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.

Obstructive HCM: Baseline Characteristics (N=17)

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

Echocardiographic Parameters	
LVEF (%), mean (SD)	65 (4)
LVOT-G (resting; mmHg), mean (SD)	59 (30)
LVOT-G (Valsalva; mmHg), mean (SD)	93 (32)
e' mean (cm/s), mean (SD)	6 (2)
Maximal LV wall thickness (mm), mean (SD)	18 (2)
LAVI (ml/m^2), mean (SD)	37 (13)
Patient-reported Outcome Measures	
KCCQ-OSS, mean (SD)	63 (16)
KCCQ-CSS, mean (SD)	69 (15)
Laboratory Measures	
NT-proBNP (geometric mean /median (IQR); pg/ml)	724 / 710 (381, 1074)

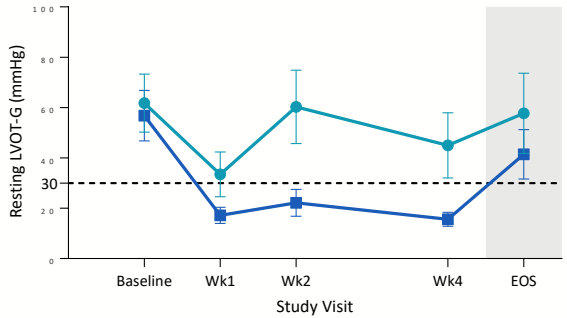
AF, atrial fibrillation; BMI, body mass index; e', early diastolic mitral annular velocity; CSS, clinical symptom score; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAVI, left atrial volume index; LV, left ventricular; LVEF, LV ejection fraction; LVOT, LV outflow tract; 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.

oHCM: LVOT-G at Rest & Post Valsalva

Strong LVOT-G Responses Seen with EDG-7500 Treatment (N=17*)

