CIRRUS-HCM: A Multiple-Dose Phase 2 Study of Safety, Tolerability, and Effects on Hemodynamics and Functional Capacity of the Novel Cardiac Sarcomere Modulator EDG-7500 in Hypertrophic Cardiomyopathy

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Disclosures

- Dr Owens has received payments as a consultant to Alexion, Avidity, Biomarin, Bayer, Bristol Myers Squibb, Cytokinetics, Lexeo, Stealth, Tenaya, Imbria, and Edgewise Therapeutics.

Background

- **EDG-7500** is a novel **cardiac sarcomere modulator** designed to slow the rate of acto-myosin engagement and speed disengagement without inactivating the myosin motor head.
- In preclinical studies and the Phase 2 single-dose oHCM study, EDG-7500 demonstrated significant **reductions** in **LVOT-G** and **NT-proBNP**, along with improvements in **diastolic function**.
- **Cardiac myosin inhibitors**, both approved and in development, might cause systolic dysfunction and require **careful LVEF monitoring** through frequent echocardiographic evaluation.
- **No meaningful reductions in LVEF** have been observed across the EDG-7500 development program so far, which potentially could eliminate the need for safety echocardiograms.

HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVOT-G, LVOT-gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide; nHCM, nonobstructive HCM; oHCM, obstructive HCM.

Baseline Characteristics: oHCM and nHCM

Demographics		
	oHCM (n=17)	nHCM (n=12)
Age (yrs), mean (SD)	61 (13)	54 (19)
Female, n (%)	12 (71%)	7 (58%)
BMI (kg/m^2), mean (SD)	28 (4)	27 (4)
Medical History		
Pathogenic sarcomere variant, n (%)	4 (24%)	4 (33%)
History of paroxysmal AF / flutter, n (%)	1 (6%)	2 (17%)
ICD, n (%)	2 (12%)	6 (50%)
Prior SRT, n (%)	1 (6%)	0%
Hypertension, n (%)	11 (65%)	2 (17%)
Diabetes, n (%)	1 (6%)	2 (17%)
NYHA Class		
Class I, n (%)	1 (6%)	0%
Class II, n (%)	10 (59%)	6 (50%)
Class III, n (%)	6 (35%)	6 (50%)

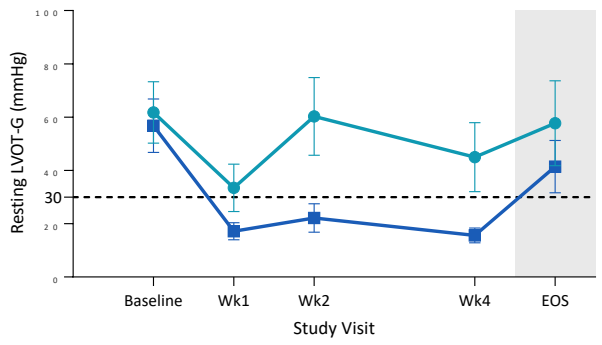
Echocardiographic Parameters		
	oHCM (n=17)	nHCM (n=12)
LVEF (%), mean (SD)	65 (4)	61 (6)
LVOT-G (resting; mmHg), mean (SD)	59 (30)	9 (6)
LVOT-G (Valsalva; mmHg), mean (SD)	93 (32)	14 (10)
e' mean (cm/s), mean (SD)	6 (2)	7 (2)
Maximal LV wall thickness (mm), mean (SD)	18 (2)	18 (3)
LAVI (ml/m^2), mean (SD)	37 (13)	31 (12)
Patient-reported Outcome Measures		
KCCQ-OSS, mean (SD)	63 (16)	57 (22)
KCCQ-CSS, mean (SD)	69 (15)	63 (23)
Laboratory Measures		
NT-proBNP (geometric mean /median (IQR); pg/ml)	724 / 710 (381, 1074)	782 / 715 (546, 1231)

AF, atrial fibrillation; BMI, body mass index; e', early diastolic mitral annular velocity; CSS, clinical summary score; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAVI, left atrial volume index; LV, left ventricular; LVEF, LV ejection fraction; LVOT, LV outflow tract; nHCM, nonobstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive HCM; OSS, overall summary score; SRT, septal reduction therapy.

