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

1. University of California Davis, Davis, CA, USA; 2. Edgewise Therapeutics, Boulder, CO, USA; 3. University of Arizona, AZ, USA

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 (HCMC1).

METHODS

- In vitro: The effects of EDG-7500 were evaluated biochemically in actin-activated myosin-1S, as well as biomechanically on LV skinned fibers.
- In vivo (PO): Seven cats (A31P MYBPC3 mutants, mean 4.3 ± 0.4 kg) with HCM were studied; LVOT obstruction was established with dobutamine (10-20 µg/kg/min IV) in 6/7 cats (LVOT >75 mm Hg). 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.

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 HCM, 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

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

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

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

DISCLOSURE INFORMATION

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