CIRRUS-HCM: 12-Week Evaluation of the Safety and Efficacy of the Novel Cardiac Sarcomere Modulator EDG-7500 in Nonobstructive and Obstructive Hypertrophic Cardiomyopathy

Anjali T Owens[1], Theodore P Abraham[2], Michael Nassif[3], Scott Solomon[4], Christopher Dufton[5], Jeffrey A Silverman[5], Michael P Ayers[5], Molly Madden[5], Maple Goh[5], James MacDougall[5], and Ahmad Masri[6]

[1]University of Pennsylvania, Philadelphia, PA; [2]University of California, San Francisco, CA; [3]Saint Luke's Mid America Heart Institute, Kansas City, MO; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [5]Edgewise Therapeutics, Boulder, CO; [6]Oregon Health and Science University, Portland, OR

Disclosures

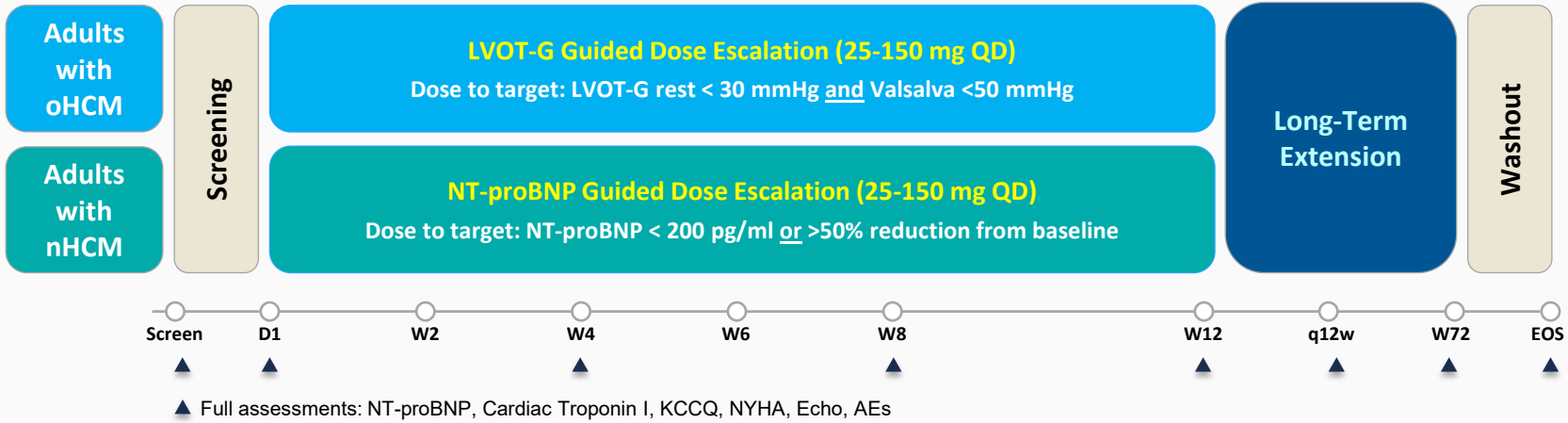
- Dr. Owens has received payments as a consultant to Alexion, Avidity, Biomarin, Bayer, Bristol Myers Squibb, Braveheart, BridgeBio, Cytokinetics, Lexeo, Stealth, Tenaya, Imbria, and Edgewise Therapeutics.

Background

- **EDG-7500** is a novel **cardiac sarcomere modulator** shown in preclinical models to:
  - Increase early diastolic relaxation while maintaining myosin availability
  - Reduce LVOT gradients by slowing early systolic pressure development
  - Preserve net systolic function
- Once-daily dosing with steady-state plasma levels achieved in ~4 days
- In Phase 2 studies of patients with oHCM and nHCM, improvements in **LVOT-G, biomarkers, NYHA** and **diastolic function** were observed following 4 weeks of once-daily EDG-7500
- **No meaningful reductions in LVEF** have been observed across the EDG-7500 program to date

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; NYHA, New York Heart Association; .

CIRRUS-HCM: 12-Week Open-Label Study Design



- 65% of oHCM participants receiving 100 or 150 mg dose by Week 12
- 84% of nHCM participants receiving 100 or 150 mg dose by Week 12

Data cut date 22May2026

D1, Day 1; EOS, End of Study, KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; nHCM, nonobstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; QD, once daily

Baseline Characteristics

Characteristic	oHCM (n=20)	nHCM (n=33)
Demographics		
Age (yrs), mean (SD)	59 (13)	49 (16)
Female, n (%)	9 (45%)	15 (45%)
BMI (kg/m^2), mean (SD)	29 (4)	27 (4)
NYHA Class		
Class II, n (%)	14 (70%)	26 (79%)
Class III, n (%)	6 (30%)	7 (21%)
Family History / Pathogenic mutation, n (%)	9 (45%)	22 (67%)
Concomitant HCM Therapy		
Beta Blockers, n (%)	15 (75%)	20 (61%)
Calcium Channel Blockers, n (%)	2 (10%)	2 (6%)

