EDG-7500, A CARDIAC SARCOMERE REGULATOR THAT PRESERVES INTRINSIC MYOSIN-MOTOR FUNCTION, IMPROVES CARDIAC FUNCTION AND RESERVE IN A MINIPIG MODEL OF HCM

Marc Evanchik | VP Discovery, Edgewise

Carlos Del Rio¹, Cassady Rupert², Jessica Tolley³, Mike Duval³, Craig Emter³, Emy DiNatale³, Natalie Hawryluk³, Alan Russell³, Marc Semigran³, Marc Evanchik³

¹Cardiac Consulting, San Mateo, CA; ²Propria, Branford CT; ³Edgewise Therapeutics, Boulder CO
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EDG-7500 is an investigational agent and is not approved in any territory

ME is an employee of Edgewise Therapeutics and shareholder in Edgewise Therapeutics
EDG-7500 PRESERVES MYOSIN MOTORS AND PARTIALLY REDUCES ATP USE

**Myosin motor-head ‘S1-subfragment’**

- Does not directly inhibit myosin motor activity

**X-ray patterns showing ON/OFF populations at low and high calcium**

- Myosin ‘ON/OFF’ populations unchanged

**Myofibrils containing the full compliment of contractile proteins**

- Partial reduction of ATP use

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* P < 0.05, ** P < 0.01, *** P < 0.001, ns = not significant

I$_{1,1}$/I$_{1,0}$ = indicator of myosin head location relative to actin

DIA = Diastole

SYS = Systole

CMI = cardiac myosin inhibitor

† data is simulated
EDG-7500 SLOWS FORCE DEVELOPMENT WITHOUT LOSS OF PEAK FORCE

-8% 

Max force and re-attachment rate (k_tr) of Xbridges maintained

Slows force development at low calcium

** P < 0.01, *** P < 0.001, n.s. = not significant

K_act = rate of activation
F_max = Maximum force
k_tr = rate of tension re-development
EDG-7500 INCREASES THE RATE OF RELAXATION IN MYH7 R403Q ENGINEERED HEART TISSUE (EHT)

Impaired relaxation in R403Q EHTs relative to WT

EDG-7500 shortens the relaxation time in R403Q EHTs
CAN THE EDG-7500 MECHANISM ALTER THE DISEASE PHENOTYPE IN A MODEL OF HCM?

**MYH7 R403Q genetic model of nHCM†**

Sensitized myofilaments (lower pCa50), particularly at diastolic calcium (increased diastolic tension)

Fibrosis and disarray

- Increased myosin ON-state
- Hyperdynamic
- Elevated LVEF
- Impaired diastole
- Elevated filling pressures
- Reduced cardiac reserve

LVEF = left ventricular ejection fraction

†Del Rio et al. Circulation. 2017;136:A20770
MYH7 R403Q MINIPIG MODEL OF nHCM ‡

Hyperdynamic, impaired relaxation, and elevated filling pressures

* P < 0.05, ** P < 0.01, *** P < 0.001
EF = ejection fraction
dP/dt\text{min} = rate of pressure development change
EDP = end diastolic pressure

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RESTORATION OF CARDIAC RESERVE WITH EDG-7500 IN A MODEL OF HCM

MYH7 R403Q genetic model of nHCM

- Ionotropy
- Ees moves elastance toward normal
- EDG-7500 increases cardiac reserve w/dobutamine

**P < 0.05, ***P < 0.001
△SV = change in stroke volume
△ESV = change in end systolic volume
Ees = End systolic elastance
Eed = End diastolic elastance
DOB = dobutamine
PRE = predose

DOB moves elastance toward normal
EDG-7500 increases cardiac reserve w/dobutamine
SUMMARY

1. In vitro studies show EDG-7500 slows force development and maintains maximal force.

2. In minipings with the HCM-pathogenic MYH7 R403Q mutation, EDG-7500 improved both diastolic function and cardiac reserve in response to β-AR stimulation.

3. EDG-7500 is currently in a phase 1 study (NCT06011317) to evaluate safety, tolerability, and PK.
THANK YOU

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