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

Anjali T Owens[1], Theodore P Abraham[2], Ronald Wharton[3], Ankit Bhatia[4], Mariko W Harper[5], Christopher Dufton[6], Daniel D Gretler[6], Jeffrey A Silverman[6], Marilyn M Mok[6], Molly Madden[6], James MacDougall[6], Natalie Hawryluk[6], and Marc J Semigran[6]

[1]University of Pennsylvania, Philadelphia PA; [2]University of California, San Francisco CA; [3]Northwell Health, New Hyde Park NY; [4]The Christ Hospital Health Network, Cincinnati OH; [5]Virginia Mason Franciscan Health, Seattle WA; [6]Edgewise Therapeutics, Boulder CO

Background

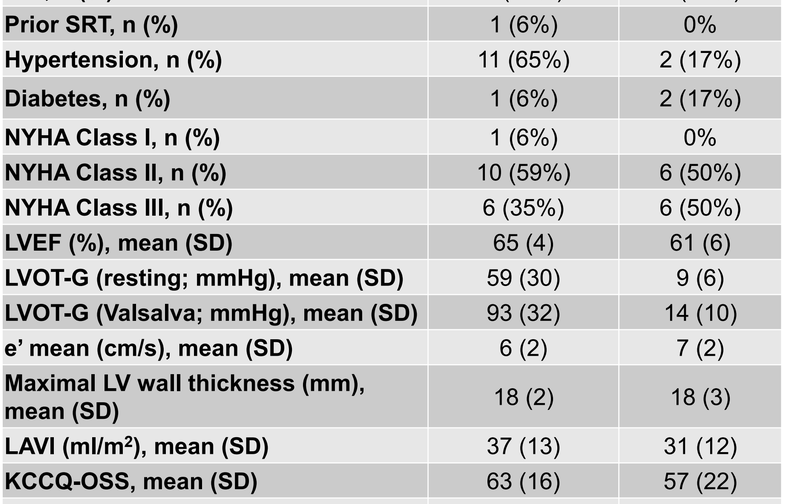
- **EDG-7500** is a novel **cardiac sarcomere modulator** designed to slow the rate of acto-myosin engagement and speed disengagement without inactivating the myosin motor head.
- In preclinical studies and the Phase 2 single-dose oHCM study, EDG-7500 demonstrated significant **reductions** in **LVOT-G** 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.

Baseline Characteristics

	oHCM (N=17)	nHCM (N=12)
Age (yrs), mean (SD)	61 (13)	54 (19)
Female, n (%)	12 (71%)	7 (58%)
BMI (kg/m²), mean (SD)	28 (4)	27 (4)
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 I, n (%)	1 (6%)	0%
NYHA Class II, n (%)	10 (59%)	6 (50%)
NYHA Class III, n (%)	6 (35%)	6 (50%)
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/m²), mean (SD)	37 (13)	31 (12)
KCCQ-OSS, mean (SD)	63 (16)	57 (22)
KCCQ-CSS, mean (SD)	69 (15)	63 (23)
NT-proBNP (geometric mean /median (IQR); pg/ml)	724 / 710 (381, 1074)	782 / 715 (546, 1231)

Obstructive HCM

LVOT-G at Rest & Post Valsalva



Mean ± SEM

% Reaching Resting LVOT-G <30mmHg (wk 4): 43% (50mg), 89% (100mg)**

% Reaching Valsalva LVOT-G <50mmHg (wk 4): 57% (50mg), 89% (100mg)**

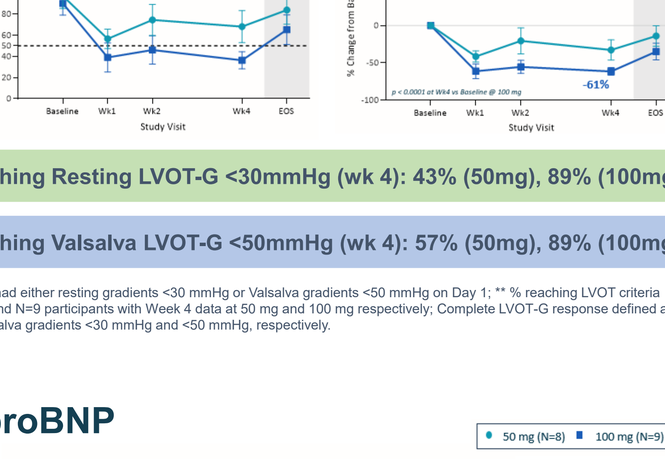
* 5 participants had either resting gradients <30 mmHg or Valsalva gradients <50 mmHg on Day 1; ** % reaching LVOT criteria based on N=7 and N=9 participants with Week 4 data at 50 mg and 100 mg respectively; Complete LVOT-G response defined as resting and Valsalva gradients <30 mmHg and <50 mmHg, respectively.

