

# **EDG-7500:** Phase 2 CIRRUS-HCM Development Program Update

April 2, 2025

# Forward Looking Statement

This presentation contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Statements in this presentation that are not purely historical are forward-looking statements. Such forward-looking statements include, among other things, statements regarding the potential of, and expectations regarding Edgewise's cash runway, Edgewise's expectations relating to its : clinical trials and clinical development of sevasemten (EDG-5506) and EDG-7500, including statements regarding timing of reporting data, timing of reporting Edgewise's future clinical trial plans; statements regarding the advancement of Edgewise's research and development programs; statements regarding Edgewise's pipeline of product candidates and programs; statements relating to Edgewise's cash runway; and statements regarding Edgewise's milestones. Words such as "believes," "anticipates," "plans," "expects," "intends," "will," "goal," "potential" and similar expressions are intended to identify forward-looking statements. The forward-looking statements contained herein are based upon Edgewise's current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results could differ materially from those projected in any forward-looking statements due to numerous risks and uncertainties, including but not limited to: risks associated with the potential unreliability of extrapolations and comparisons of published results without head-to-head comparison included in the topline result from Parts B and C of Phase 2 of CIRRUS-HCM trial of EDG-7500 in individuals with either obstructive or non-obstructive Hypertrophic Cardiomyopathy; Edgewise's limited operating history, its products being early in development and not having products approved for commercial sale; risks associated with Edgewise not having generated any revenue to date; Edgewise's ability to achieve objectives relating to the discovery, development and commercialization of its product candidates, if approved; Edgewise's need for substantial additional capital to finance its operations; Edgewise's substantial dependence on the success of sevasemten and EDG-7500; Edgewise's ability to develop and commercialize sevasemten and EDG-7500 and discover, develop and commercialize product candidates in future programs; risks related to Edgewise's clinical trials of its product candidates not demonstrating safety and efficacy; risks related to Edgewise's product candidates causing serious adverse events, toxicities or other undesirable side effects; the outcome of preclinical testing and early clinical trials not being predictive of the success of later clinical trials and the risks related to the results of Edgewise's clinical trials not satisfying the requirements of regulatory authorities; delays or difficulties in the enrollment and/or maintenance of patients in clinical trials; risks related to failure to capitalize on other indications or product candidates; risks related to competition; risks relating to interim, topline and preliminary data from Edgewise's clinical trials changing as more patient data becomes available; risks related to the regulatory approval processes of domestic and foreign authorities being lengthy, time consuming and inherently unpredictable; risks related to production of drugs by Edgewise's third-party manufacturers; risks related to changes in methods of product candidate manufacturing or formulation; risks related to not achieving adequate market acceptance; risks related to the patient population for our product candidates having a small patient population; risks related to regulatory authorities not accepting data from trials conducted in locations outside of their jurisdiction; risks relating to Edgewise's ability to attract and retain highly skilled executive officers and employees; Edgewise's ability to obtain and maintain intellectual property protection for its product candidates; Edgewise's reliance on third parties; general economic and market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section entitled "Risk Factors" in documents that Edgewise files from time to time with the U.S. Securities and Exchange Commission. These forward-looking statements are made as of the date of this presentation, and Edgewise assumes no obligation to update the forward-looking statements, or to update the reasons why actual results could differ from those projected in the forward-looking statements, except as required by law.

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# Agenda

1. Introduction to Edgewise Therapeutics
2. The continued unmet need in HCM
3. Topline results: Phase 2 CIRRUS-HCM trial EDG-7500 28-day data in oHCM and nHCM
4. EDG-7500 future development plans
5. Closing remarks
6. Q & A



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**Dr. Robert Blaustein**

*Chief Development Officer*

## Focused on muscle science

- Global leader in muscle disease therapeutic development
- Deep knowledge of integrated muscle physiology
- Combined expertise in muscle biology and small molecule drug discovery to build our novel and differentiated muscle-focused platform

## Rapidly advancing portfolio

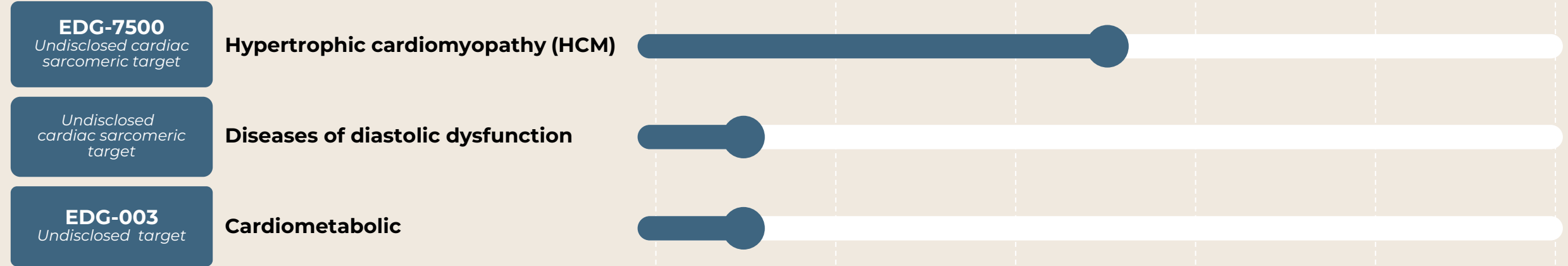
- Advancing EDG-7500 in oHCM and nHCM
- Advancing sevasemten in muscular dystrophies, including Becker for which there are no approved treatments
- Novel cardiometabolic targets in discovery

## Unwavering patient commitment

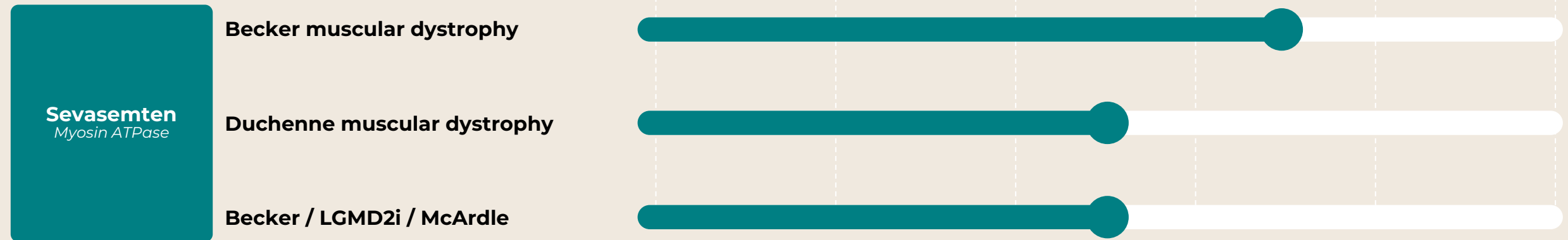
- Mission-driven focus on unmet needs in severe muscle conditions
- Patients & families are critical voices in all development programs

# Our Pipeline

## Cardiovascular



## Muscular Dystrophy



# Treatments for HCM Have Key Limitations Leaving Substantial Unmet Need for Patients

## LIMITED BENEFIT ACROSS THE SPECTRUM OF HCM



**Efficacy & safety limitations** with interventions in oHCM<sup>4</sup>



**No approved therapies** for nHCM

## RISK OF HEART FAILURE<sup>1,2</sup>



Mavacamten **black box warning** for HF<sup>3</sup>



**HF risk** limits intervention<sup>2</sup>

## SAFETY RISKS WORSEN PATIENT EXPERIENCE



Frequent **echo monitoring**<sup>1-3</sup>



Echo-based **dose titration for safety**<sup>1-3</sup>

HCM, hypertrophic cardiomyopathy; HF, heart failure; nHCM, nonobstructive hypertrophic cardiomyopathy; oHCM, obstructive hypertrophic cardiomyopathy.

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;

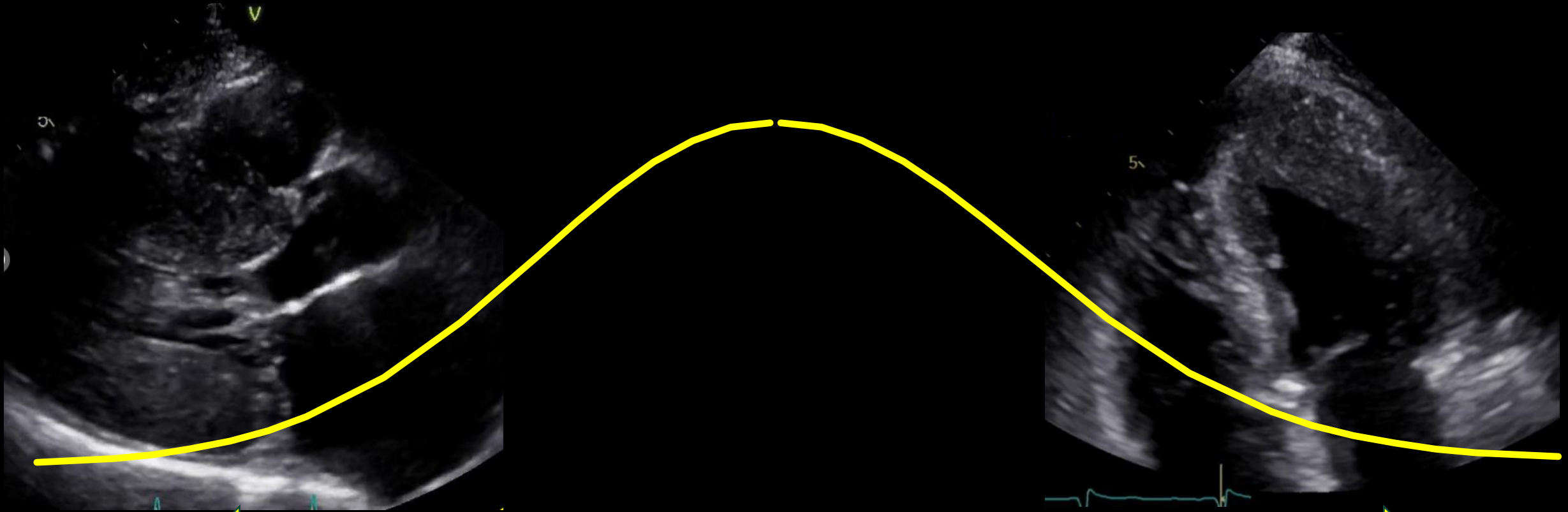
4. Olivetto I et al. *Lancet*. 2020;396(10253):759-769.

