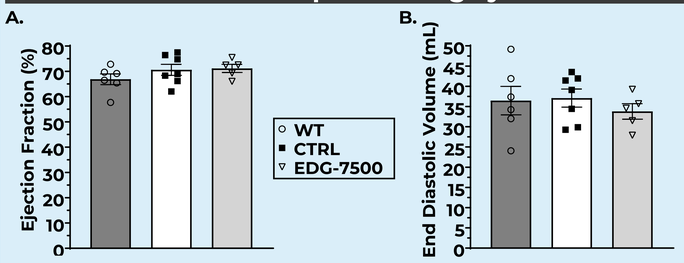


Figure 2. Chronic daily treatment with EDG-7500 does not **(A)** decrease resting ejection fraction or affect **(B)** end diastolic volume assessed by cardiac MRI.

EDG-7500 prevents cardiac remodeling measured both *in vivo* and postmortem

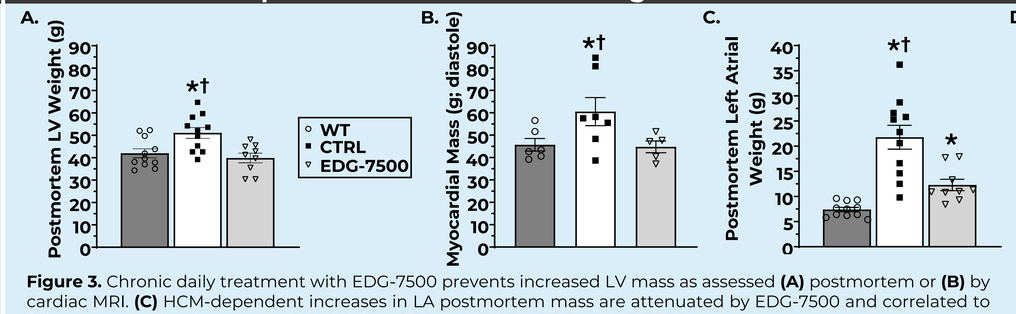


Figure 3. Chronic daily treatment with EDG-7500 prevents increased LV mass as assessed **(A)** postmortem or **(B)** by cardiac MRI. **(C)** HCM-dependent increases in LA postmortem mass are attenuated by EDG-7500 and correlated to **(D)** p-wave amplitude. one way ANOVA; *P < 0.05 vs. WT; †P < 0.05 vs. EDG-7500

EDG-7500 prevents LV diastolic impairment

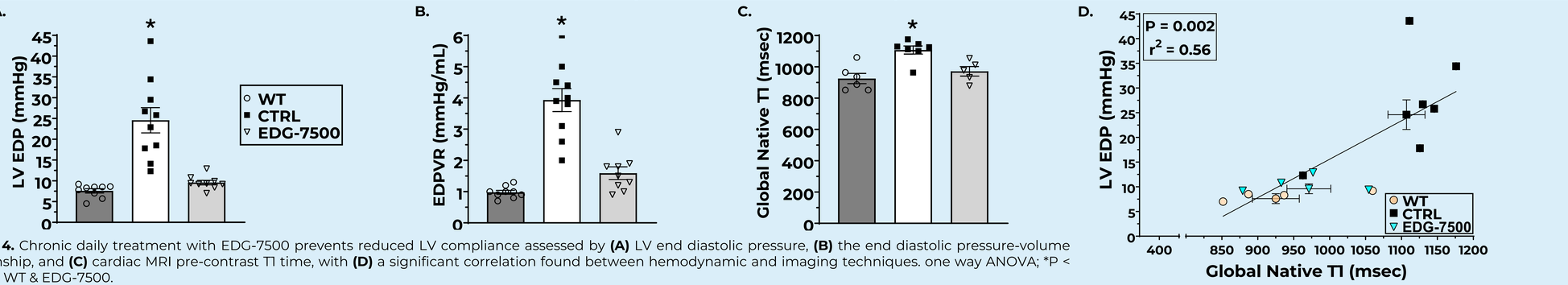


Figure 4. Chronic daily treatment with EDG-7500 prevents reduced LV compliance assessed by **(A)** LV end diastolic pressure, **(B)** the end diastolic pressure-volume relationship, and **(C)** cardiac MRI pre-contrast T1 time, with **(D)** a significant correlation found between hemodynamic and imaging techniques. one way ANOVA; *P < 0.05 vs. WT & EDG-7500.