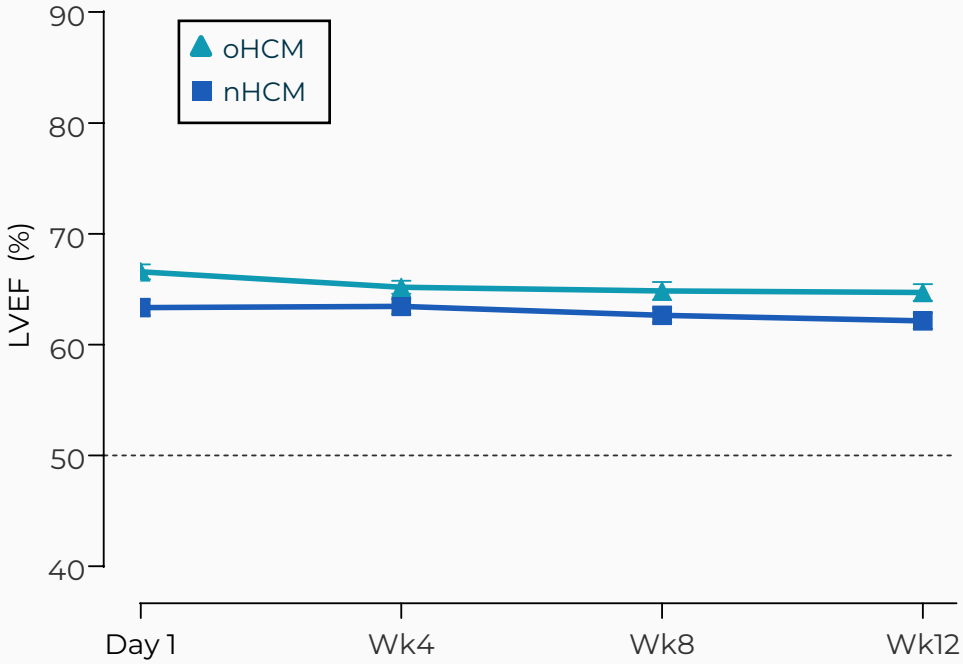
Characteristic	oHCM (n=20)	nHCM (n=33)
Echocardiographic Parameters		
LVEF (%), mean (SD)	67 (3)	63 (4)
LVOT-G Resting (mmHg), mean (SD)	40 (20)	7 (3)
LVOT-G Valsalva (mmHg), mean (SD)	85 (30)	8 (5)
Wall thickness (mm), mean (SD)	18 (3)	20 (5)
Patient-reported Outcome Measures		
KCCQ-OSS, mean (SD)	61 (23)	61 (19)
KCCQ-CSS, mean (SD)	65 (21)	66 (18)
Laboratory Measures		
NT-proBNP (pg/ml), geometric mean / median [IQR]	387 / 406 [220-664]	781 / 753 [423-1598]
hs-cTnI (pg/ml), geometric mean / median [IQR]	19 / 16 [7 - 36]	56 / 42 [13 - 161]

BMI, body mass index; CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; NYHA, New York Heart Association; OSS, overall summary score.

CIRRUS HCM

Left Ventricular Systolic Function

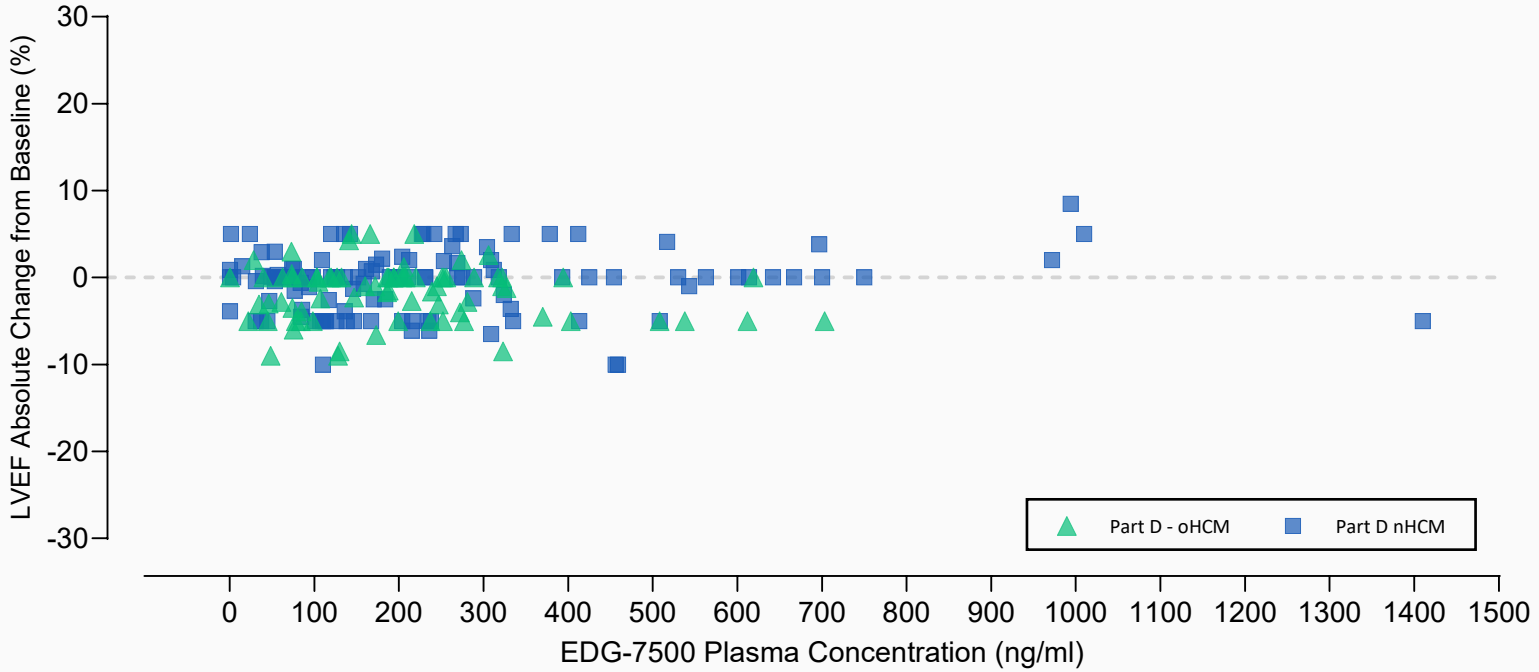
No Clinically Meaningful Change in LVEF Observed with EDG-7500