# The Unmet Need in Hypertrophic Cardiomyopathy

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Disclosures: research grants from Pfizer, Ionis, Attralus, and Cytokinetics and consulting fees from Edgewise, Cytokinetics, Bristol Myers Squibb (BMS), BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Alnylam, Haya, Alexion, Akros, Lexeo, Prothena, BioMarin, AstraZeneca, and Tenaya.

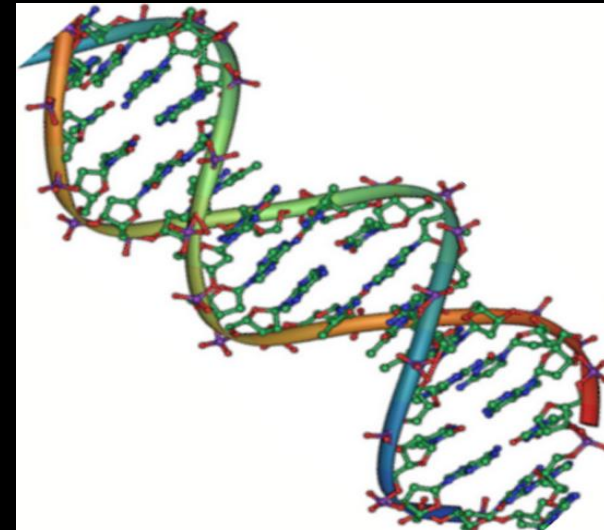
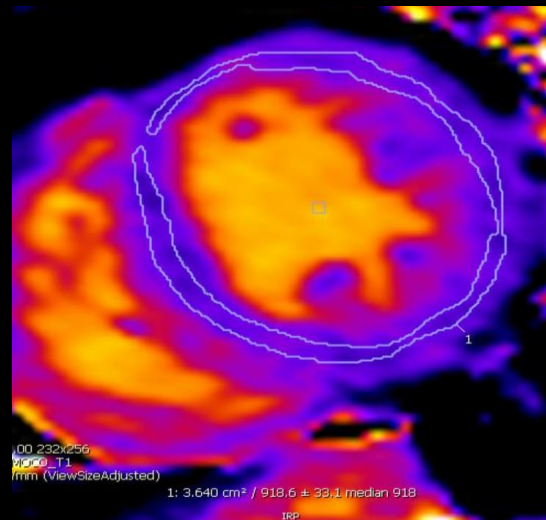
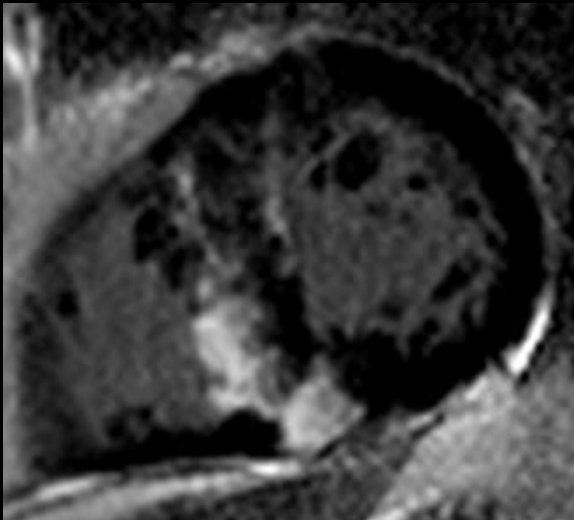
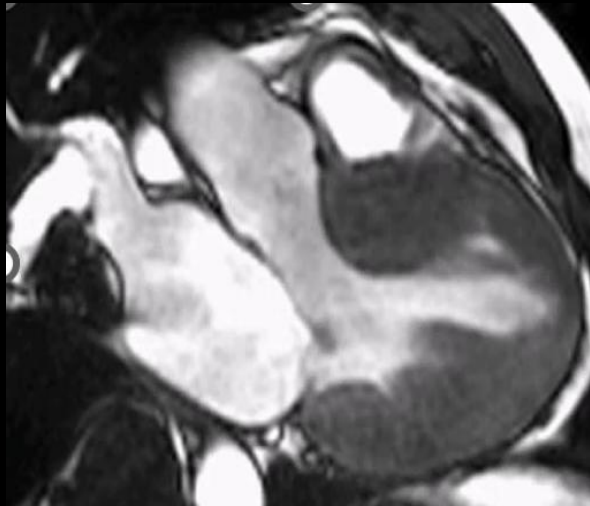
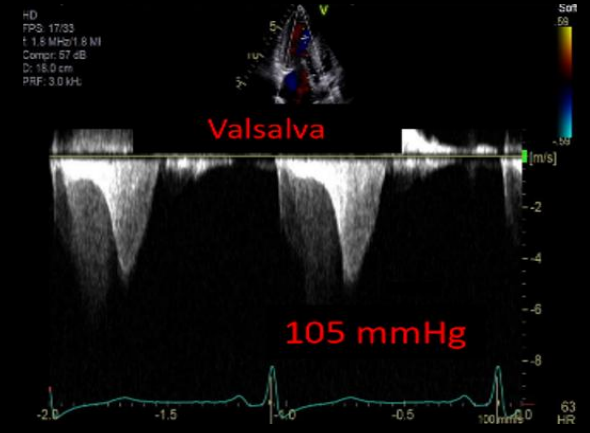
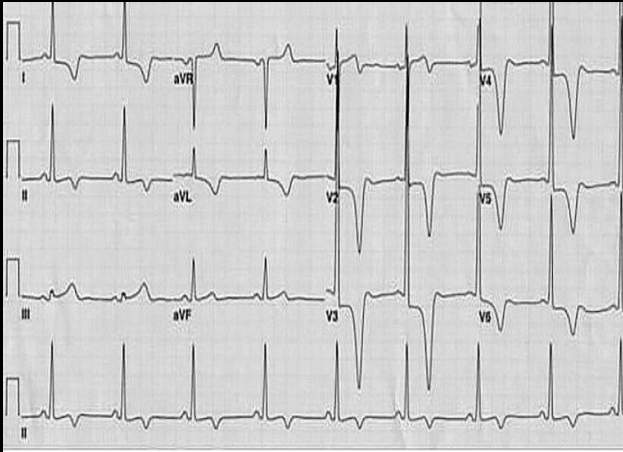
# The Continuum in Hypertrophic Cardiomyopathy



Myocyte hypertrophy, interstitial fibrosis, diastolic dysfunction underlie the continuum of HCM

