Hypertrophic Cardiomyopathies – New Challenges for Future Trials

Industry Viewpoint

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Disclosures

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

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Key Challenges in HCM Clinical Trials

Heterogeneity of condition: achieving uniformity in patient selection and treatment protocols for both oHCM and nHCM can be difficult

- HCM varies in its genetic causes, clinical presentations, and disease progression.
- Inherent variability in some measures (LVOTO, LVEF) complicates assessments.

Outcome measures: determining appropriate and meaningful endpoints is complex

- Traditional measures such as mortality and hospitalization rates do not fully capture the scope of this long-term debilitating disease.
- Prior trials used assessments of symptoms (NYHA, KCCQ), exercise capacity (pVO_2), and PROs that were initially developed for HF.
- Diastolic dysfunction is an important underlying mechanism for both oHCM and nHCM. It is not well understood how/if current therapies directly impact diastolic dysfunction.

Safety concerns: ensuring safety of participants in testing new therapies requires vigorous monitoring and risk management

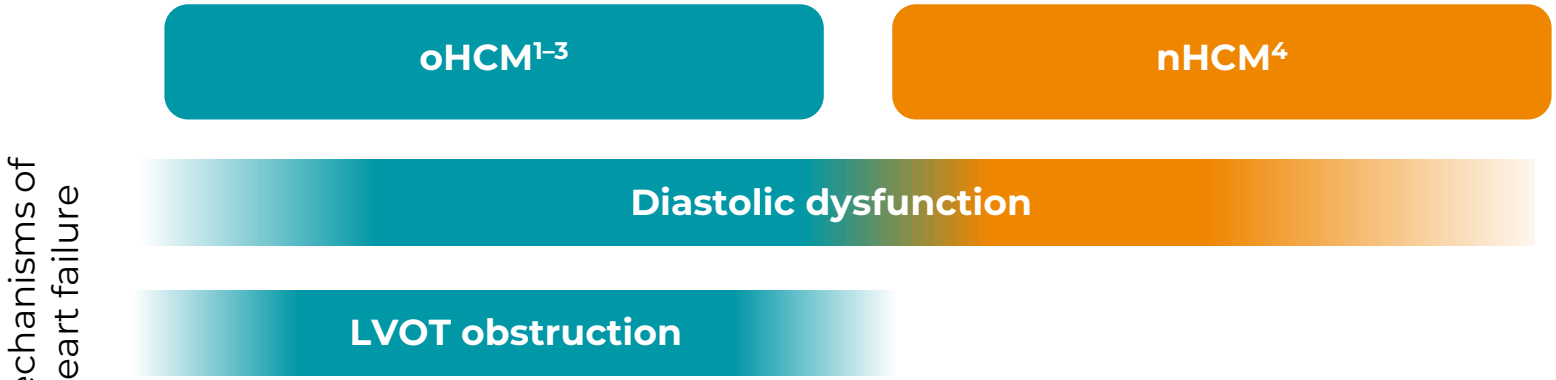
- New treatment options may come at a cost of reducing systolic function.

Long term follow up needed

- HCM is a chronic disease and assessing the long-term durability of new therapies take time.
- Disease modification is not well defined.

Heart Failure in HCM Primarily Results from Two Key Mechanisms

Both LVOT obstruction and diastolic dysfunction contribute to the **development of heart failure** in HCM[1–3]



Addressing **LVOT obstruction alone** will not resolve heart failure across the spectrum of HCM

HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; nHCM, nonobstructive HCM; oHCM, obstructive HCM.

1. Maron MS et al. *N Engl J Med* 2003;348:4: 295-303; 2. Elliott PM et al. *Eur Heart J* 2006;27:16: 1933-1941; 3. Lee HJ et al. *Korean Circ J*. 2022; 52(8) 563–575; 4. Rowin EJ et al. *Circ Heart Fail*. 2014;7(6):967-75.

