EDG-7500, a novel cardiac sarcomere modulator, normalizes left ventricular pre-ejection period in obstructive hypertrophic cardiomyopathy patients through selective reduction of myosin step-size

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Study Aims

EDG-7500 is an investigational cardiac sarcomere modulator targeting the regulatory light chain and is currently under development for symptomatic HCM. Following administration of EDG-7500 in participants with oHCM, reduction of LVOT gradient (PG_{LVOT}), preservation of systolic function, and a generally well tolerated safety profile was observed[1].To better understand the enzymatic and mechanical reasons behind these unique observations, this preclinical study was designed to determine if EDG-7500 decreases myosin step size while preserving key enzymatic transitions of the myosin ATPase. Furthermore, a clinical HFR echocardiographic sub-study sought to support these preclinical observations by measuring early systolic pressure generation.

Background

Inhibition of myosin ATPase enzymatic activity with CMIs reduces LVOT gradients at **net systolic cost**.

Myosin step size is hypothesized to be a principal determinant of early systolic pressure generation. Early systolic force generation initiates systolic anterior motion and LVOT obstruction.

Hypothesis: EDG-7500 alters myosin lever arm compliance potentially reflected as reduced myosin step size independent of key enzymatic transitions of the myosin ATPase. This unique mechanism will attenuate early systolic pressure generation to normalize LV pre-ejection period (PEP) and reduce LVOT obstruction.

Methods

- Preclinically, stopped-flow kinetics were used to determine the effects of EDG-7500 on key steps of the myosin ATPase cycle.
- Optical trapping was used to measure the myosin step size.
- In CIRRUS-HCM (NCT06347159), participants with oHCM received once-daily EDG-7500 using a fixed-dose titration (25-150 mg) based on clinical target parameters for 12 weeks.
- High-frame-rate echocardiographic images were acquired at baseline and week 12 at dose trough to assess LV PEP, PEP/ET, and LVOT gradients (N=14).
- Statistical significance was set at $P \leq 0.05$ (*denotes vs. baseline) using independent/paired samples t-tests with data reported as mean ± SE.

Results: *In vitro* myosin Step Size and ATPase

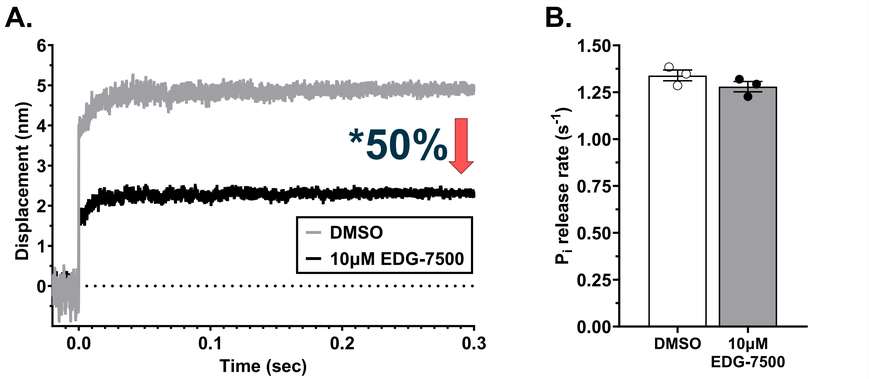
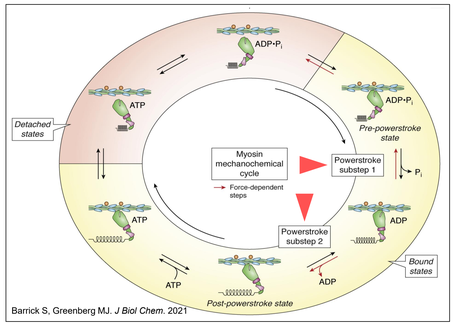


Table 1: ATPase Kinetics

ATPase Cycle Kinetic Parameter	DMSO	10μM EDG-7500
ADP Binding Affinity (μM)	17.9 ± 5.7	19.7 ± 6.9
ADP Binding Rate ($\mu M^{-1}\ s^{-1}$)	5.2 ± 1.8	3.9 ± 0.7
ADP Release Rate (s^{-1})	76.8 ± 3.6	73.4 ± 2.7
ATP Hydrolysis Rate (s^{-1})	67.7 ± 4.9	59.7 ± 0.9
ATP Binding (2nd order, $\mu M^{-1}\ s^{-1}$)	3.7 ± 0.3	4.1 ± 1.7
ATP Induced Dissociation Max. Rate (s^{-1})	922 ± 38	1012 ± 34
Single Turnover Detachment Rate ($\mu M^{-1}\ s^{-1}$)	3.6 ± 0.5	5.1 ± 0.5
Single Turnover Attachment Rate ($\mu M^{-1}\ s^{-1}$)	0.0074 ± 0.0002	0.0080 ± 0.0003