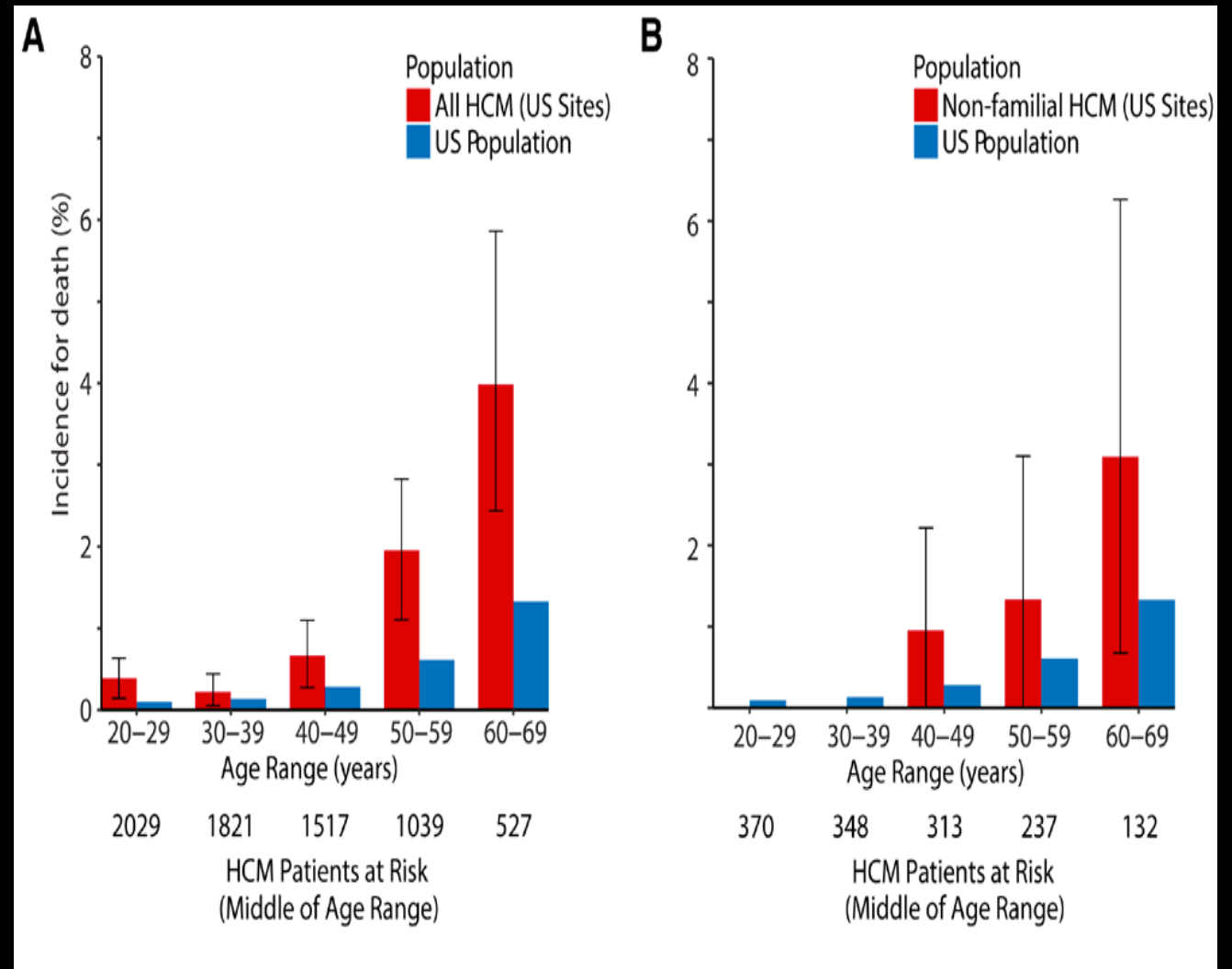
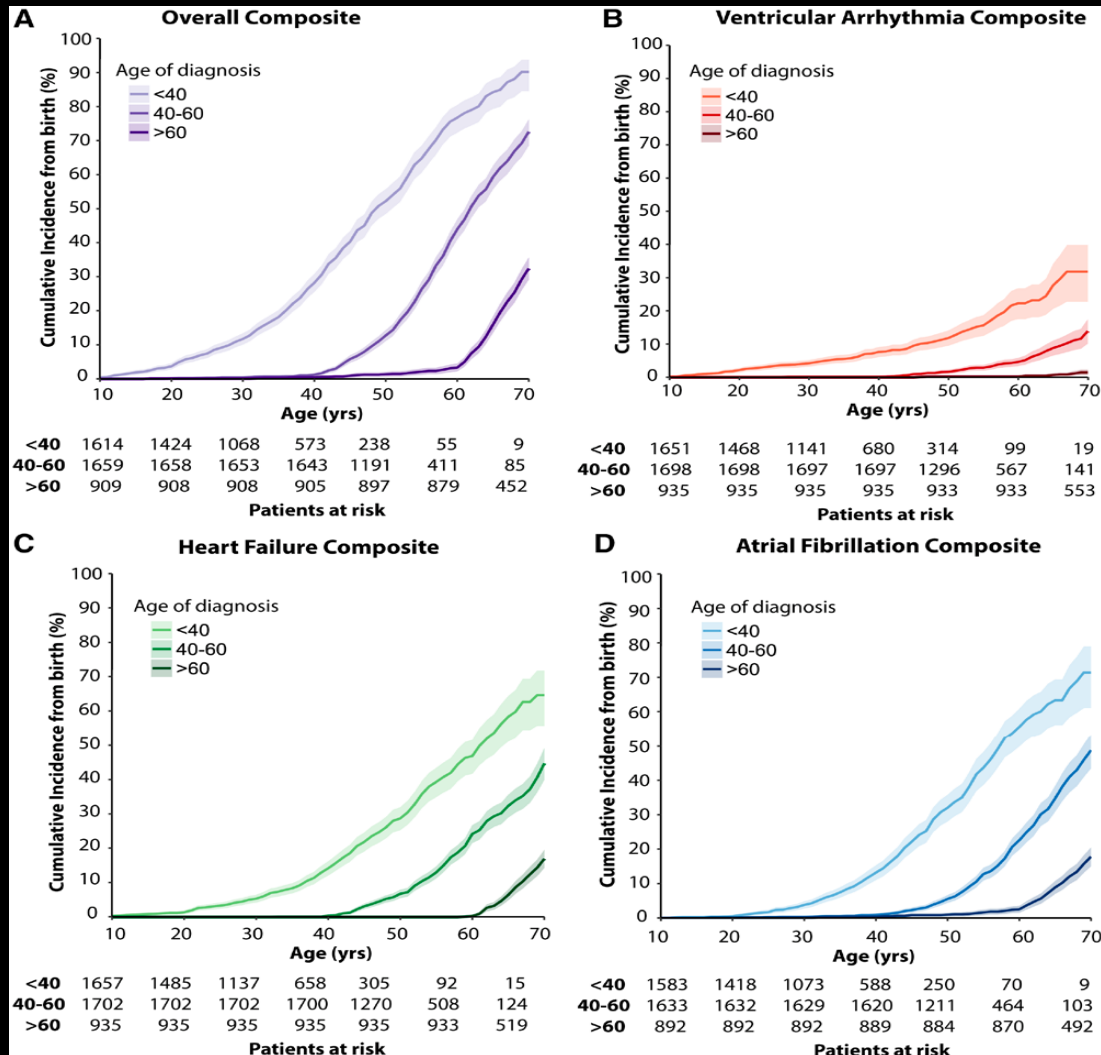


# HCM Disease Complexity Requires Thorough Evaluation



# Burden of HCM is Substantial

## Data from the SHaRe Registry



# Goals of Therapies in HCM

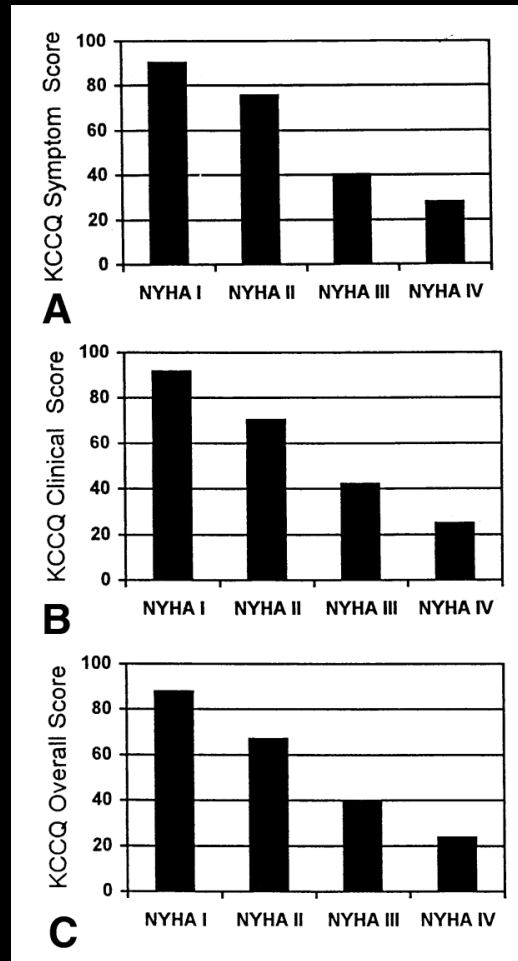
- Rapid and consistent relief of symptoms
- Improvement in quality of life
- Improvement in exercise capacity
- Favorable remodeling and in turn, less complications and better outcomes

# Unmet Need

- Non-obstructive HCM
  - No approved therapies
- Obstructive HCM
  - Non responders
  - Mild obstruction
  - Diastolic dysfunction
  - Monitoring burden
    - Systolic dysfunction

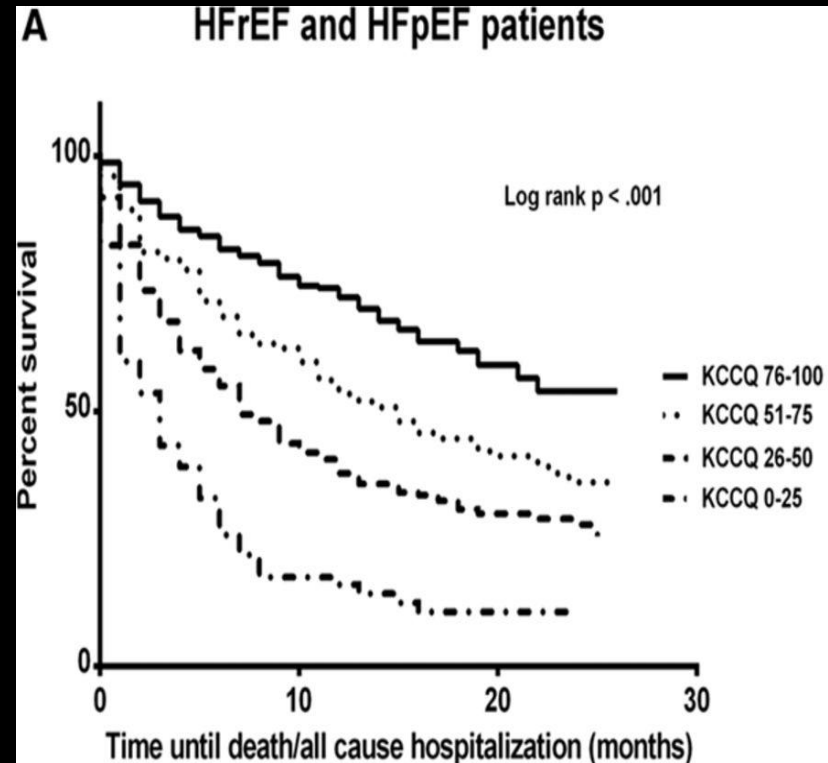
# Principles of Therapy → Improvement in Quality of Life\*