REST

Absolute Value

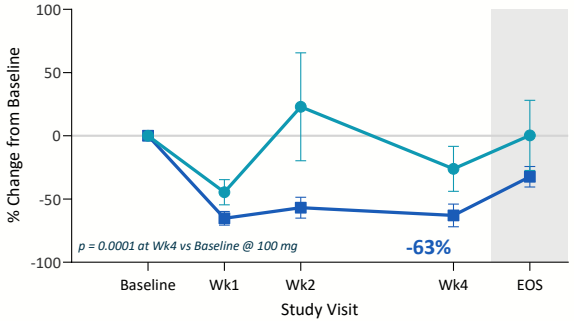


% Reaching LVOT <30 mmHg (Week 4)**

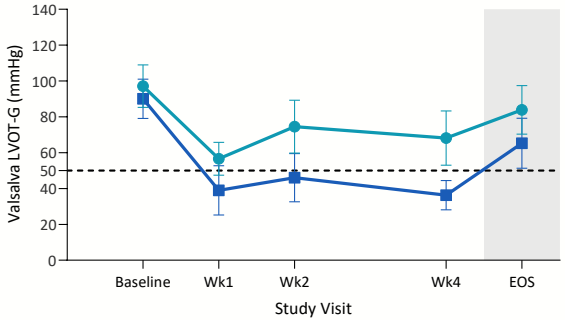
50 mg: **43%**

100 mg: **89%**

% Change from Baseline



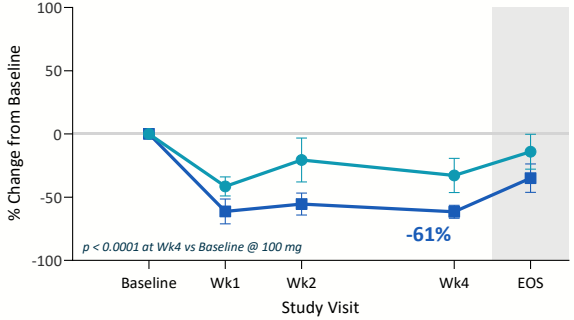
VALSALVA



% Reaching LVOT <50 mmHg (Week 4)**

50 mg: **57%**

100 mg: **89%**



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

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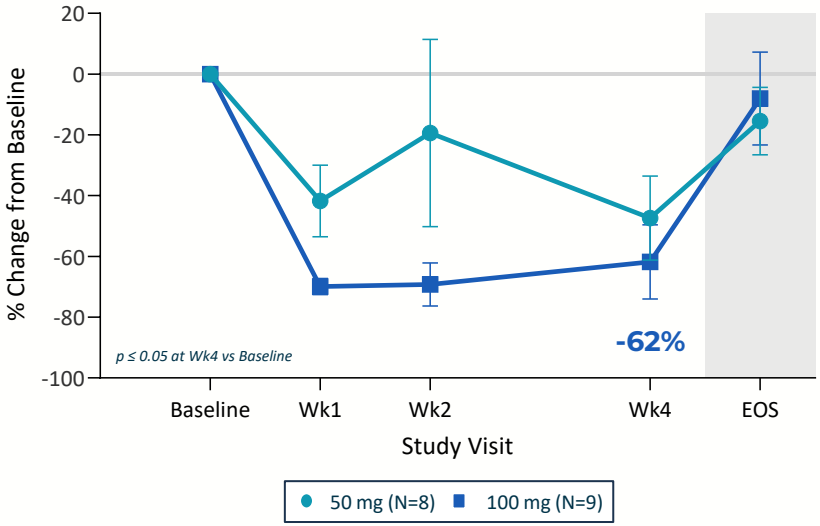
Mean ± SEM

* 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; LVOT, left ventricular outflow tract.

oHCM: NT-proBNP



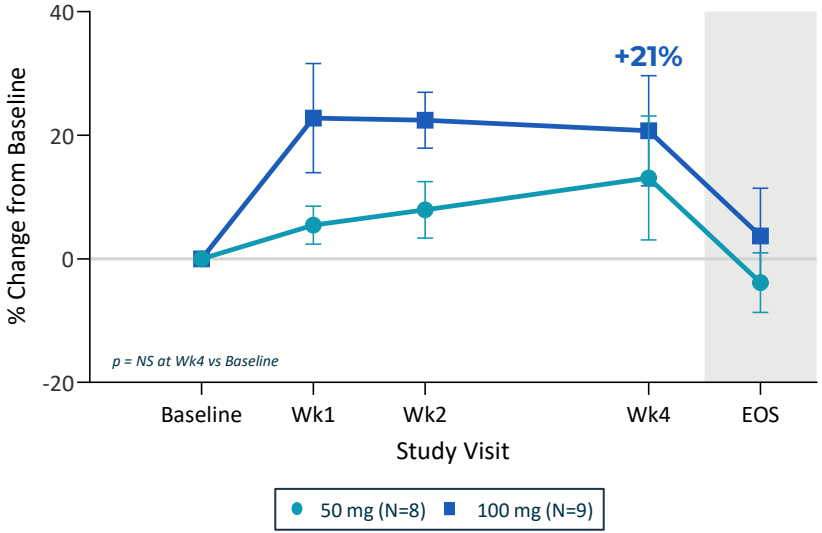
- **5/9 (56%)** at 100 mg achieved NT-proBNP <150 pg/mL
- Improvements in NT-proBNP have shown a strong correlation to improvements in pVO_2[1]

[1]Coats CJ et al., *Eur Heart J* 2024 Nov 8;45(42)

Mean ± SEM

EOS, end of study; NT-proBNP, N-terminal pro-B-type natriuretic peptide; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2, peak oxygen consumption.

oHCM: Early Diastolic Mitral Annular Velocity (e')