- **No reductions in LVEF to below 50%**
- **No clinical heart failure or hospitalizations due to drops in LVEF**

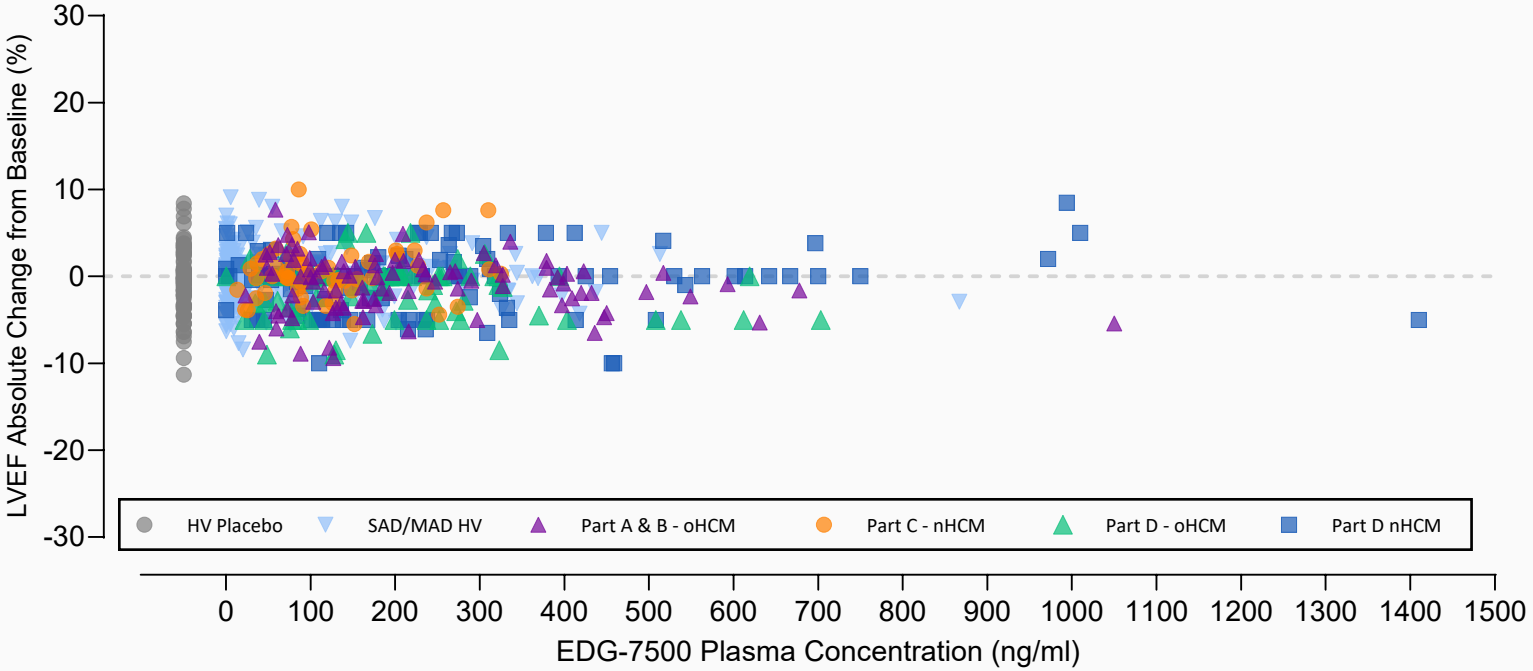
Mean±SEM
HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; nHCM, nonobstructive HCM; oHCM, obstructive HCM.

No Correlation Between EDG-7500 Exposure and LVEF Change



Based on echo core lab reads.
HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; MAD, multiple ascending dose; nHCM, nonobstructive HCM; oHCM, obstructive HCM; SAD, single ascending dose.

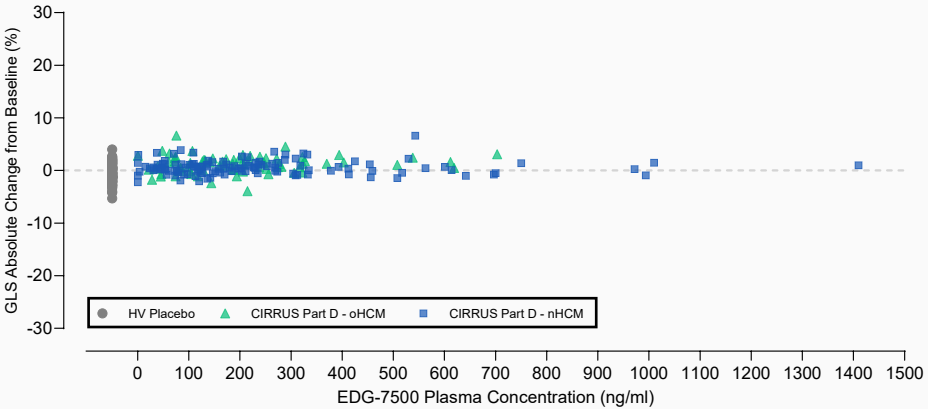
No Correlation Between EDG-7500 Exposure and LVEF Change