Validated tool in heart failure and in HCM



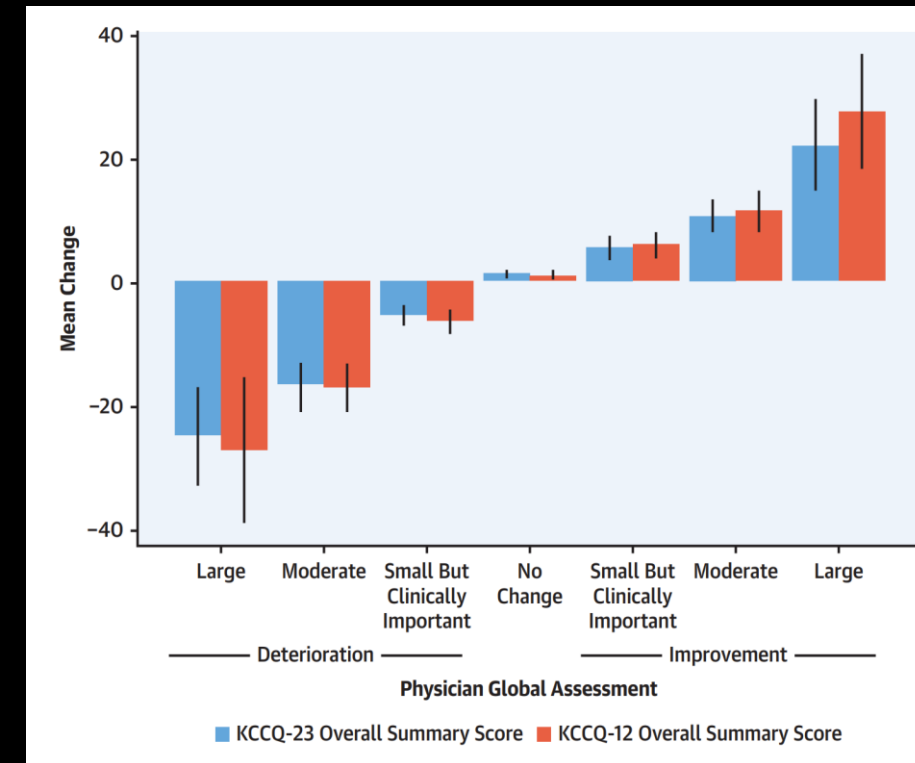
Green et al. JACC 2000

Prognostic tool in heart failure



Joseph et al. Circ HF 2013

Beyond directionality, KCCQ is a robust measure of magnitude of benefit



Spertus et al. JACC 2020

\*ACC/AHA Guidelines, Ommen et al. 2024

# Phase 2 CIRRUS-HCM Trial Part B (oHCM) and Part C (nHCM)

Dr. Anjali Owens

*Medical Director, Center for Inherited Cardiac Disease Associate Professor of Medicine (Cardiovascular Medicine) at the Hospital of the University of Pennsylvania*

**Disclosures:**

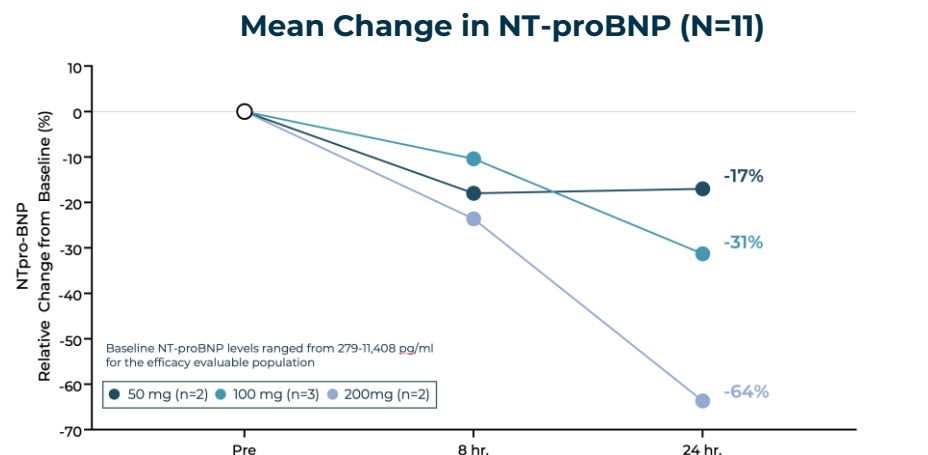
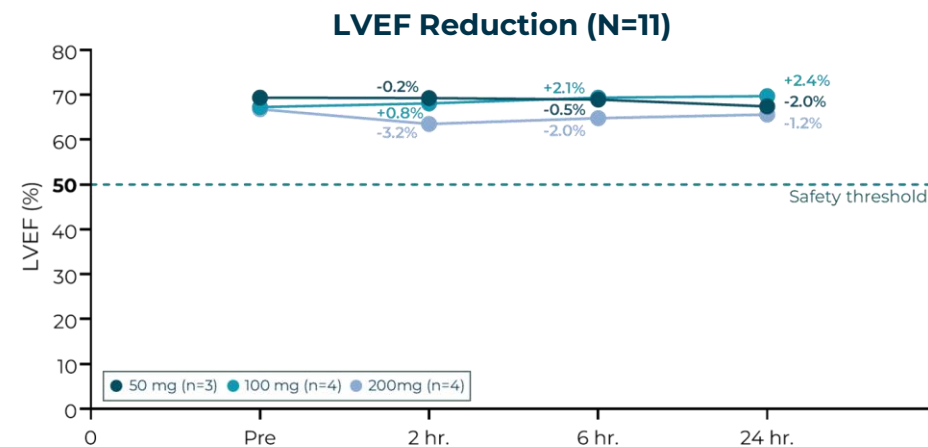
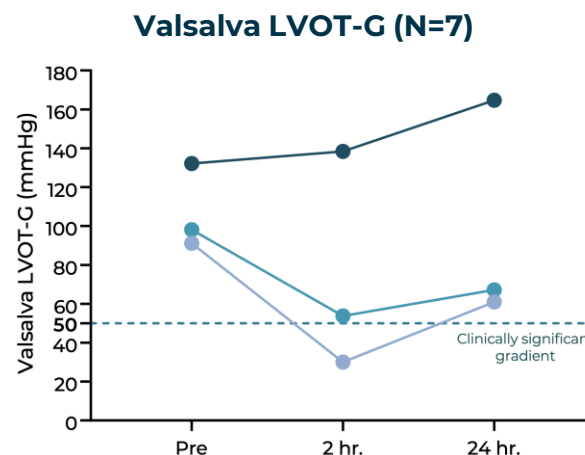
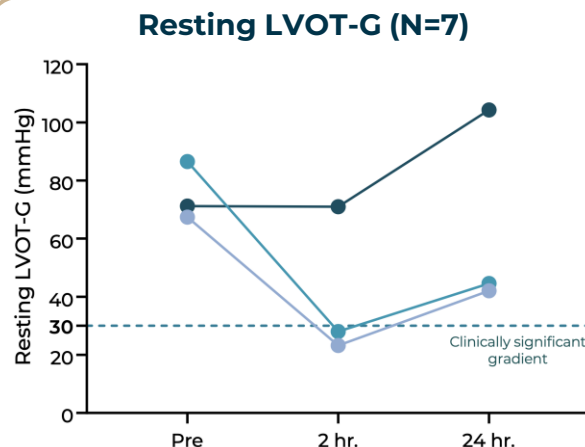
Consulting/advisory boards for Alexion, Avidity, Bayer, BMS, Cytokinetics, Corvista, Edgewise, Imbria, irhythm, Lexeo, Biomarin, Stealth, Tenaya and grant to institution from BMS



# Single Dose Study in oHCM Highlighted the Potential for EDG-7500 as a Novel Therapy for Patients with HCM

## Observations from CIRRUS-HCM Single Dose Study Highlighted EDG-7500's Potentially Differentiated Profile in HCM

- EDG-7500 was well tolerated across all doses studied in oHCM patients
- Reduction in resting LVOT-G of **67%** for the 100/200 mg cohorts combined
- Reduction in Valsalva LVOT-G of **55%** for the 100/200 mg cohorts combined
- LVOT-G relief was achieved **without reductions in LVEF**
- EDG-7500 led to a mean **31%** (100 mg) and **64%** (200 mg) decrease in NT-proBNP