Preliminary data as of May 2025

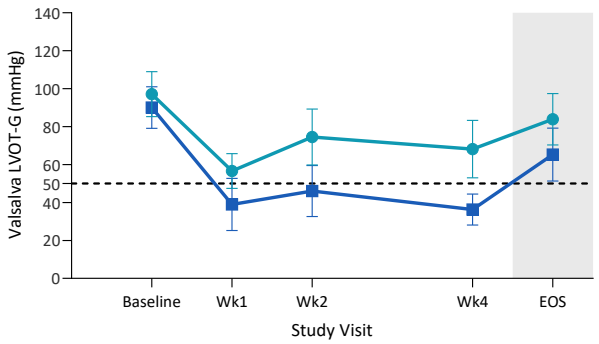
CIRRUS-HCM Part B summary: multiple-dose 4-week study in oHCM

Resting LVOT-G*

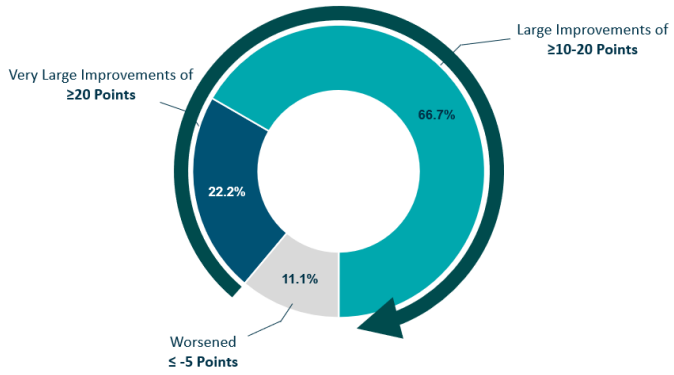


50mg (N=8) 100mg (N=9)

Valsalva LVOT-G*

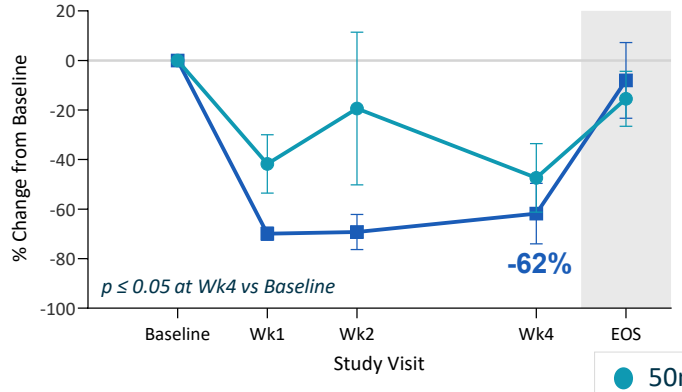


KCCQ-CSS (100mg)

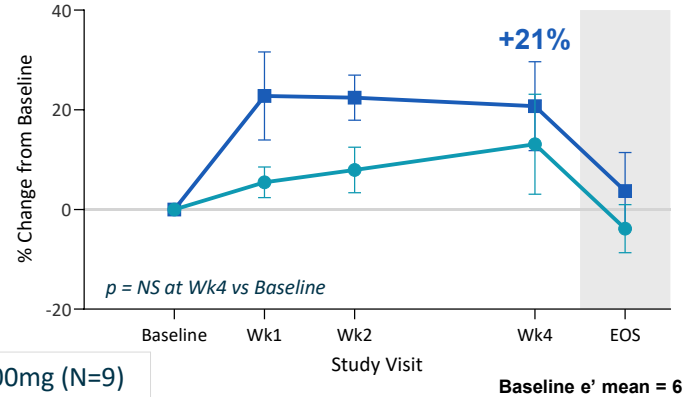


- **89%** at 100mg reached resting LVOT <30mmHg and Valsalva LVOT <50mmHg
- **56%** at 100mg achieved NT-proBNP <150 pg/mL
- **89% with clinical improvements** in KCCQ-CSS (100mg) after 4 weeks
- **43%** at 50mg and **78%** at 100mg achieved ≥ 1 NYHA Class improvement at week 4