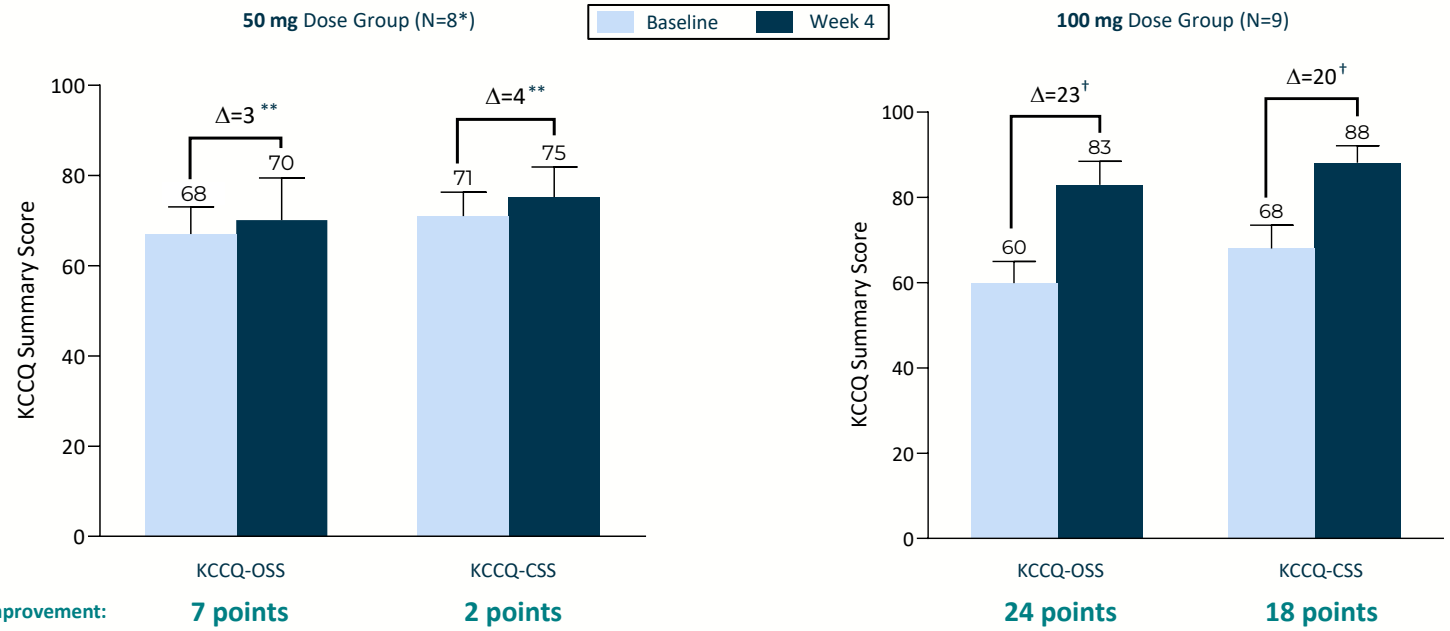
Baseline e' mean = 6 ± 2 cm/s

- **Rapid dose-responsive improvements in mean e' observed as early as 1 week after initiation of treatment with EDG-7500**

Mean ± SD for baseline value; Mean ± SEM for % change from baseline
e', early diastolic mitral annular velocity; EOS, end of study; NS, not significant.

oHCM: KCCQ-OSS and KCCQ-CSS

KCCQ Changes with EDG-7500 Treatment in oHCM after 4 Weeks vs. Baseline



Median KCCQ Improvement:

50 mg Dose Group (N=8*)		100 mg Dose Group (N=9)	
KCCQ-OSS	KCCQ-CSS	KCCQ-OSS	KCCQ-CSS
7 points	2 points	24 points	18 points

***p = NS at Wk4 vs Baseline*

†p < 0.005 at Wk4 vs Baseline

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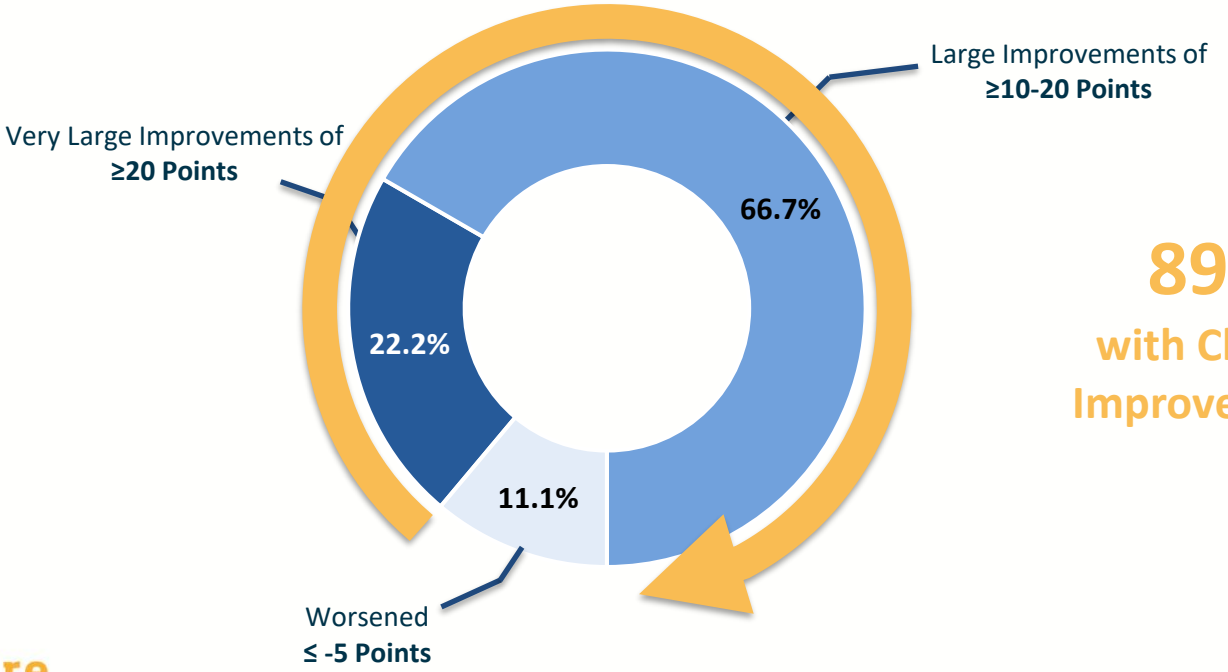
Mean ± SEM * Represents 7 individuals who were evaluated for KCCQ at week 4
CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; NS, not significant; oHCM, obstructive hypertrophic cardiomyopathy; OSS, overall summary score.