# EDG-7500 Fixed Daily Dosing 28-Days in oHCM (Part B) and nHCM (Part C) Study Design



## PRIMARY OBJECTIVE

Safety & tolerability  
in adults with HCM

## KEY INCLUSION CRITERIA

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

## TOTAL CIRRUS TARGET ENROLLMENT

~70

## KEY OUTCOME MEASURES

Cardiovascular PD, LVEF,  
Biomarkers, PK

## Focus of Today's Presentation

### PART A: Single Dose (oHCM)

ADULTS  
WITH oHCM

Single dose EDG-7500

### PART B (28 Days): Fixed Daily Dosing (oHCM)

ADULTS  
WITH oHCM

Once-daily dose EDG-7500

### PART C (28 Days): Fixed Daily Dosing (nHCM)

ADULTS  
WITH nHCM

Once-daily dose EDG-7500

### PART D (12 weeks): Extended Dose (oHCM & nHCM)

ADULTS  
WITH oHCM  
& nHCM

Once-daily dose EDG-7500

# CIRRUS-HCM Part B and C: Baseline Demographic and Clinical Characteristics

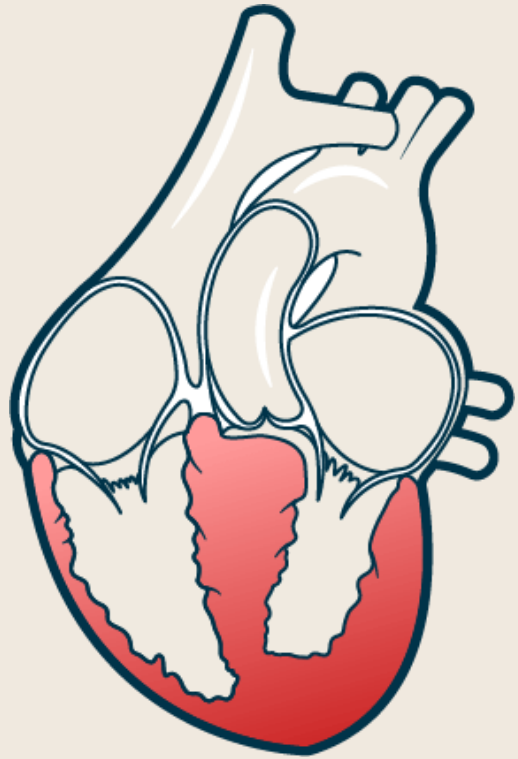
Baseline Characteristics	CIRRUS oHCM (Safety; n=17)	CIRRUS nHCM (Safety; n=12)
Age (yrs.)	61	54
Sex, % females	71%	58%
BMI (kg/m <sup>2</sup> )	28	27
History of AF	6%	8%
ICD	12%	50%
Prior SRT	6%	0%
Hypertension	65%	17%
Diabetes	6%	17%
NYHA I	6%	0%
NYHA II	59%	50%
NYHA III	35%	50%
KCCQ-OSS	63	57
LVEF	65%	61%
LVOT-G (resting; mmHg)	59	9
LVOT-G (Valsalva; mmHg)	93	14
NT-proBNP (geometric mean/median; pg/ml)	724 / 710	782 / 715

Abbreviations: LVOT, left ventricular outflow tract; SRT, septal reduction therapy; NYHA, New York Heart Association; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator



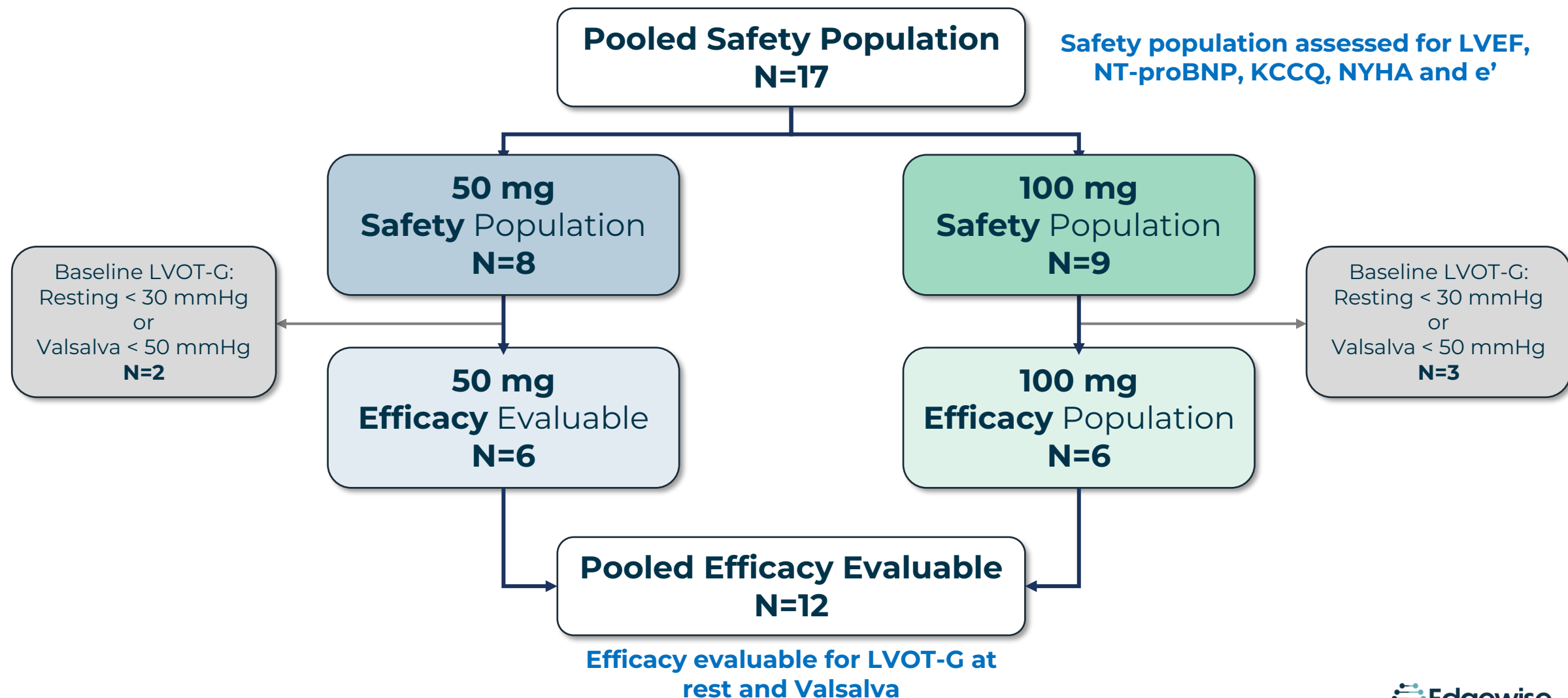
# Prespecified oHCM Efficacy Evaluable Population for LVOT-G

1. Received at least **1 dose of EDG-7500**
2. Baseline LVOT peak gradient  **$\geq 30$  mmHg measured at rest** and  **$\geq 50$  mmHg measured during the Valsalva** maneuver as determined by echocardiography
3. A **good acoustic window** and ability to obtain a high-quality transthoracic echocardiogram
4. No clinically significant cardiac structural abnormalities



## Part B – Obstructive HCM

# Cohort B (oHCM): 17 Patients Assessed as Part of the Safety Population; 12 Patients Met the Efficacy Evaluable Criteria



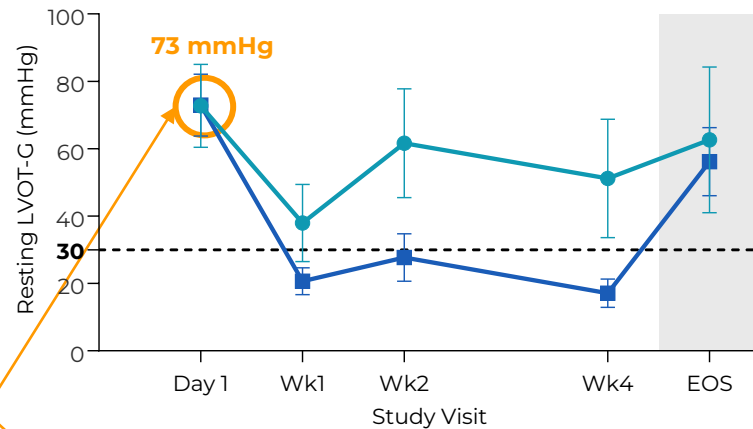
# EDG-7500 Led to Meaningful Reductions in LVOT-G at Rest & Post Valsalva Even at 50 mg, with Greater Reduction at 100 mg