NT-proBNP



Early diastolic mitral annular velocity (e')



50mg (N=8) 100mg (N=9)

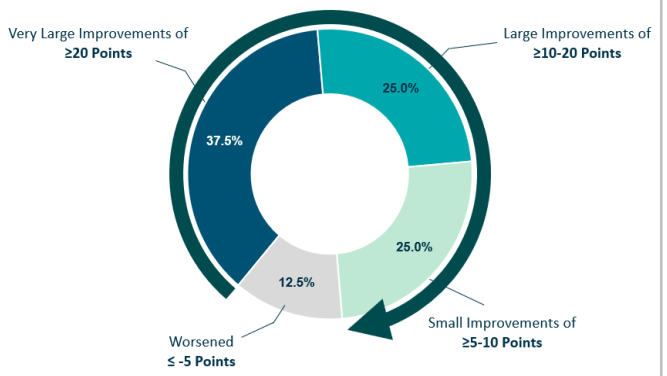
Baseline e' mean = 6 ± 2 cm/s

Mean ± SEM
7 individuals were evaluated for NYHA at week 4
5 participants had either resting gradients <30 mmHg or Valsalva gradients <50 mmHg on Day 1; *% reaching LVOT criteria based on N=7 and N=9 participants with Week 4 data at 50 mg and 100 mg respectively; Complete LVOT-G response defined as resting and Valsalva gradients <30 mmHg and <50 mmHg, respectively.
EOS, end of study; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS, KCCQ-Clinical Summary Score; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association oHCM, obstructive hypertrophic cardiomyopathy.

Preliminary data as of May 2025

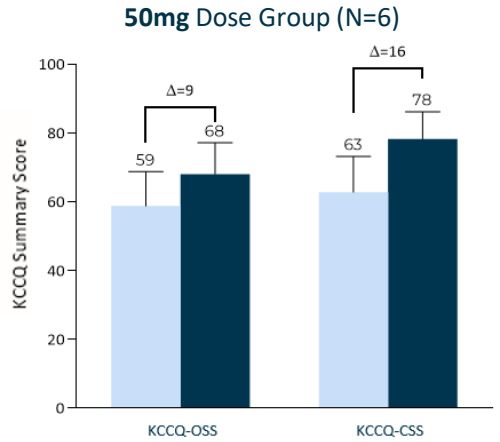
CIRRUS-HCM Part C summary: multiple-dose 4-week study in nHCM

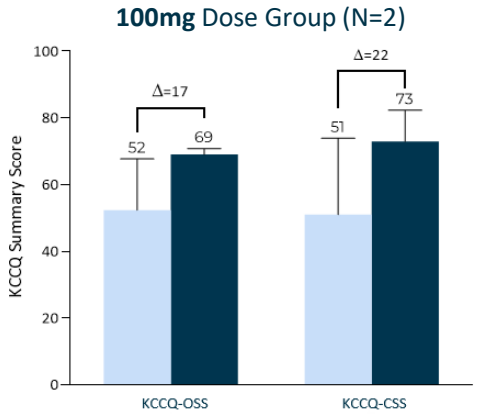
KCCQ-CSS (50mg and 100mg)