NT-proBNP

Mean ± SEM

- **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]

Early Diastolic Mitral Annular Velocity (e')



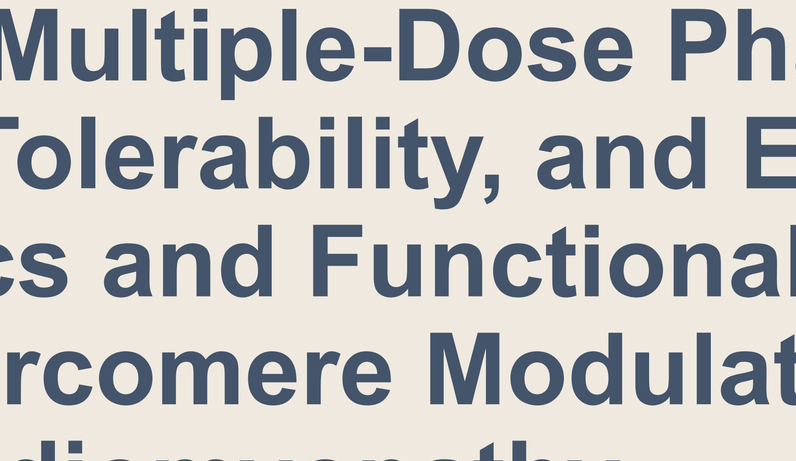
Baseline e' mean = 6 ± 2 cm/s

Mean ± SD for baseline value; Mean ± SEM for % change from baseline

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

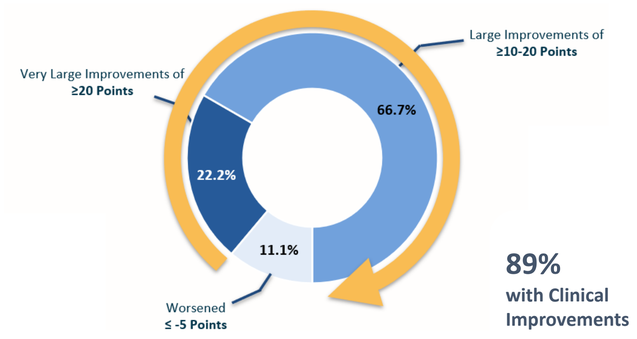
Obstructive HCM

KCCQ-OSS and KCCQ-CSS
4 Weeks vs. Baseline



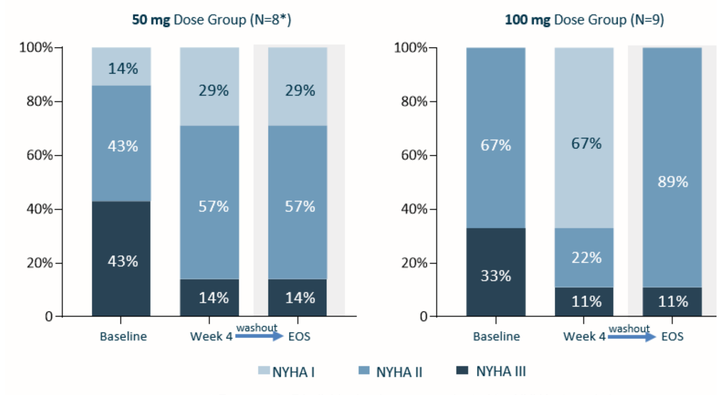
Mean ± SEM * Represents 7 individuals who were evaluated for KCCQ at week 4

KCCQ-CSS
100mg after 4 Weeks vs. Baseline



89%
with Clinical Improvements

NYHA Functional Class

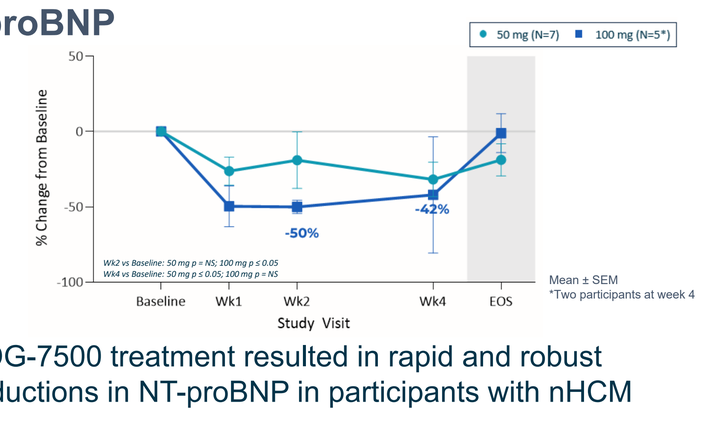


* Represents 7 individuals who were evaluated for NYHA at week 4

- **43%** in the 50 mg group and **78%** in the 100 mg group had **≥ 1 NYHA Class improvement** at week 4