Efficacy Evaluable

## Strong LVOT-G Responses Even in the Absence of Intra-Patient Dose-Optimization (N=12)

REST

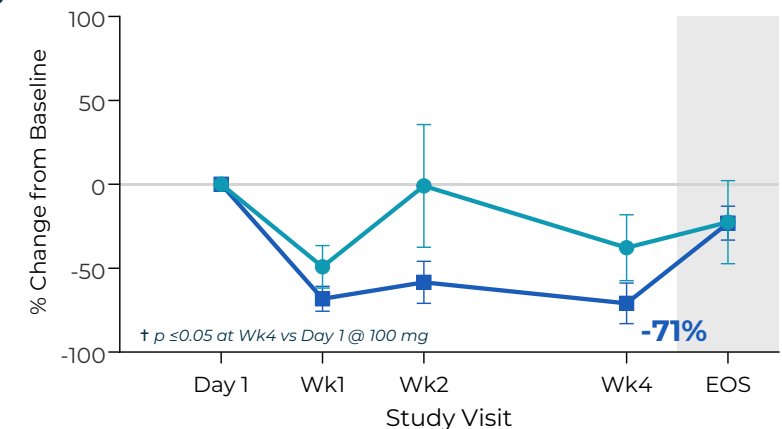
Absolute Value



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

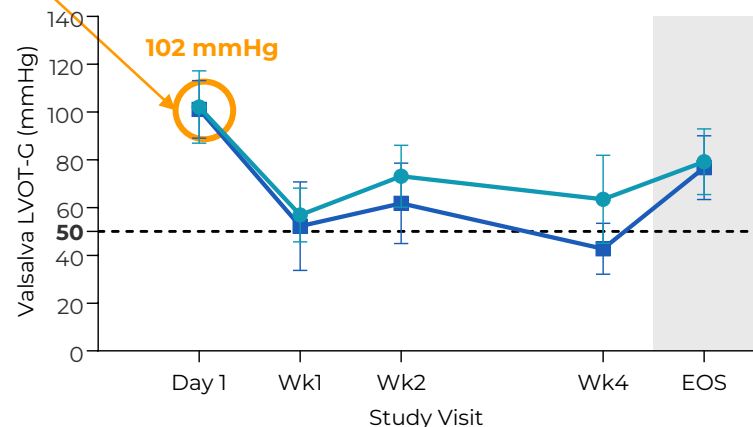
50 mg: **40%**  
100 mg: **83%**

% Change from Baseline



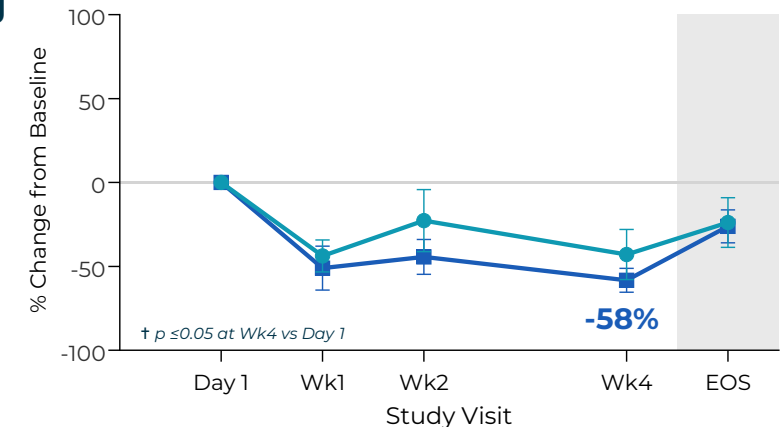
High Baseline Gradients

VALSALVA



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

50 mg: **60%**  
100 mg: **83%**



Means ± Std Err presented

\* % reaching LVOT criteria based on N=5 and N=6 participants with Week 4 data at 50 mg and 100 mg respectively.

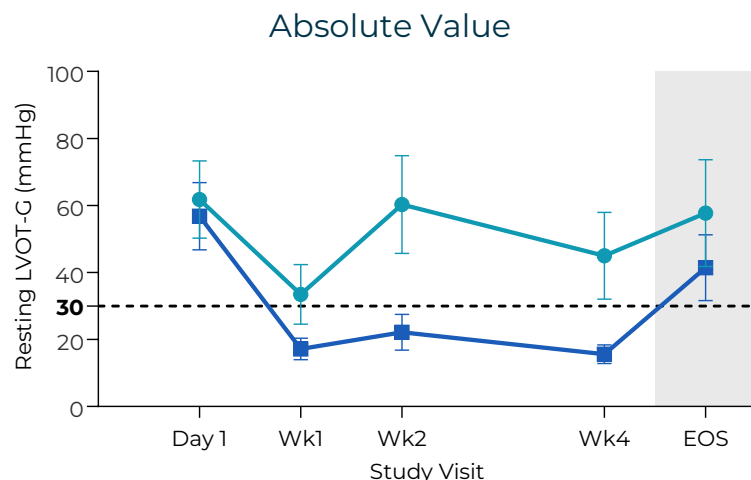
Edgewise Therapeutics – Data on file

# After Only 4 Weeks of Treatment, ~80% of oHCM Patients in the Safety Population Showed a Complete LVOT-G Response

Safety Population

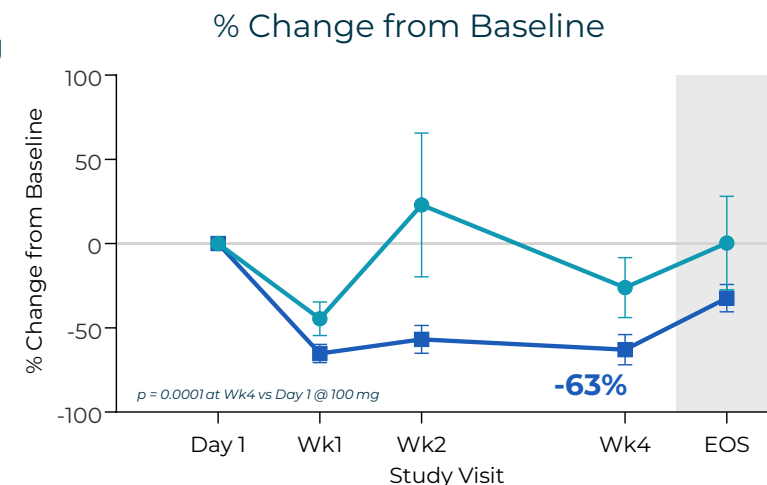
## Strong LVOT-G Responses Even in the Absence of Intra-Patient Dose-Optimization (N=17\*\*)

REST

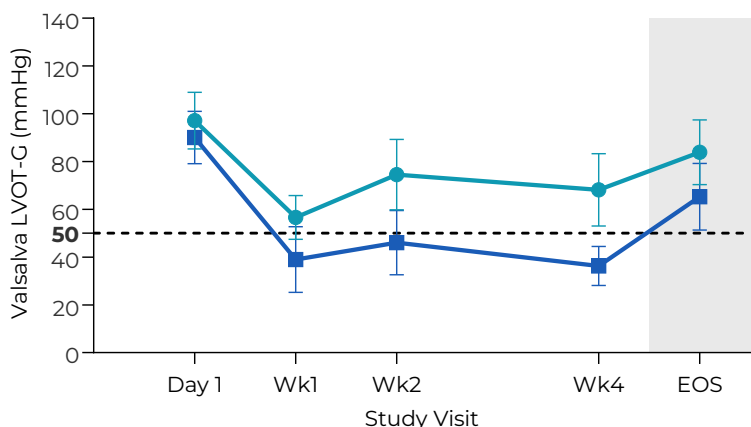


%\* Reaching LVOT <30 mmHg  
(Week 4)

50 mg: **43%**  
100 mg: **89%**

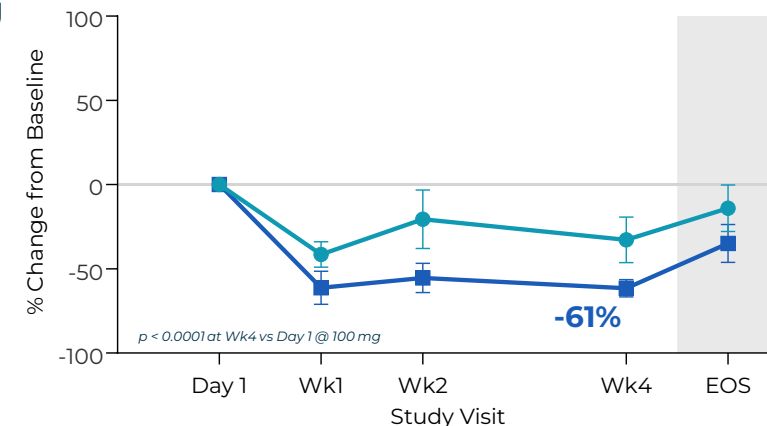


VALSALVA



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

50 mg: **57%**  
100 mg: **89%**



Means ± Std Err presented

Edgewise Therapeutics – Data on file. Complete LVOT-G response defined as resting and Valsalva gradients <30 mmHg and <50 mmHg, respectively