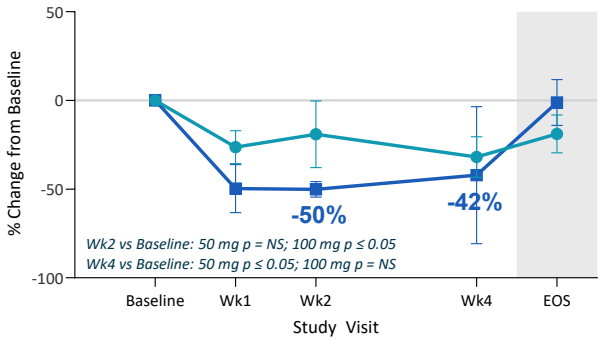
- **Rapid and robust reductions** in NT-proBNP
- Mean e' changes in as **early as one week** following dosing
- **88% with clinical improvements** in KCCQ-CSS after 4 weeks (50mg/100mg combined)

KCCQ-OSS and KCCQ-CSS



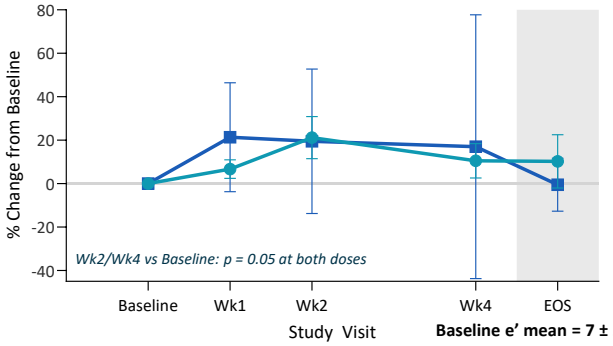


NT-proBNP



50mg (N=7) 100mg (N=5*)

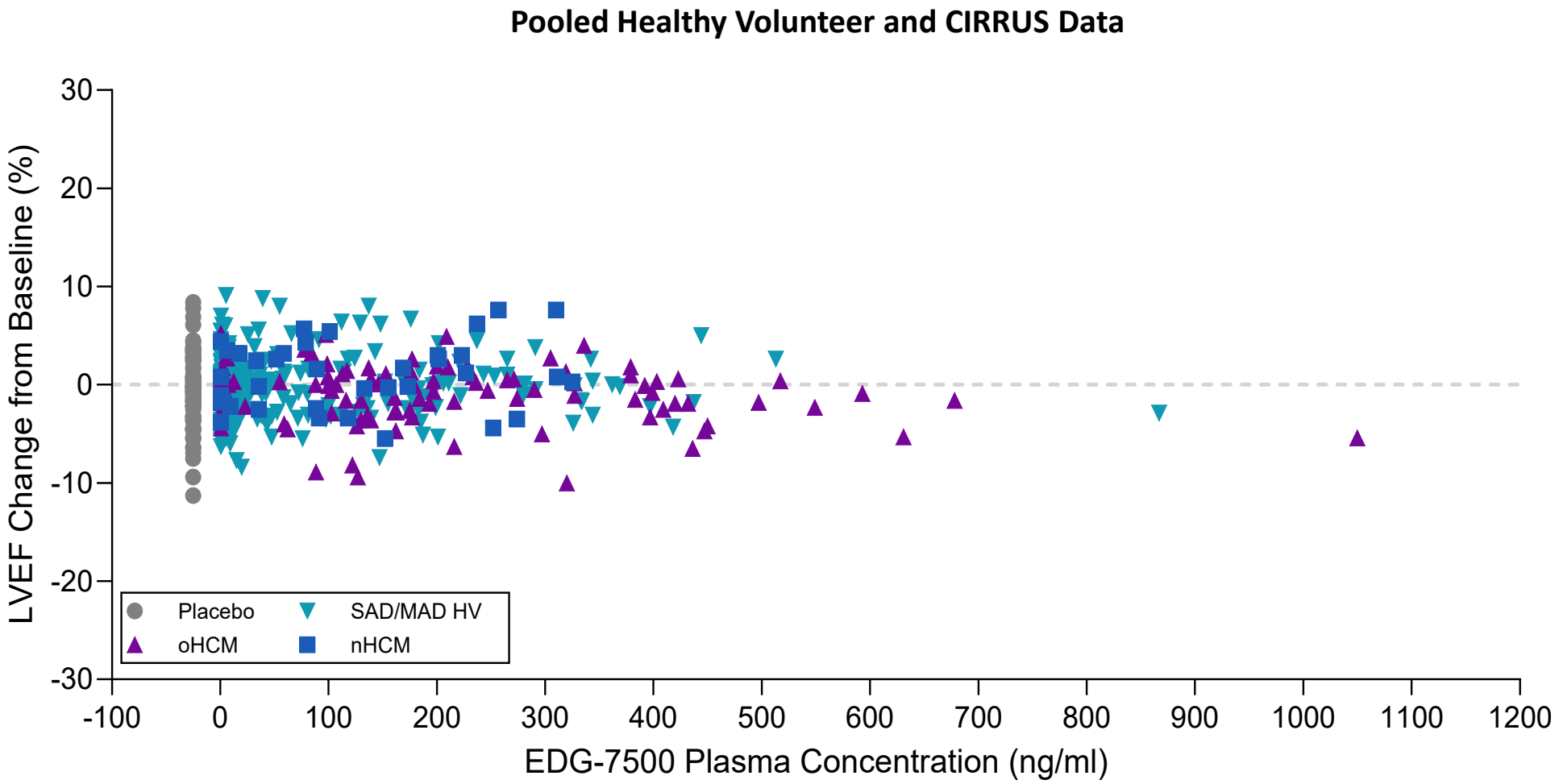
Early diastolic mitral annular velocity (e')