Current Treatment Options for HCM Have Limitations Leaving Substantial Unmet Needs for Patients

LIMITED BENEFIT ACROSS THE SPECTRUM OF HCM

Efficacy and safety limitations with interventions in oHCM[4]

- BB and CCBs have **limited efficacy** and associated side effects
- SRT interventions are **highly invasive**
- CMI efficacy may be **limited by intrinsic mechanism** tied to LVEF changes and are not recommended for patients with LVEF <55%

No approved therapies for nHCM

- SOC for nHCM includes the need for heart transplant
- Limited efficacy of off-label therapies

RISK OF HEART FAILURE[1,2]

Mavacamten black box warning for HF[3]

- The US prescribing information for mavacamten contains a boxed warning regarding heart failure

HF risk limits intervention[2]

- Guidelines recommend an **interruption in treatment** for patients who develop **LVEF <50%**

SUBOPTIMAL PATIENT EXPERIENCE

Safety-driven frequent echo monitoring[1-3]

- Treatment with mavacamten requires **echocardiography monitoring** for both the initiation and maintenance phases
- **Extensive titration and adjustment of dosage** needed to find a safe window of efficacy avoiding EF drop risk

CMI, cardiac myosin inhibitor; LVEF, left ventricular ejection fraction; LVOT, left ventricle outflow tract; oHCM, obstructive hypertrophic cardiomyopathy; SOC, standard of care.

1. Ommen SR et al. *Circulation*. 2024;149(23):e1239-e1311; 2. Maron MS et al. *N Engl J Med.* 2024;390:1846-61; 3. CAMZYOS [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2023; 4. Olivotto I et al. *Lancet*. 2020;396(10253):759-769.

Preclinical Studies have Demonstrated EDG-7500 MOA, A Novel Sarcomere Modulator, Targeted to Address both oHCM and nHCM

Targets when obstruction begins*

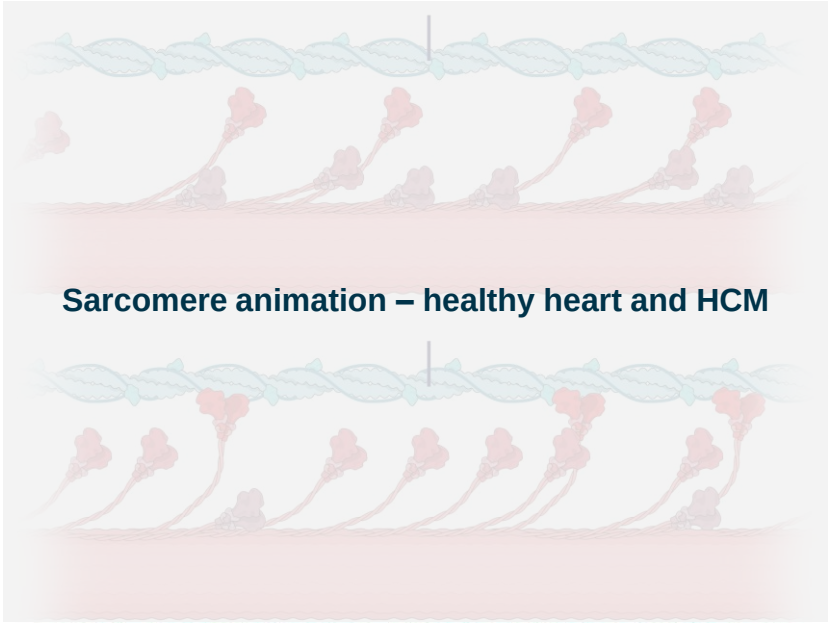
EDG-7500 slows the rate of acto-myosin **cross-bridge formation** during isovolumic contraction, **exactly where obstruction formation starts**

Improves diastolic dysfunction*

EDG-7500 speeds the rate of acto-myosin **cross-bridge detachment** to **improve relaxation rate and ventricular filling**

*Based on preclinical data with EDG-7500.
HCM, hypertrophic cardiomyopathy; MOA, mechanism of action. Edgewise Therapeutics data on file.