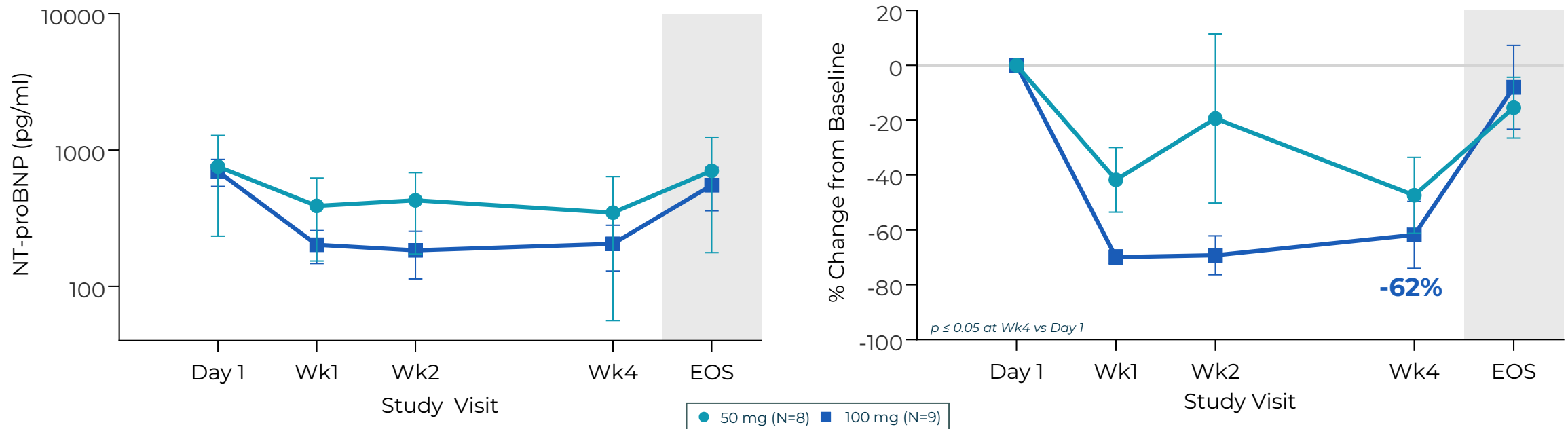
\*% reaching LVOT criteria based on N=7 and N=9 participants with Week 4 data at 50 mg and 100 mg respectively.

\*\* Five of the patients included in the Safety Population evaluation for LVOT had either resting or Valsalva gradients below clinical meaningful thresholds on Day 1

# EDG-7500 Resulted in Rapid and Robust Reductions in NT-proBNP, a Key Marker of Heart Failure in oHCM<sup>1</sup>

Safety Population

**5/9 (56%)** Patients at 100 mg Achieved <150 pg/ml NT-proBNP, the Threshold for Normal



**Improvements in NT-proBNP are Known to Show Strong Correlation to Improvements in pVO2**

Geometric means  $\pm$  Std Err for presented for values. Means  $\pm$  Std Err for % Change from Baseline

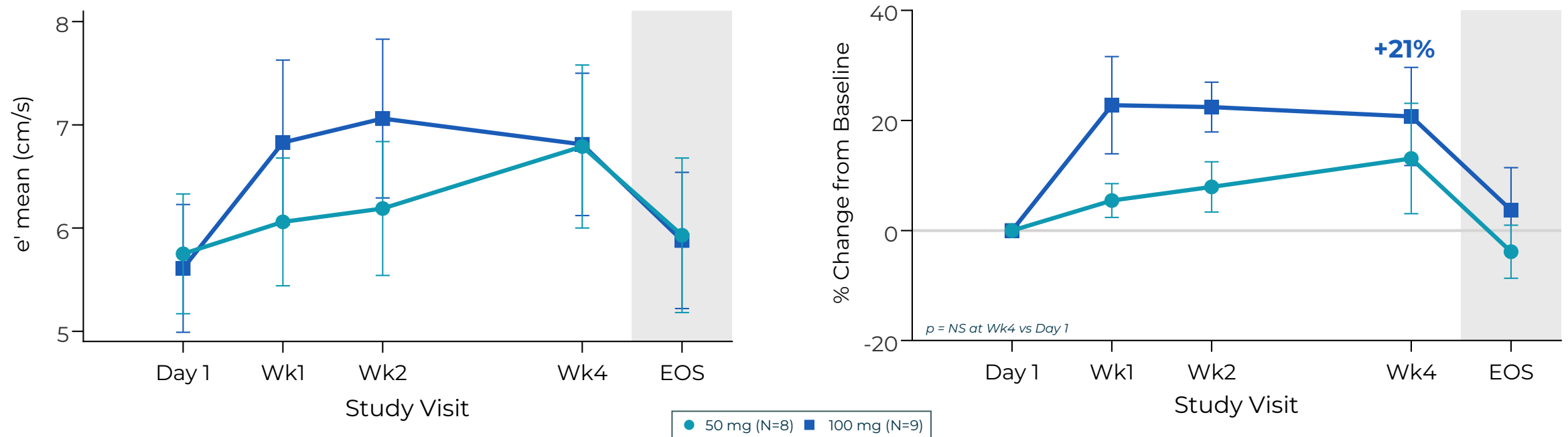
<sup>1</sup>Coats C.J. et al. European Heart Journal. 2013; 34(32), 2529–2537; Cytokinetics Presentation at the European Society of Cardiology Congress, 2024; London, UK; September 1, 2024 (Clinical Application of Biomarkers in Obstructive HCM: Insights from SEQUOIA-HCM)

Edgewise Therapeutics – Data on file

# Rapid and Sustained Increase in Early Diastolic Mitral Annulus Velocity (e') Suggesting an Improvement in Diastolic Function

Safety Population

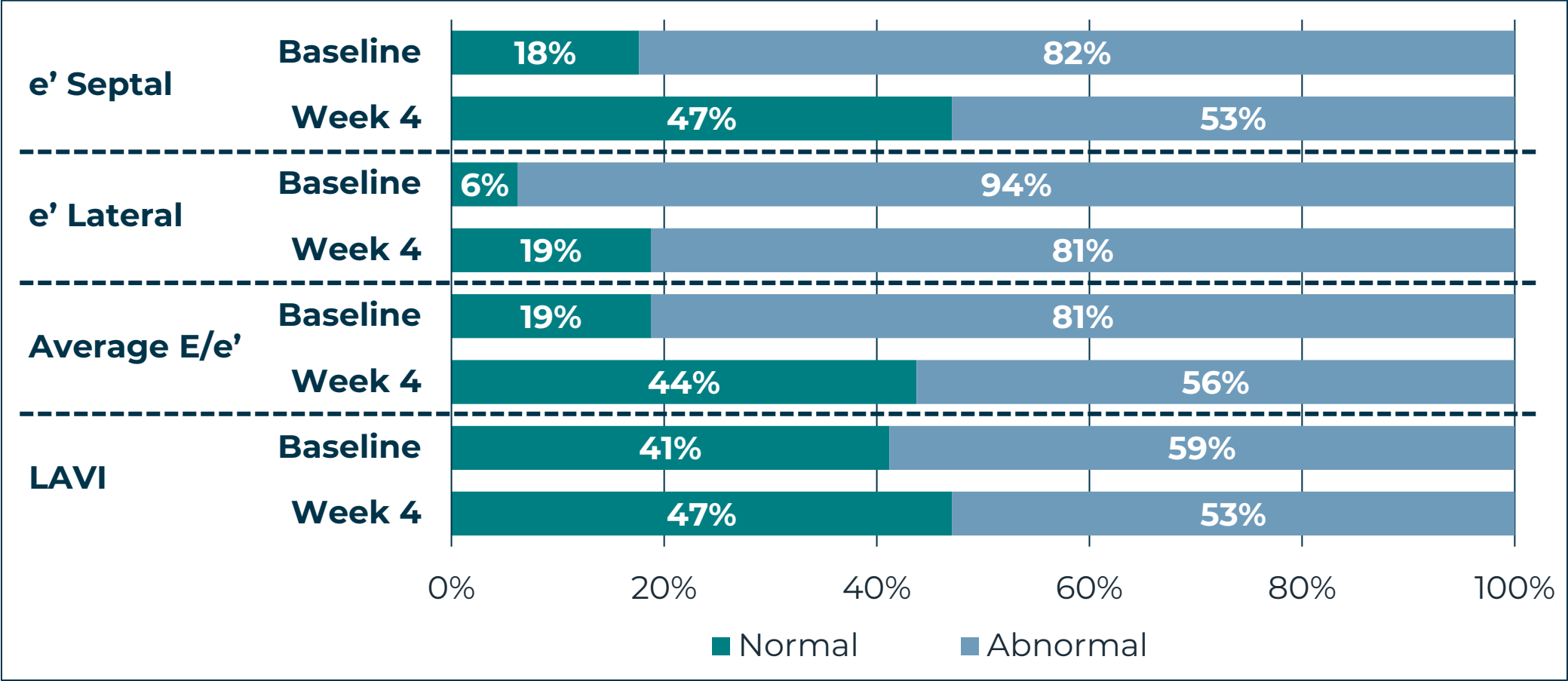
## Rapid Dose Responsive Improvements in Mean e' Observed as Early as 1 Week After Initiation of Treatment with EDG-7500