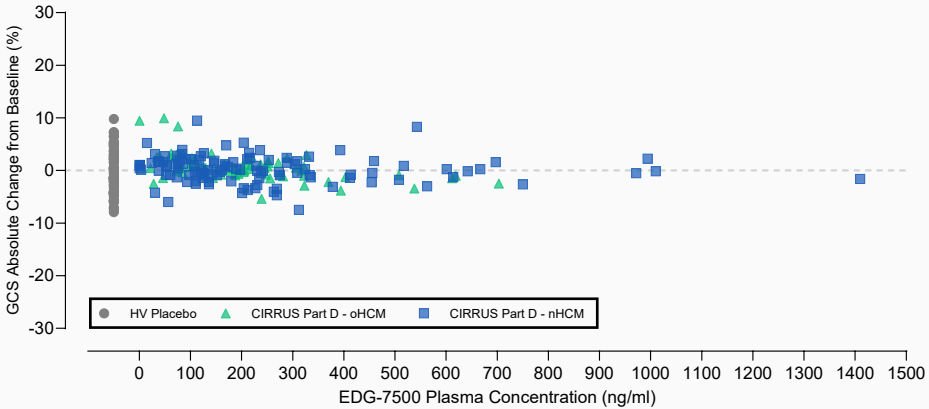
Based on echo core lab reads.
HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; MAD, multiple ascending dose; nHCM, nonobstructive HCM; oHCM, obstructive HCM; SAD, single ascending dose.

No Correlation Between EDG-7500 Exposure and GLS or GCS Change

Global Longitudinal Strain (GLS)



Global Circumferential Strain (GCS)



Based on core lab read echoes

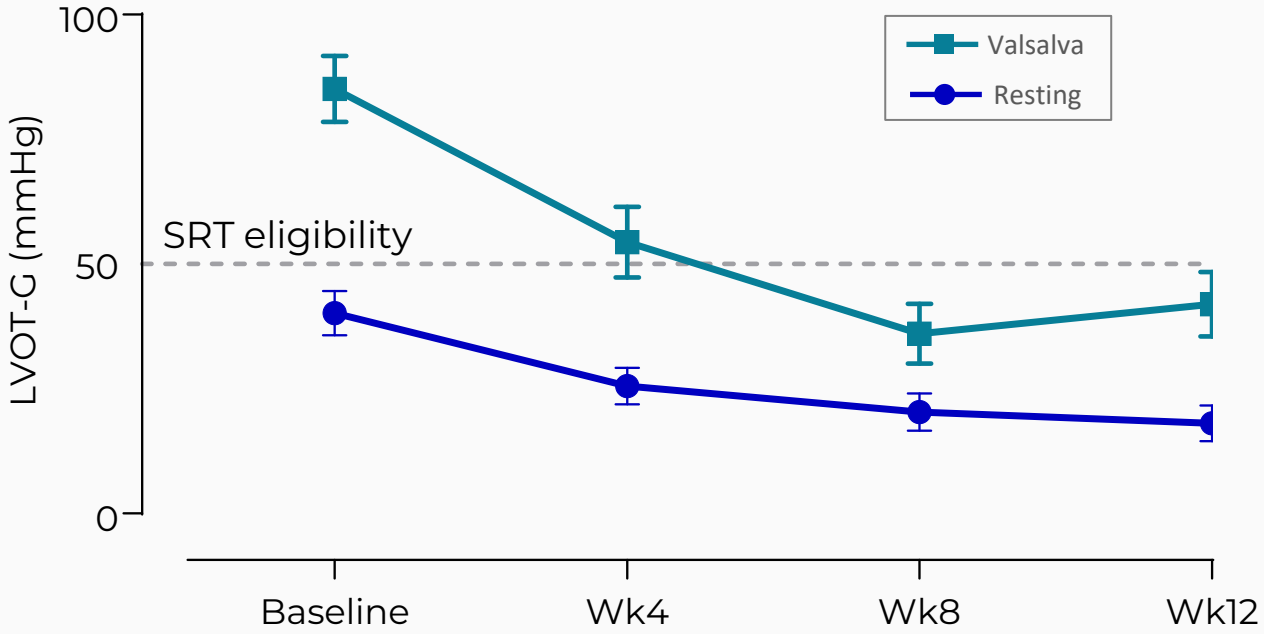
GCS, global circumferential strain; GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; nHCM, nonobstructive HCM; oHCM, obstructive HCM

CIRRUS HCM

oHCM Efficacy Results

Clinically Meaningful Improvement in LVOT Gradient Observed in 90% of oHCM Particpants[1]

oHCM



Valsalva

↓ **51%** vs baseline

Resting

↓ **55%** vs baseline

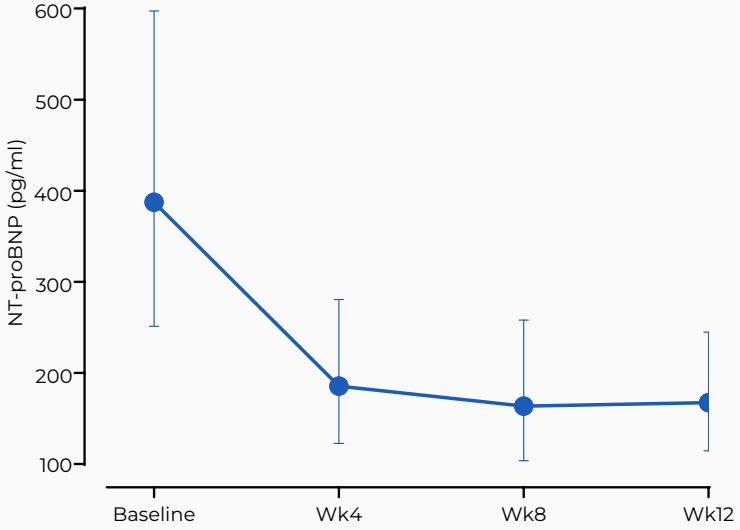
Mean±SEM;
LVOT-G, left ventricular outflow tract gradient. [1]Defined as resting <30 mmHg or Valsalva <50 mmHg.