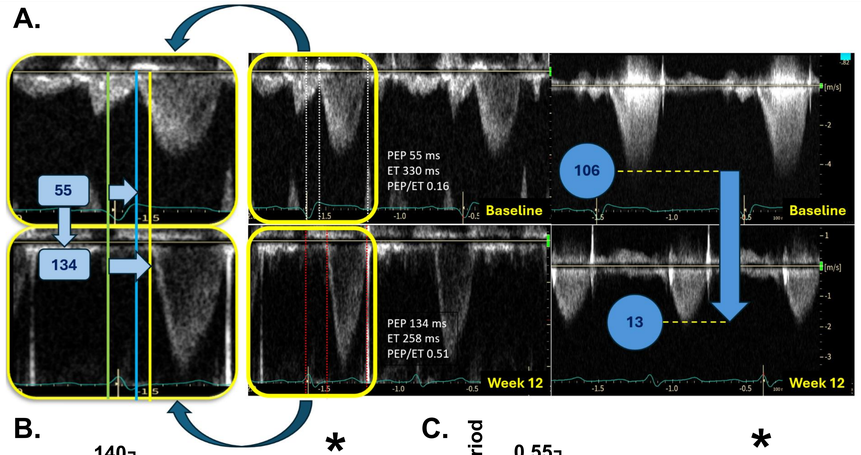
Values are means ± S.D.; N=3 for all experiments

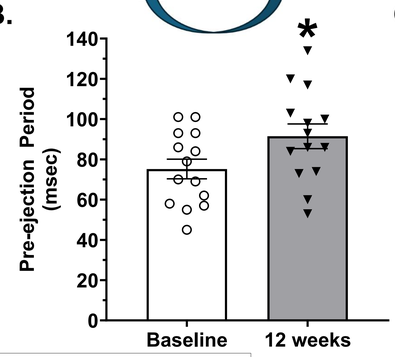


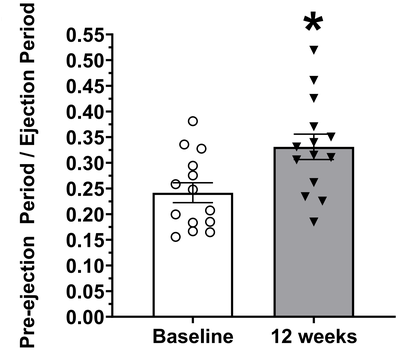
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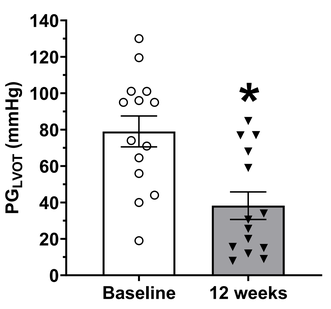
[1]Owens AT, CIRRUS-HCM: 12-Week Evaluation of the Safety and Efficacy of the Novel Cardiac Sarcomere Modulator EDG-7500 in Nonobstructive and Obstructive Hypertrophic Cardiomyopathy, ESC Aug 2026. *Eur Heart J* [supplement pending]

Results: Clinical Echocardiography









Conclusions

These findings support the hypothesis that EDG-7500 potentially alters myosin lever arm compliance, reflected as a decrease in step size, independent of enzymatic activity of the myosin ATPase.

This may explain how administration of EDG-7500 has been observed to relieve LVOT obstruction and preserve systolic function in clinical studies to date.

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EDG-7500 is an investigational agent that is not approved for use by any regulatory authority in any territory and its safety and efficacy have not been established.

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ADP, adenosine diphosphate; ATP, adenosine triphosphate; DMSO, dimethyl sulfoxide; HFR, high frame rate echocardiography; ET, ejection time; LV, left ventricle; LVOT, left ventricular outflow tract; oHCM, obstructive hypertrophic cardiomyopathy; PEP, pre-ejection period; SE, standard error.

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