EDG-7500: Designed to Slow the Rate of Acto-myosin Engagement & Speed Disengagement Without Inactivating the Myosin Motor Head



Healthy

Healthy Heart

Healthy level of acto-myosin interactions

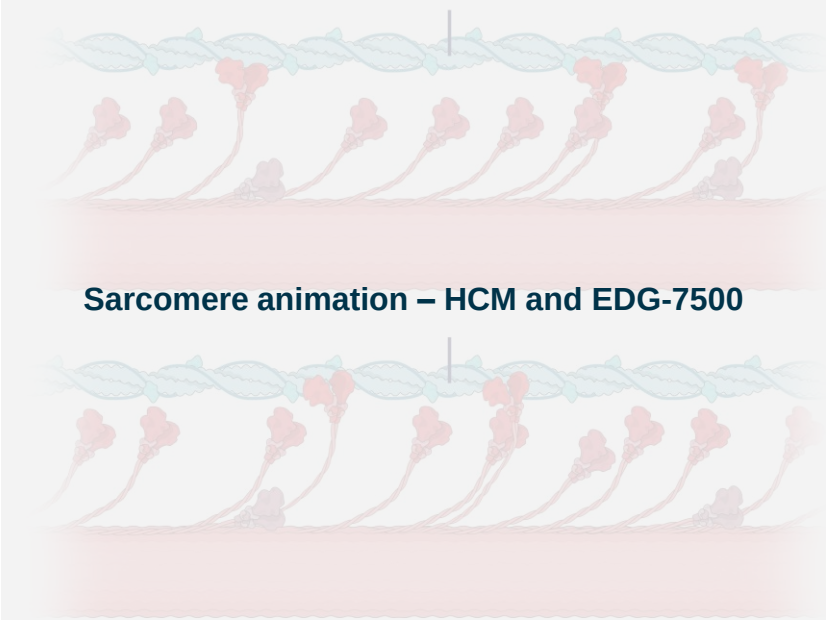
HCM

Myosin ON state

Disease causes an increase in acto-myosin motor head engagement

HCM, hypertrophic cardiomyopathy

EDG-7500: Designed to Slow the Rate of Acto-myosin Engagement & Speed Disengagement Without Inactivating the Myosin Motor Head



HCM

Myosin ON state

Disease causes an increase in acto-myosin motor head engagement

EDG-7500 in HCM Models

Alters Rate

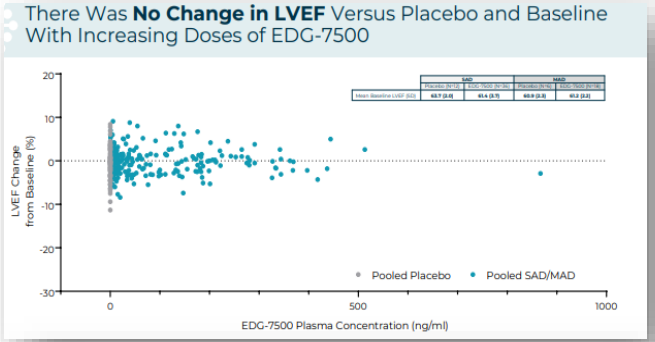
Slows acto-myosin engagement & promotes faster disengagement

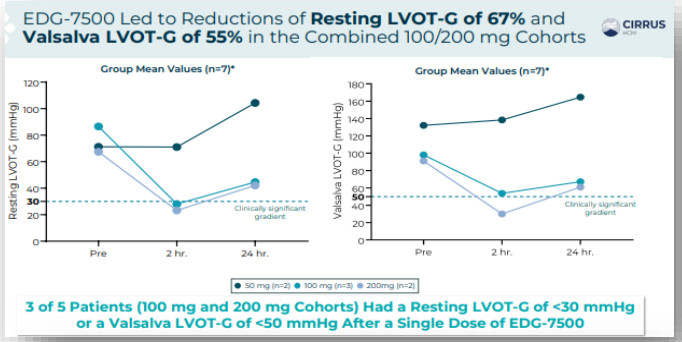
HCM, hypertrophic cardiomyopathy

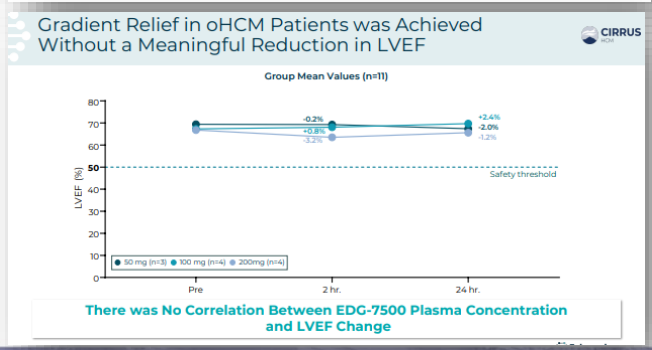
Clinical Data Highlighted in Poster Session