Nonobstructive HCM

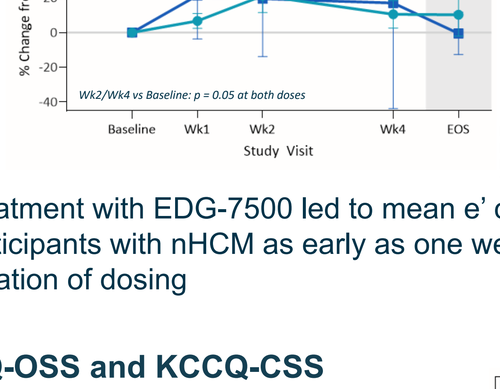
NT-proBNP



Mean ± SEM
*Two participants at week 4

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

Early Diastolic Mitral Annular Velocity (e')

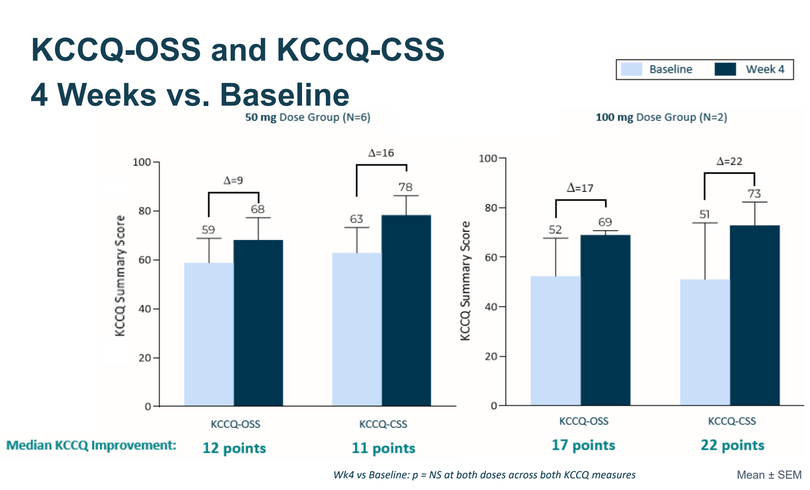


Baseline e' mean = 7 ± 2 cm/s

Mean ± SD for baseline value; Mean ± SEM for % change from baseline
* Two participants at week 4

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

KCCQ-OSS and KCCQ-CSS
4 Weeks vs. Baseline



Mean ± SEM

AF, atrial fibrillation; BMI, body mass index; e', early diastolic mitral annular velocity; CSS, clinical summary score; EOS, end of study; 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; LVOT-G, LVOT-gradient; NS, not significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive HCM; OSS, overall summary score; pVO_2, peak oxygen consumption; SRT, septal reduction therapy.

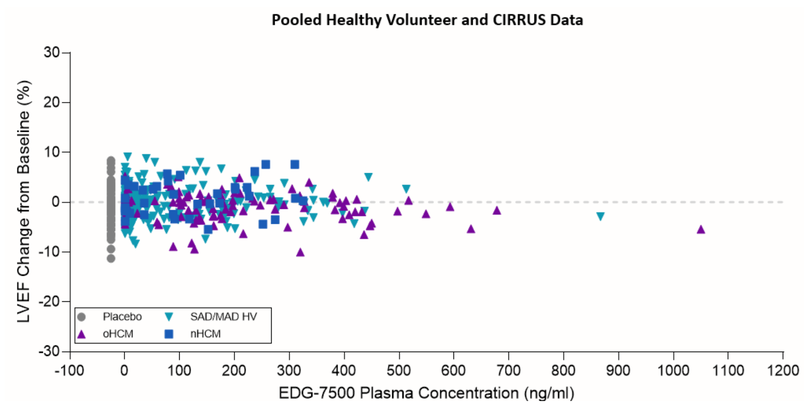
Nonobstructive HCM

KCCQ-CSS
100mg after 4 Weeks vs. Baseline

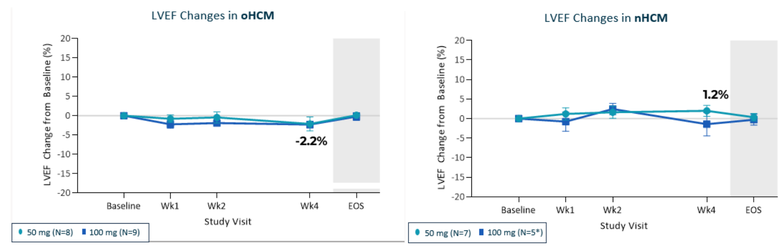
88%
with Clinical Improvements

Safety

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



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%

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

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

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

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

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