Improvements in Cardiac Biomarkers

oHCM

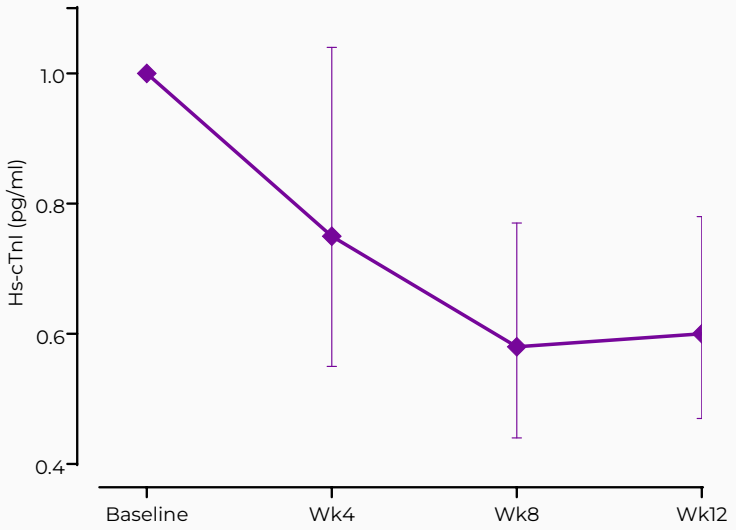
NT-proBNP (geometric mean)

56% decrease from baseline to Week 12



Hs-cTnI (geometric mean ratio)

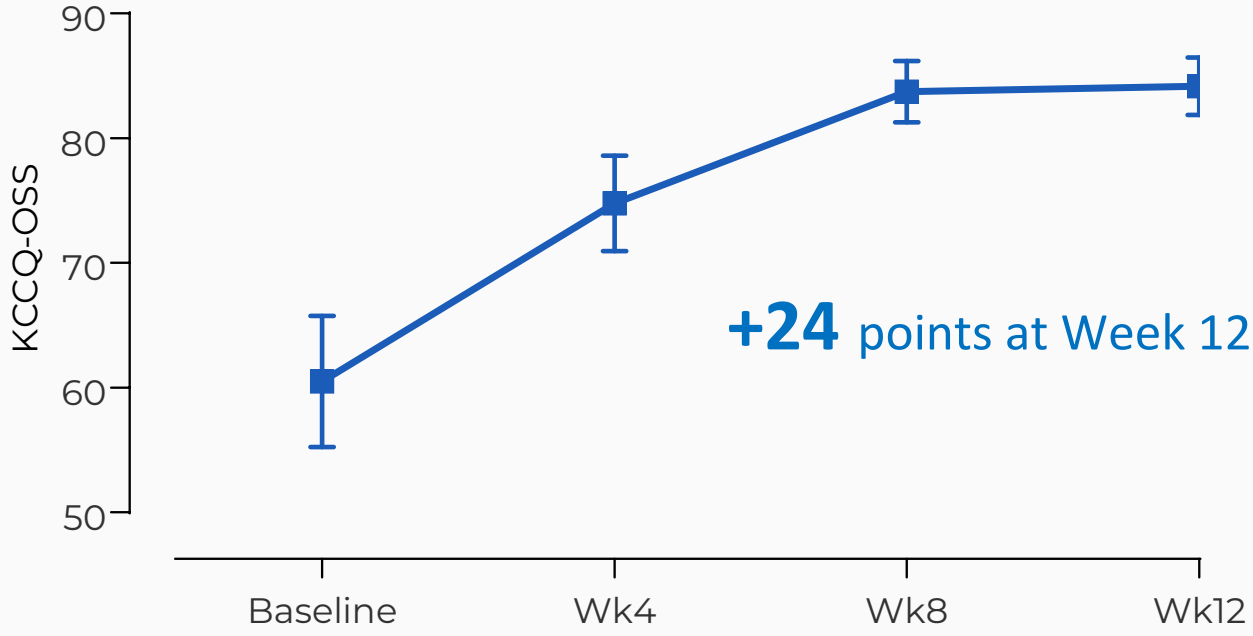
40% decrease from baseline to Week 12



Error bars = 95% CI
Hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Very Large (≥20 points) Increase in KCCQ-OSS at Week 12