EDG-7500 prevents increases in biomarkers associated with disease progression

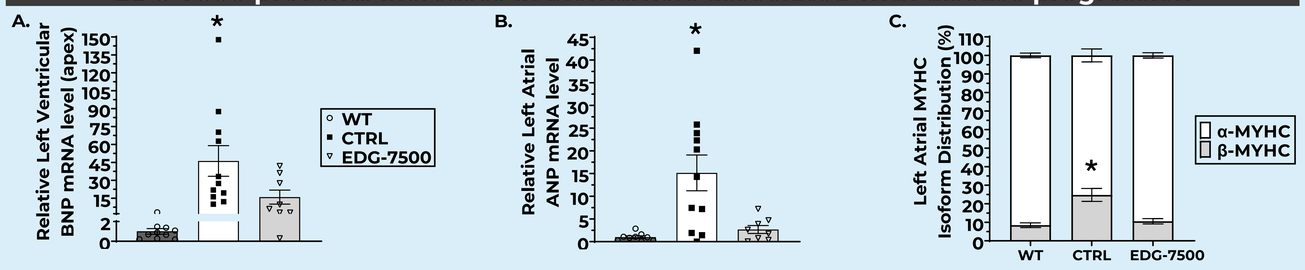
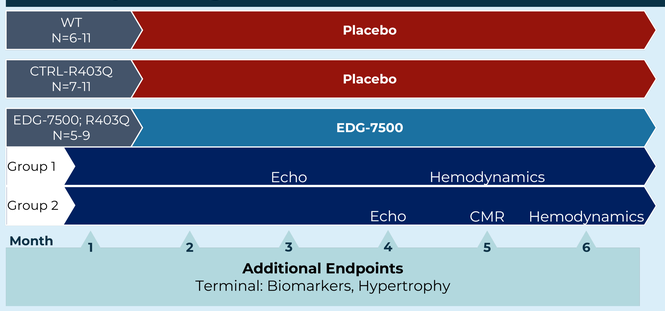
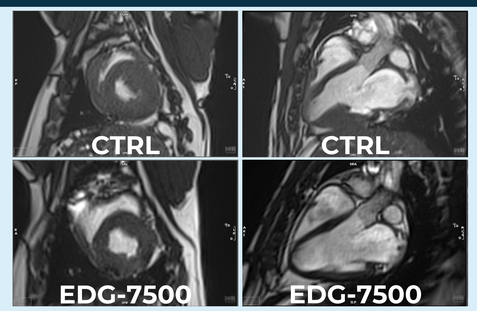


Figure 5. Chronic daily treatment with EDG-7500 attenuates increases in traditional biomarkers associated with general cardiovascular health including **(A)** LV brain natriuretic peptide, **(B)** LA atrial natriuretic peptide, and **(C)** LA β-myosin heavy chain. one way ANOVA; *P < 0.05 vs. WT & EDG-7500.

Study Design





- Cardiac MRI sequences were collected in 12-16 parallel, short-axis views using a Siemens 3T scanner for calculation of left ventricular (LV) EF, volumes, T1-time, and LV mass.
- LV and left atrial (LA) mass were also measured postmortem.
- LV end diastolic pressure (EDP) and the end diastolic pressure-volume relationship (EDPVR) were measured *in vivo* via P-V catheter techniques.
- Myocardial atrial and brain natriuretic peptide (ANP and BNP) mRNA and α and β myosin heavy chain (MYHC) proteins were evaluated.
- Statistical significance was set at P≤0.05 using one way ANOVA or linear regression with data reported as mean ± SE.

Summary and Conclusions

In a mini-pig model of non-obstructive HCM (nHCM) caused by heterozygous *MYH7* R403Q mutation, chronic EDG-7500:

- **Prevents pathologic cardiac remodeling** assessed both postmortem and by cardiac MRI without significant effect on systolic performance.
- **Prevents decreased LV compliance** with substantial agreement between gold standard hemodynamic and imaging techniques.
- **Prevents increases in biomarkers** associated with disease progression and general cardiovascular health.

These findings support ongoing development of EDG-7500 in nHCM

Disclosures: CAE, SL, LL, ED, AP, MH, MJS, AR, ME are all employees and stockholders of Edgewise Therapeutics; DAB is a consultant for Edgewise Therapeutics & GE Heathcare; CLDR is a consultant for Edgewise Therapeutics; DLT & SR have no disclosures.

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