oHCM: KCCQ-CSS

KCCQ-CSS Changes with EDG-7500 Treatment in oHCM (100 mg) after 4 Weeks vs. Baseline

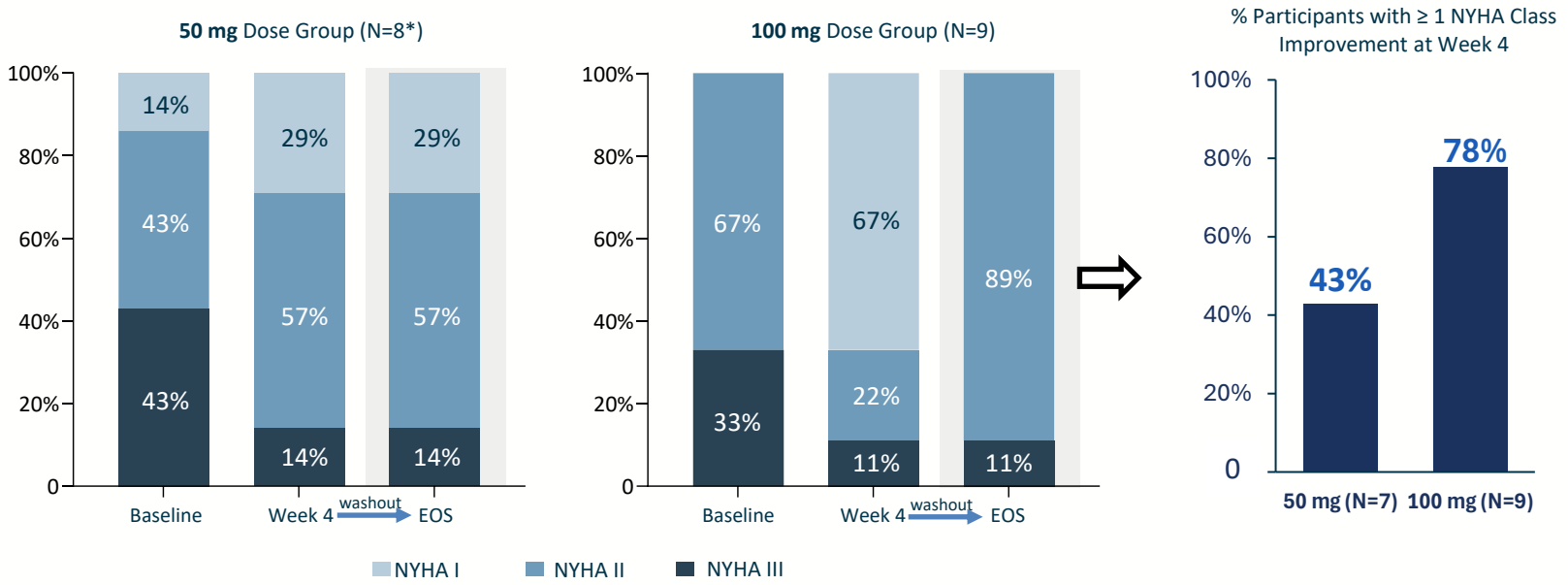


89%
with Clinical Improvements

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; oHCM, obstructive hypertrophic cardiomyopathy.

oHCM: NYHA Functional Class

NYHA Functional Class Improvements with EDG-7500 Treatment in oHCM at 4 Weeks



* Represents 7 individuals who were evaluated for NYHA at week 4
EOS, end of study; NYHA, New York Heart Association.