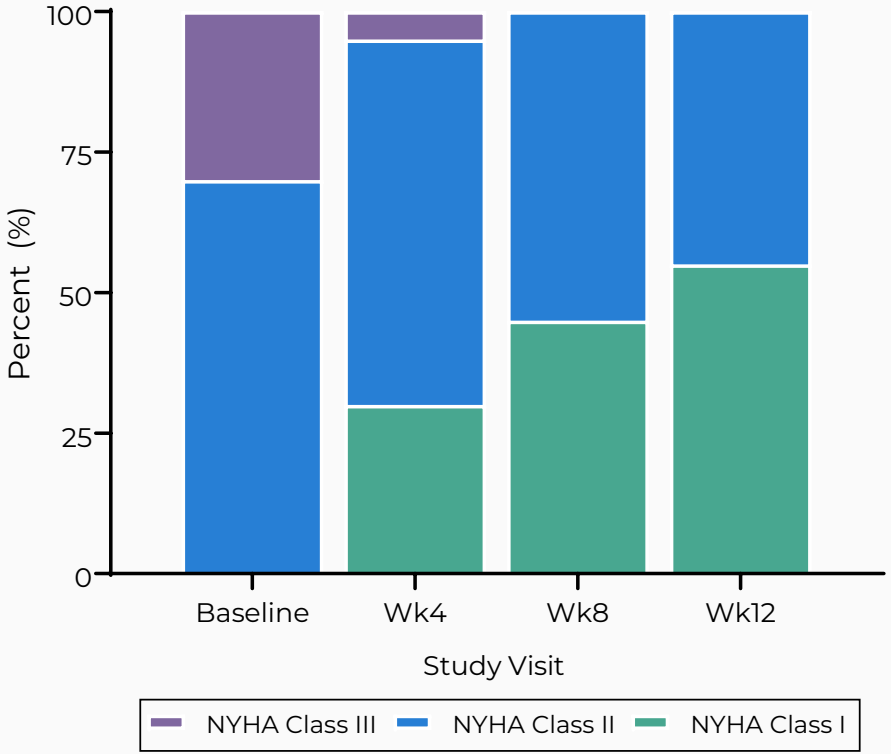
oHCM



Mean±SEM
KCCQ, Kansas City Cardiomyopathy Questionnaire; oHCM, obstructive hypertrophic cardiomyopathy; OSS, overall summary score.

Rapid and Sustained Improvements in NYHA Class

oHCM



55%

NYHA Class I by Week 12

70%

≥1 NYHA class improvement at Week 12

50%

NYHA Class III at baseline improved to **NYHA Class I** at Week 12

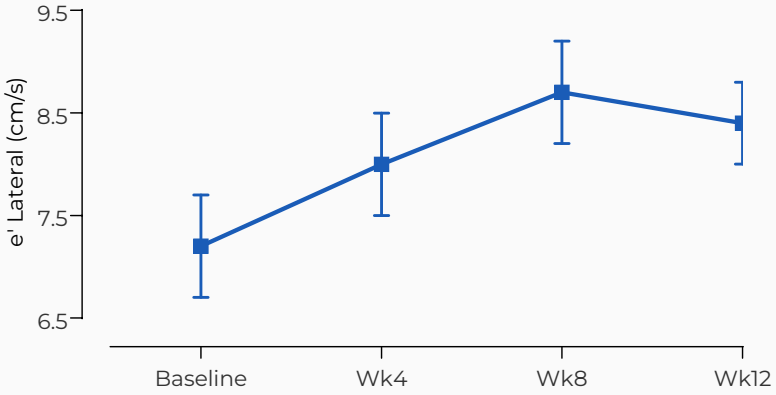
NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; wk, week.

Improvements in Echo Measures of Diastolic Function

oHCM

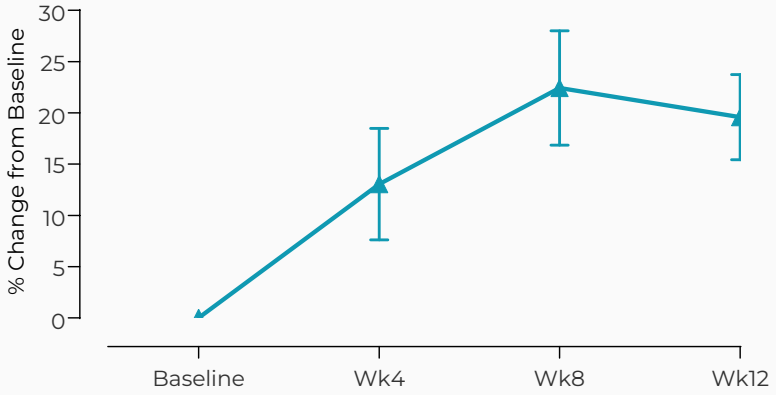
+1.2 cm/s

Improvement in e' lateral at Week 12



+20%

Improvement in e' lateral at Week 12



Mean±SEM
e' lateral, early diastolic tissue velocity of the lateral mitral annulus; oHCM, obstructive hypertrophic cardiomyopathy.