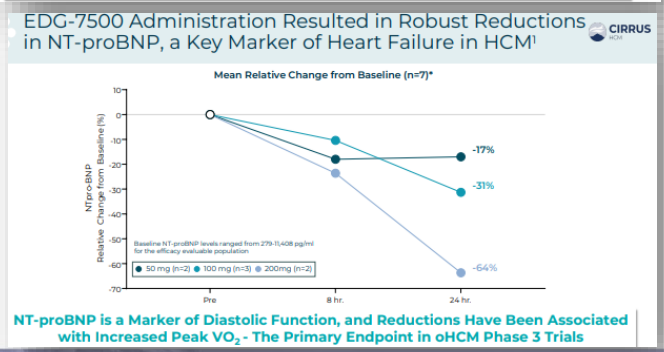
P4 –00037: EDG-7500, a First-in-Class Cardiac Sarcomere Modulator, Demonstrates Favorable Tolerability, Safety, Pharmacokinetic and Hemodynamic Effects in Healthy Adults and Patients with Hypertrophic Cardiomyopathy

On display throughout conference Q&A: Tuesday Dec 10th 7:30-9:00pm









CIRRUS-HCM: Clinical Trial Design

CIRRUS HCM

PRIMARY OBJECTIVE

Safety & tolerability in adults with HCM

KEY INCLUSION CRITERIA

Male and female patients ≥ 18 years of age with HCM
LVEF ≥ 60%

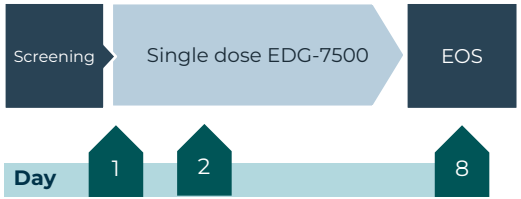
TARGET ENROLLMENT

~75

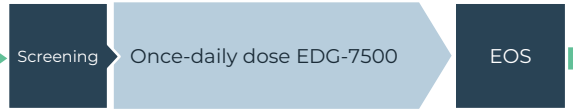
KEY OUTCOME MEASURES

Cardiovascular PD, LVEF, Biomarkers, PK

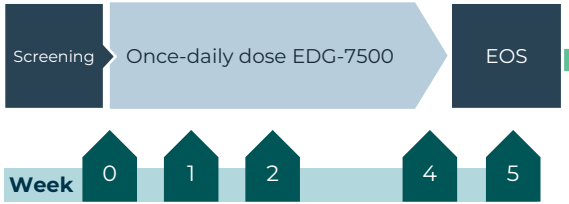
PART A: Single Dose ~15 oHCM patients



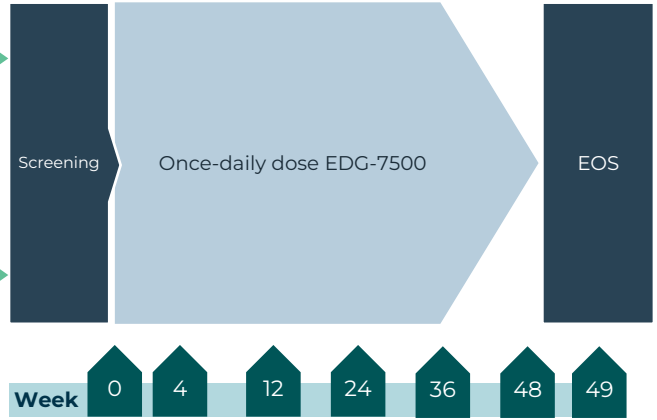
PART B: Multiple Dose ~30 oHCM patients



PART C: Multiple Dose ~30 nHCM patients



PART D: Extended Dose (Patients from Parts B/C)



EOS, end of study; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; PD, pharmacodynamics; PK, pharmacokinetics.