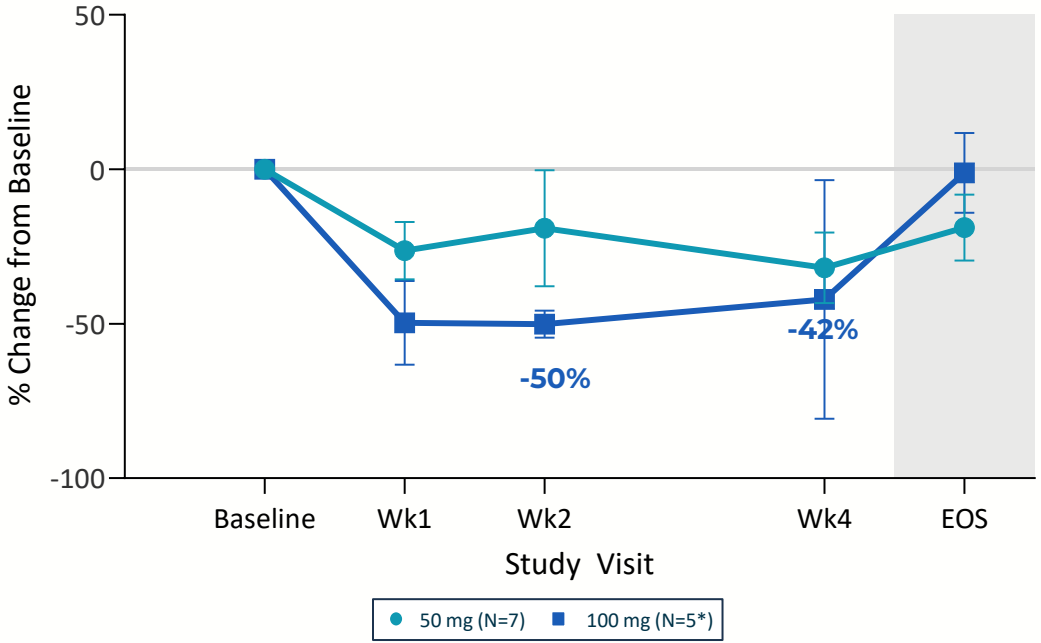
Nonobstructive HCM: Baseline Characteristics (N=12)

Demographics	
Age (yrs), mean (SD)	54 (19)
Female, n (%)	7 (58%)
BMI (kg/m^2), mean (SD)	27 (4)
Medical History	
Pathogenic sarcomere variant, n (%)	4 (33%)
History of paroxysmal AF / flutter, n (%)	2 (17%)
ICD, n (%)	6 (50%)
Prior SRT, n (%)	0%
Hypertension, n (%)	2 (17%)
Diabetes, n (%)	2 (17%)
NYHA Class	
Class I, n (%)	0%
Class II, n (%)	6 (50%)
Class III, n (%)	6 (50%)

Echocardiographic Parameters	
LVEF (%), mean (SD)	61 (6)
LVOT-G (resting; mmHg), mean (SD)	9 (6)
LVOT-G (Valsalva; mmHg), mean (SD)	14 (10)
e' mean (cm/s), mean (SD)	7 (2)
Maximal LV wall thickness (mm), mean (SD)	18 (3)
LAVI (ml/m^2), mean (SD)	31 (12)
Patient-reported Outcome Measures	
KCCQ-OSS, mean (SD)	57 (22)
KCCQ-CSS, mean (SD)	63 (23)
Laboratory Measures	
NT-proBNP (geometric mean/median (IQR); pg/ml)	782 / 715 (546, 1231)

AF, atrial fibrillation; BMI, body mass index; e', early diastolic mitral annular velocity; CSS, clinical symptom 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 HCM; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; SRT, septal reduction therapy.

nHCM: NT-proBNP

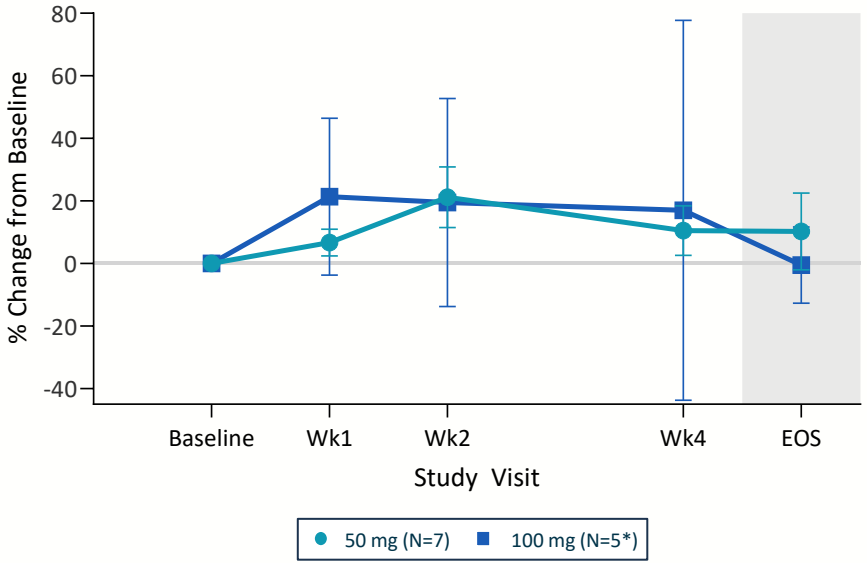


EDG-7500 treatment resulted in rapid and robust reductions in NT-proBNP in participants with nHCM

Wk2 vs Baseline: 50 mg p = NS; 100 mg p ≤ 0.05
Wk4 vs Baseline: 50 mg p ≤ 0.05; 100 mg p = NS