CIRRUS HCM

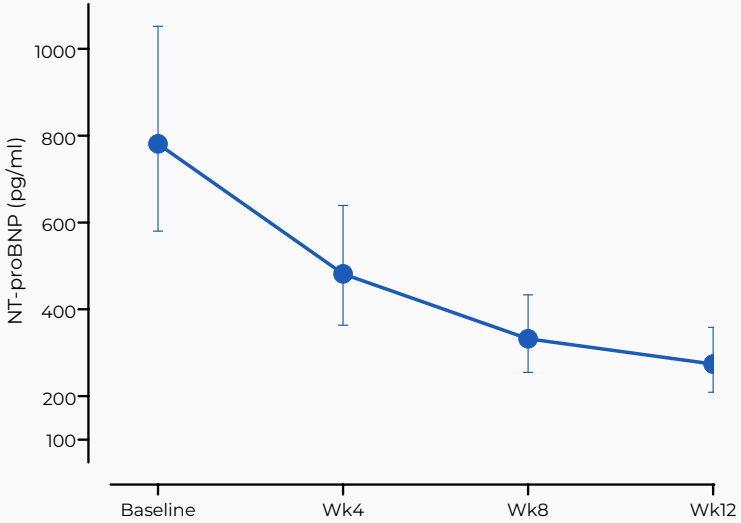
nHCM Efficacy Results

Improvements in Cardiac Biomarkers

nHCM

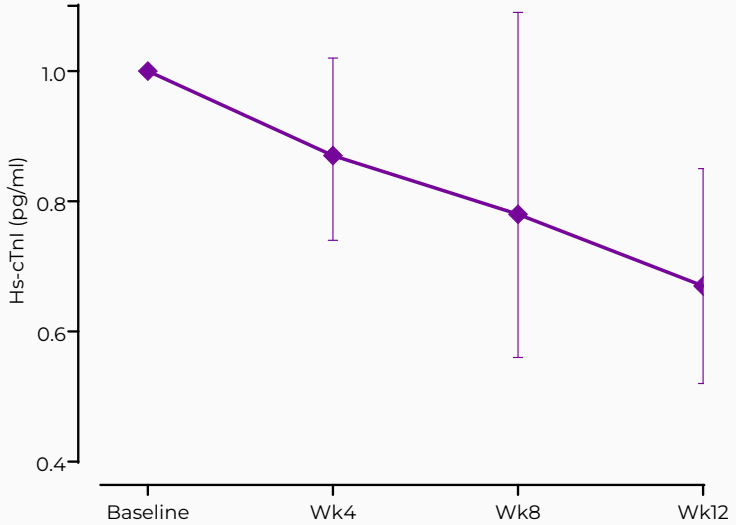
NT-proBNP

65% decrease from baseline to Week 12



hs-cTnI

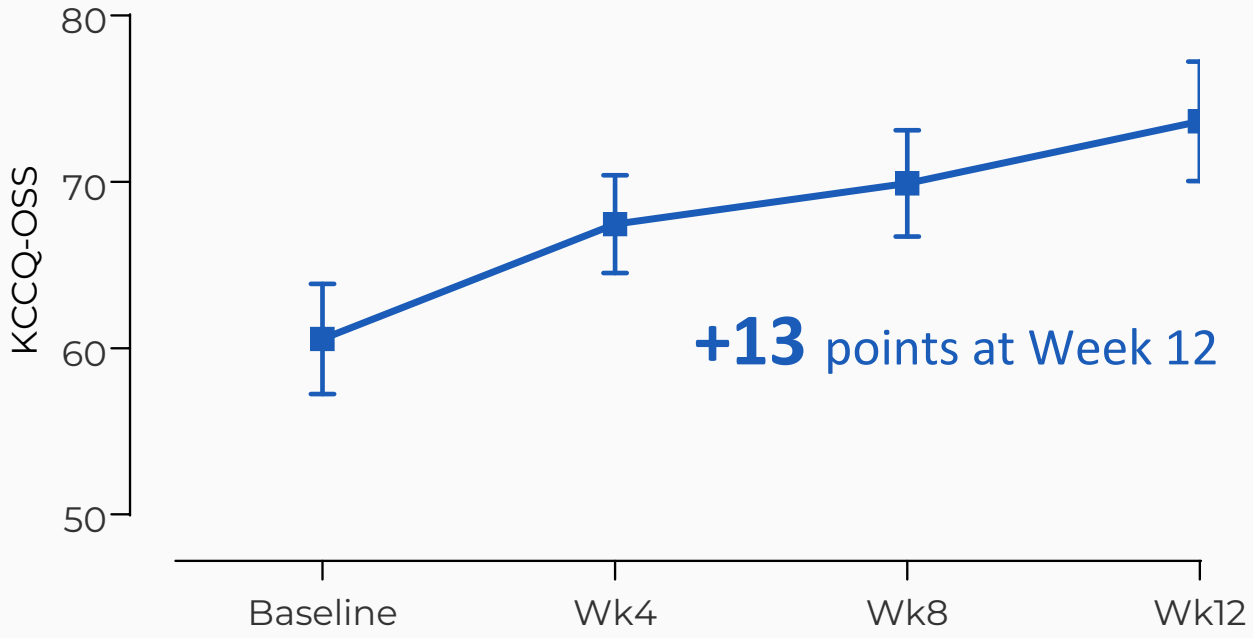
33% decrease from baseline to Week 12



NT-proBNP: geometric mean and 95% CI. Hs-cTnI: geometric mean ratio and 95% CI.
hs-cTnI, high-sensitivity cardiac troponin I; nHCM, nonobstructive HCM; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Large (≥10 points) Improvement in KCCQ-OSS at Week 12