Baseline e' mean = 7 ± 2 cm/s

Mean ± SEM * Two participants at week 4
EOS, end of study; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS, KCCQ-Clinical Summary Score; KCCQ-OSS, KCCQ-Overall Summary Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association nHCM, nonobstructive hypertrophic cardiomyopathy.
Preliminary data as of May 2025

No Meaningful Reductions in LVEF or LVEF <50% Across a Broad Exposure Range Observed After EDG-7500 Treatment



HV, healthy volunteer; LVEF, left ventricular ejection fraction; nHCM, nonobstructive hypertrophic cardiomyopathy; oHCM, obstructive cardiomyopathy.

Preliminary data as of May 2025

Parts B (oHCM) and C (nHCM): Safety Summary

Treatment-Emergent Adverse Events (TEAE), n (%)	N=29
Dizziness (mostly mild and transient in duration)	8 (27.6%)
Upper respiratory tract infection	5 (17.2%)
Atrial fibrillation*	4 (13.8%)
Influenza like illness	3 (10.3%)
Palpitations	3 (10.3%)
Constipation	2 (6.9%)
Diarrhea	2 (6.9%)
Headache	2 (6.9%)

Treatment emergent adverse events in >1 participant in the combined oHCM and nHCM cohorts.

* A total of 3 oHCM participants and 1 nHCM participant had new onset symptomatic atrial fibrillation; two of these events were considered SAEs

- **None of the participants who had atrial fibrillation experienced LVEF <50% at any time**
- One oHCM participant discontinued treatment due to moderate dizziness

LVEF, left ventricular ejection fraction; nHCM, nonobstructive hypertrophic cardiomyopathy; oHCM, obstructive hypertrophic cardiomyopathy; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Preliminary data as of May 2025

Conclusions

- EDG-7500 has the potential to emerge as an **exciting new therapeutic** option for both oHCM and nHCM
- EDG-7500 treatment appears to be **generally well tolerated** across a broad exposure range **without meaningful impact on LVEF**
- Treatment with EDG-7500 was shown to improve **LVOT-G, NT-proBNP, e', KCCQ,** and **NYHA**
- In the longer-term cohort of CIRRUS-HCM, intra-patient dose optimization is being explored

KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.