Mean ± SEM * Two participants at week 4
EOS, end of study; nHCM, nonobstructive hypertrophic cardiomyopathy; NS, not significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

nHCM: Early Diastolic Mitral Annular Velocity (e')



Baseline e' mean = 7 ± 2 cm/s

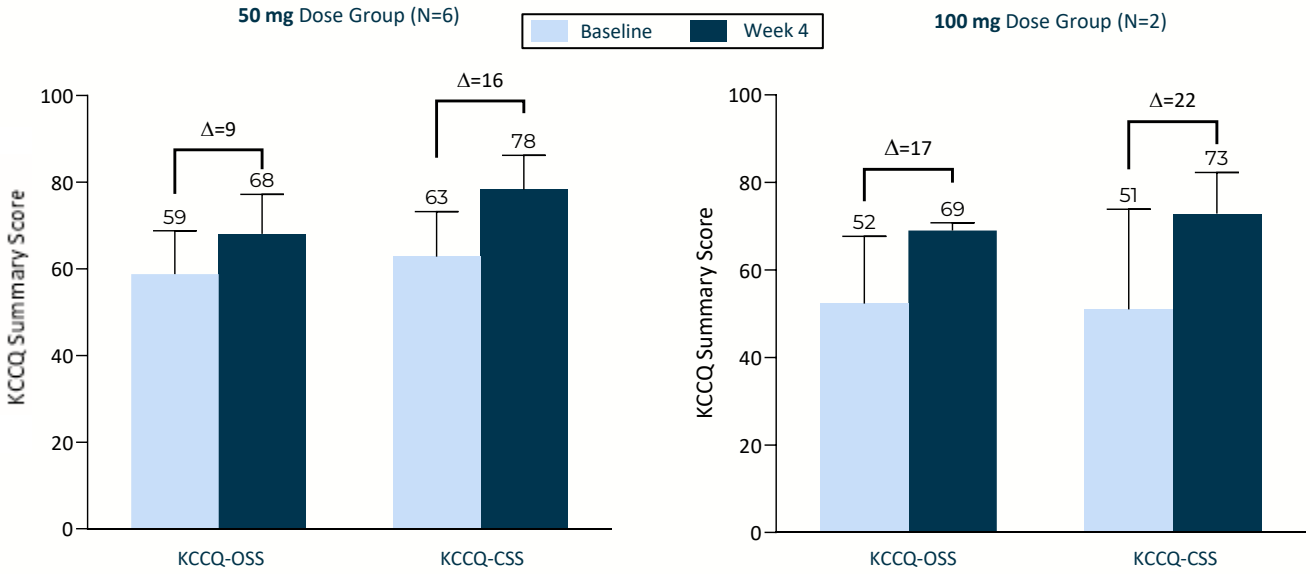
Treatment with EDG-7500 led to mean e' changes in participants with nHCM as early as one week following initiation of dosing

Wk2/Wk4 vs Baseline: p = 0.05 at both doses

Mean ± SD for baseline value; Mean ± SEM for % change from baseline
* Two participants at week 4
e', early diastolic mitral annular velocity; EOS, end of study; nHCM, nonobstructive hypertrophic cardiomyopathy.