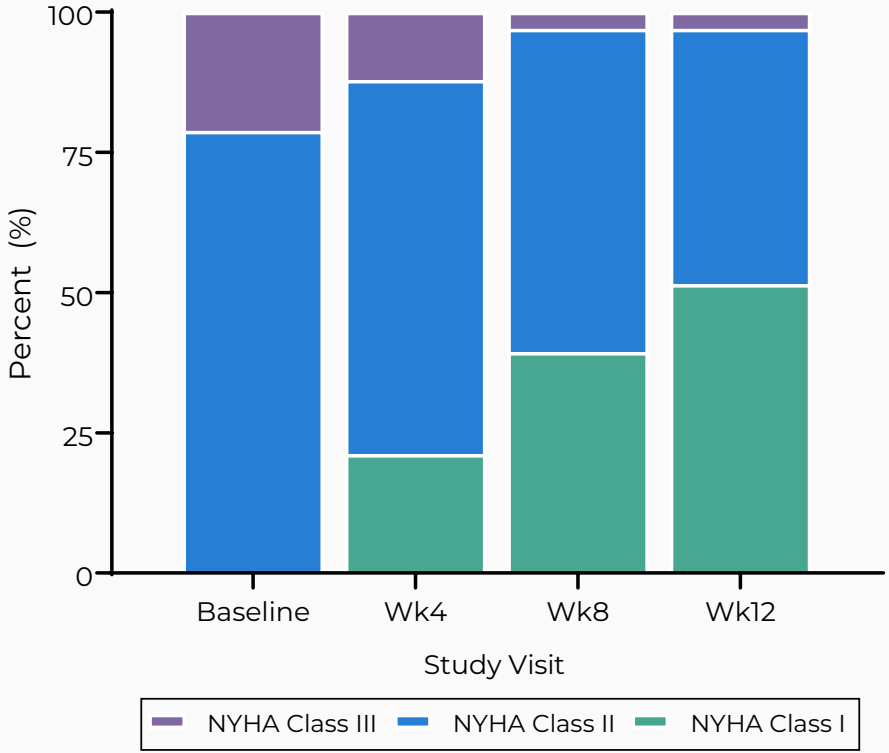
nHCM



Mean±SEM
KCCQ, Kansas City Cardiomyopathy Questionnaire; nHCM, nonobstructive hypertrophic cardiomyopathy; OSS, overall summary score.

Rapid and Sustained Improvements in NYHA Class

nHCM



52%

NYHA Class I by Week 12

64%

≥1 NYHA class improvement at Week 12

29%

NYHA Class III at baseline improved to **NYHA Class I** at Week 12

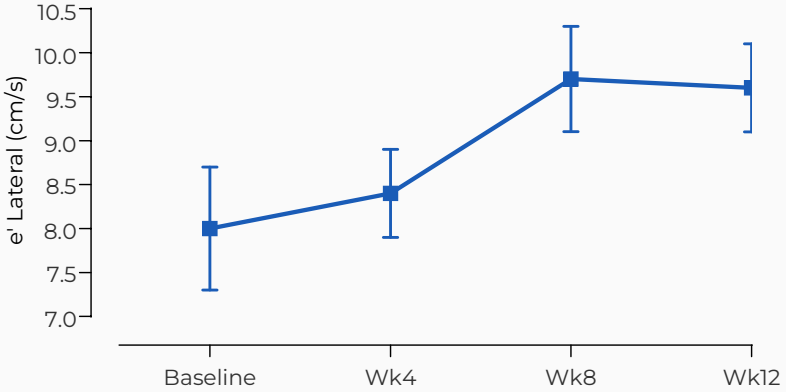
NYHA, New York Heart Association; nHCM, nonobstructive hypertrophic cardiomyopathy; wk, week.

Improvements in Echo Measures of Diastolic Function

nHCM

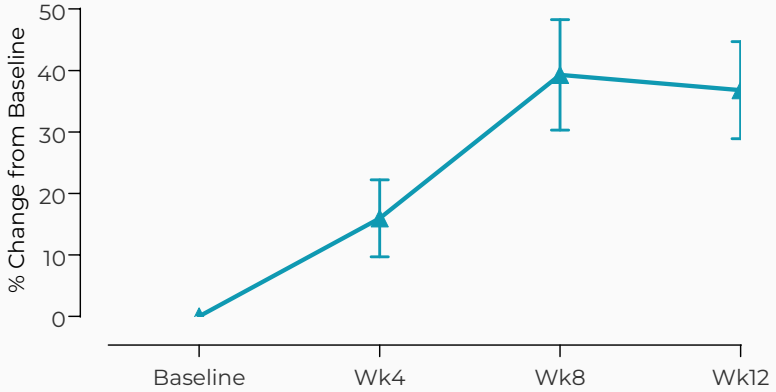
+1.6 cm/s

Improvement in e’ lateral at Week 12



+37%

Improvement in e’ lateral at Week 12



Mean±SEM;
e’ lateral, early diastolic tissue velocity of the lateral mitral annulus; nHCM, nonobstructive hypertrophic cardiomyopathy.

CIRRUS HCM

Safety Summary

12-weeks of EDG-7500 was Well Tolerated with No LVEF < 50%

Treatment Emergent Adverse Events (TEAEs)	
Participants with ≥1 TEAE, n (%)	34 (64%)
Mild	23 (43%)
Moderate	9 (17%)
Severe	2 (3.8%)
Serious Adverse Events (SAEs)	
Participants with ≥1 SAE – Related, n (%)	0 (0%)
Participants with ≥1 SAE – Unrelated, n (%)	5 (9.4%)
Other Cardiac Safety Events	
New onset AF/AFL, n (%)	2 (3.8%)
Treatment emergent HF, n (%)	0 (0%)
LVEF <50% (with or without symptoms), n (%)	0 (0%)
Dose reductions based on LVEF, n (%)	0 (0%)

AF, atrial fibrillation; HF, heart failure; LVEF, left ventricular ejection fraction; TEAE, treatment emergent adverse event; SAE, serious adverse event

EDG-7500: Summary and Next Steps

- **Novel once-daily mechanism with potential for differentiated safety profile**
  - >240 participants exposed to EDG-7500 to date (all studies)
  - No measurable change in global systolic performance
  - No observed LVEF <50%
  - No observed HF events
- **Clinical meaningful improvements** observed across multiple endpoints following 12-weeks of once-daily EDG-7500 in patients with oHCM and nHCM
- Initial echocardiographic data consistent with a **direct lusitropic effect**
- Phase 3 on track to initiate by **4Q 2026**

CIRRUS HCM

Thank You!

We would like to thank all the investigators, coordinators, site staff, and **especially the patients who participated in this trial.**
The advancement of **new therapies to patients** can only happen with your incredible efforts and commitment to clinical research!