nHCM: KCCQ-OSS and KCCQ-CSS

KCCQ Changes with EDG-7500 Treatment in nHCM after 4 Weeks vs. Baseline



Median KCCQ Improvement:	12 points	11 points	17 points	22 points

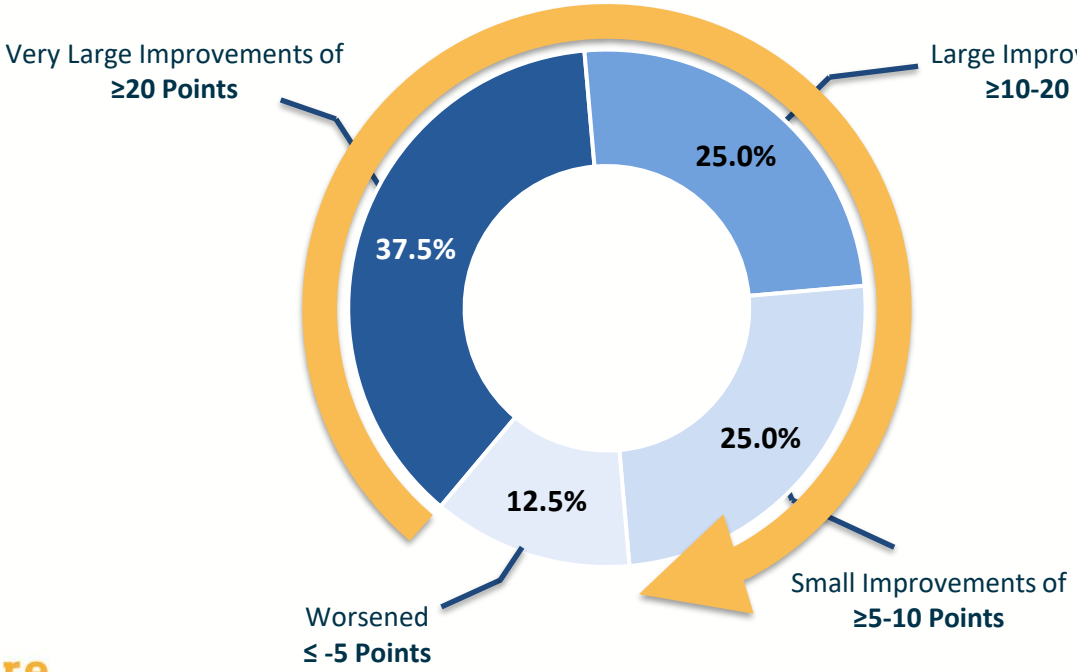
Wk4 vs Baseline: p = NS at both doses across both KCCQ measures

Mean ± SEM

CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; nHCM, nonobstructive hypertrophic cardiomyopathy; NS, not significant; OSS, overall summary score.

nHCM: KCCQ-CSS

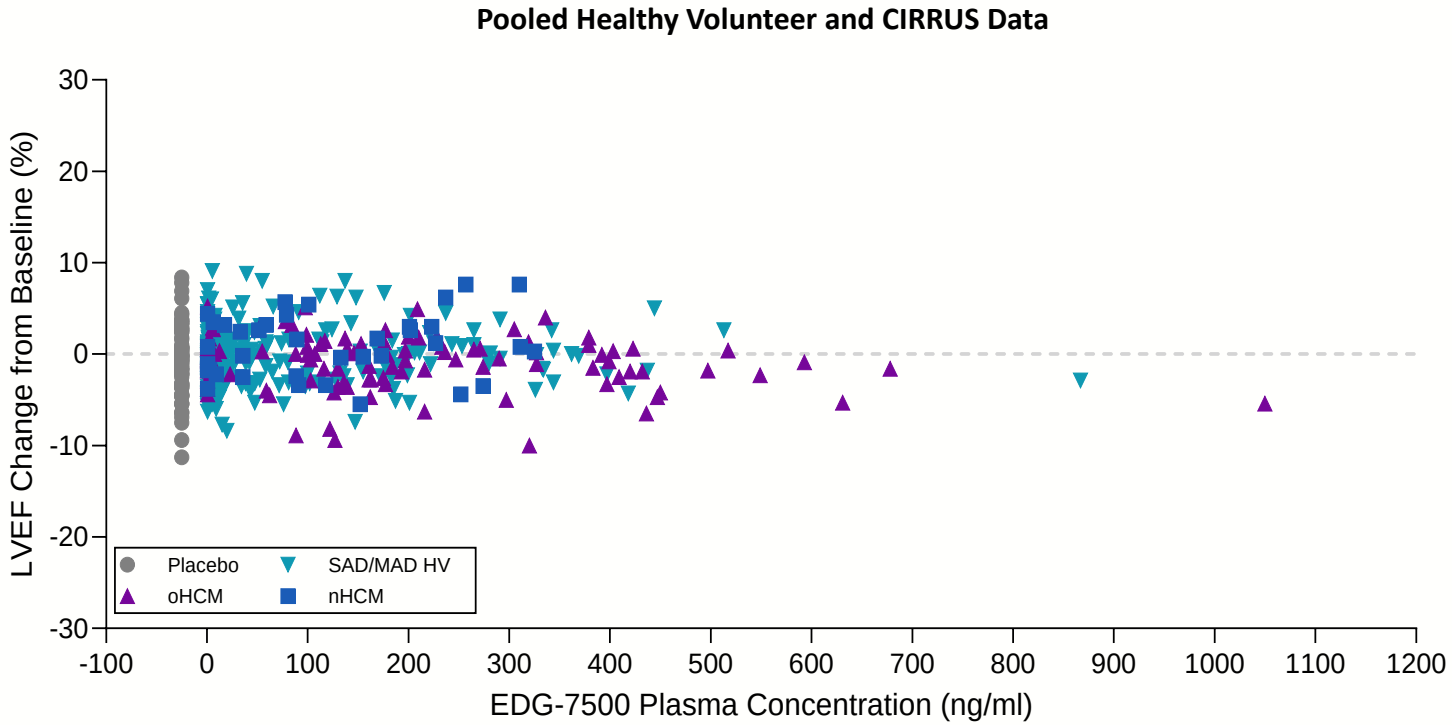
KCCQ-CSS Changes with EDG-7500 Treatment in nHCM (50 mg and 100 mg) after 4 Weeks vs. Baseline



88% with Clinical Improvements

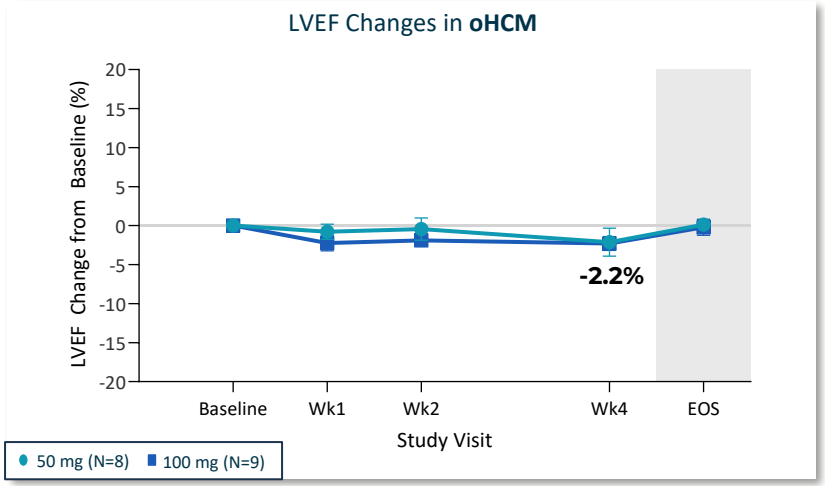
KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; nHCM, nonobstructive hypertrophic cardiomyopathy.

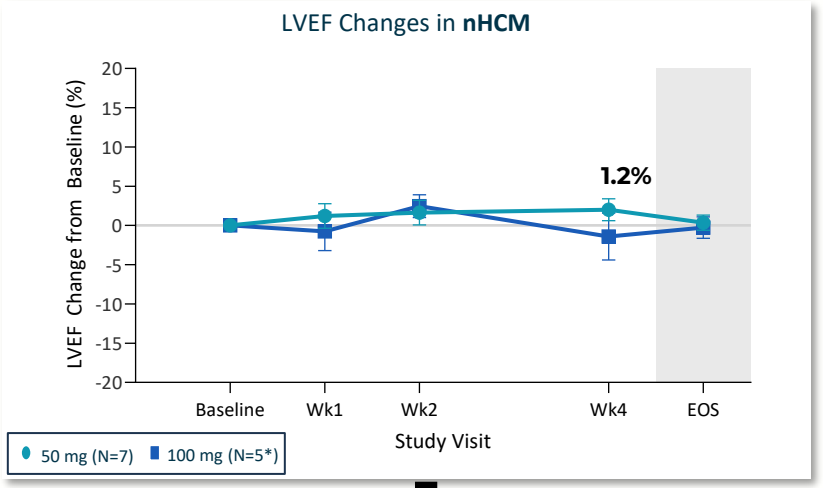
No Meaningful Reductions in LVEF or LVEF <50% Across a Broad Exposure Range Observed After EDG-7500 Treatment



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

No Meaningful Reductions in LVEF Observed After EDG-7500 Treatment





- 4/12 (33%) participants with nHCM had a baseline LVEF <60% by core lab; all 4 remained stable throughout the treatment period
- No LVEF below 50%; change from baseline was +2.5% for the 4 nHCM participants

Subject	Dose (mg)	Baseline	Week 4	Change
1	100	56.0%	57.6%	1.60%
2	50	53.4%	56.0%	2.60%
3	50	55.8%	55.5%	-0.30%
4	50	52.4%	58.6%	6.20%

Mean ± SEM * Two participants at week 4
EOS, end of study; LVEF, left ventricular ejection fraction.

oHCM and 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
  oHCM
  Pt #1 (66, F, 50 mg): Hx of hypertension, diabetes, obstructive lung disease. Echo: significant mitral annular calcification with mild/moderate mitral stenosis
  Pt #2 (67, F, 100 mg): Hx of hypertension, diabetes, and obstructive lung disease
  Pt #3 (54, M, 100 mg): Hx of hypertension, obstructive lung disease, and disopyramide discontinuation three weeks before the first dose
  nHCM
  Pt #1 (61, F, 100 mg): Hx of hypertension, LAVI: 50.2 ml/m^2

- **None of the patients 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.

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
- Intra-patient dose titration will be explored soon in CIRRUS-HCM for dose optimization

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.

Acknowledgments

- We thank all patients and their families for participating in the CIRRUS-HCM trial