# EDG-7500 Led to Improvements in Left Ventricular Diastolic Function in Patients with oHCM

Safety Population

## More Patients Achieving Normal Diastolic Function Across a Number of Parameters



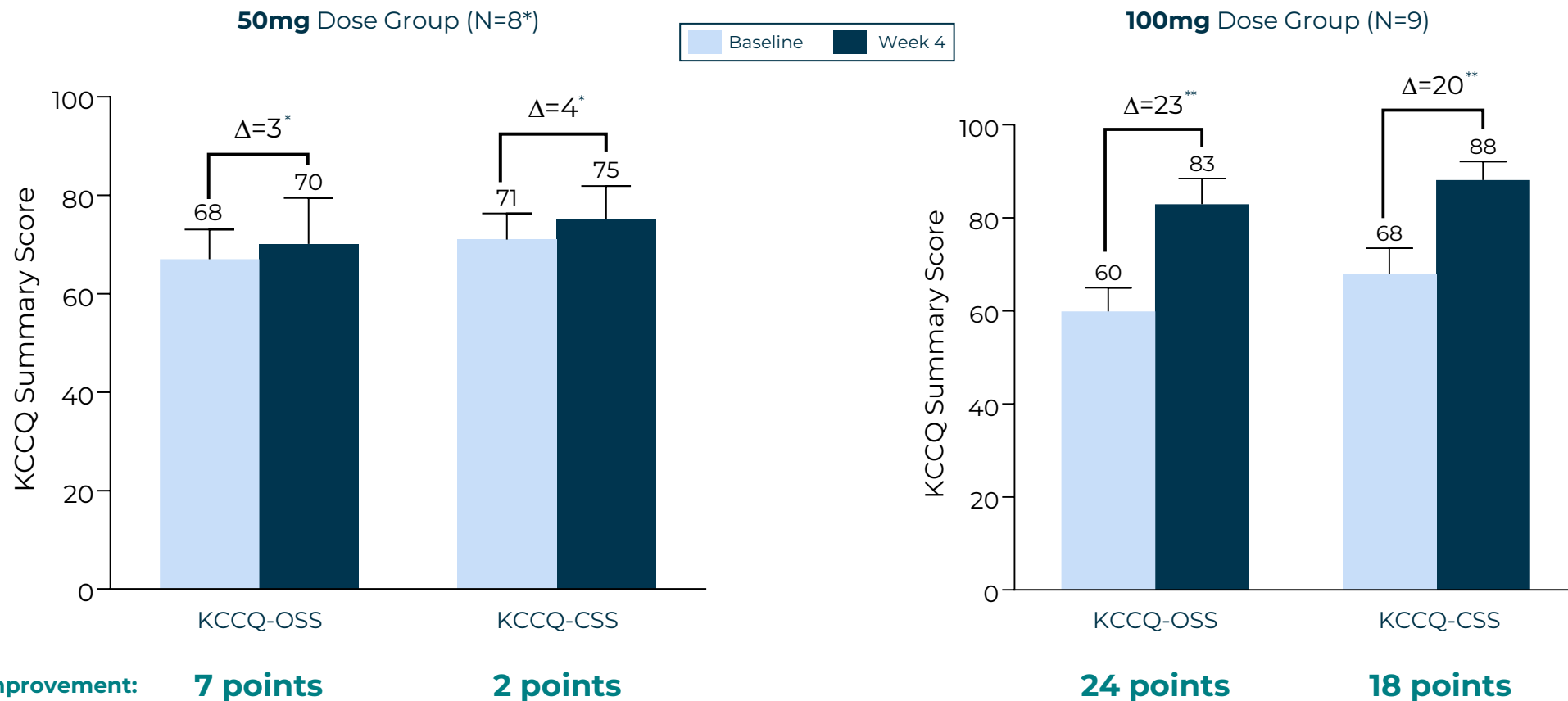
Abnormal Criteria: e' Septal < 7, e' Lateral < 10, E/e' mean >14, LAVI >34 (Criteria based on Hegde 2024)  
Note: if a Week 4 value was missing, the last non-missing value in the treatment period was used (LOCF).



# 89% of Participants on 100 mg had Improvements in Patient Reported Outcomes; Mean Increase in KCCQ-OSS of **23** points

Safety Population

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



\*p = NS at Wk4 vs Day 1

\*\*p < 0.005 at Wk4 vs Day 1

Means ± Std Err presented

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; CSS, clinical summary score; oHCM, obstructive hypertrophic cardiomyopathy

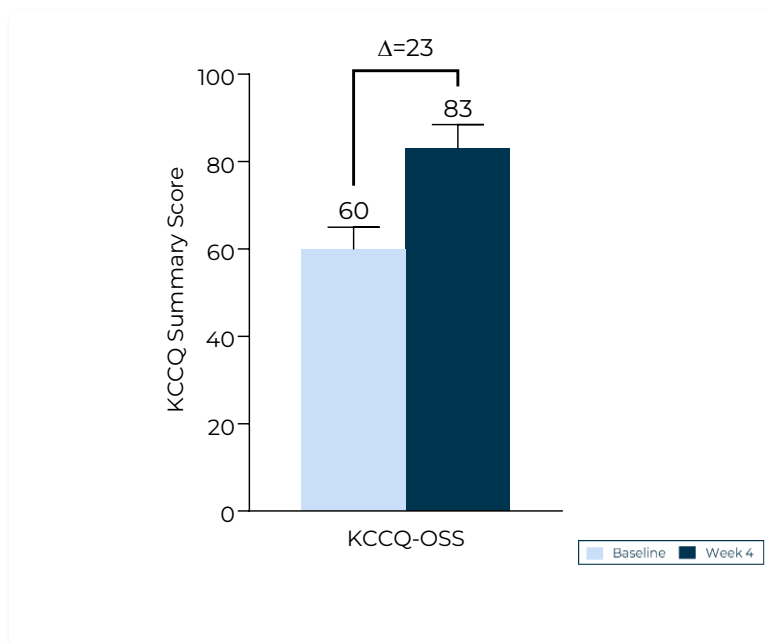
Edgewise Therapeutics – Data on file

\* Represents 7 individuals who were evaluated for KCCQ at week 4

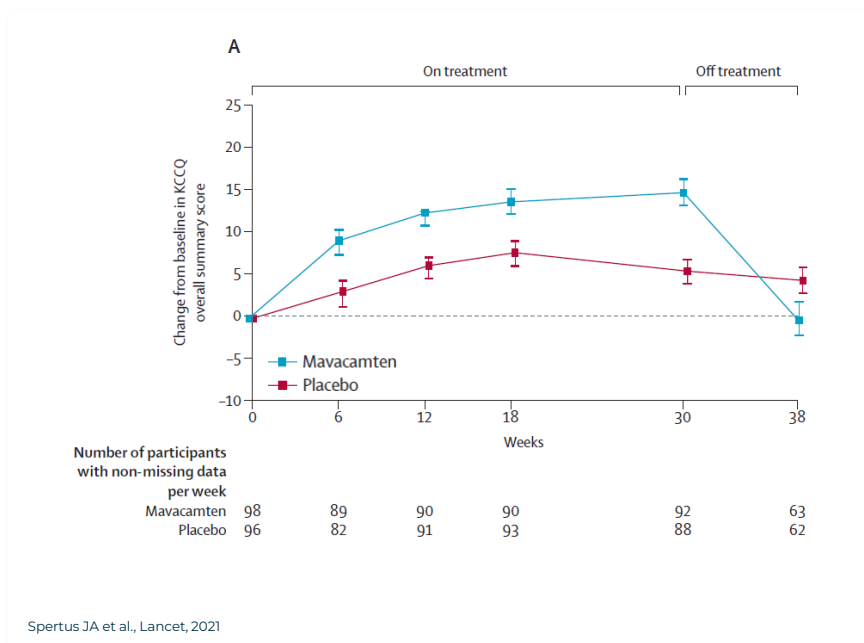
# The Positive KCCQ-OSS Changes with EDG-7500 in oHCM are Compelling Relative to What CMLs have Reported

## Safety Population

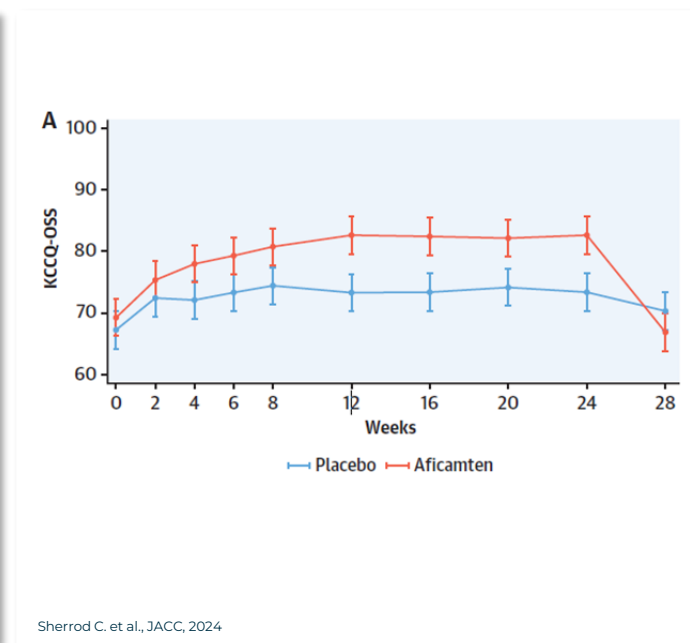
### 100 mg EDG-7500 KCCQ (N=9; 4 Weeks)



### KCCQ-OSS Changes with Mavacamten in EXPLORER-HCM (6 Months)



### KCCQ-OSS Changes with Aficamten in SEQUOIA-HCM (6 Months)



- Larger increases in KCCQ scores for EDG-7500 relative to Mavacamten and Aficamten
- Across multiple studies, KCCQ-OSS placebo effect accounted for 5-7 point increases

Note: To-date, no head-to-head comparisons of any other products to any of our product candidates in any clinical trial have been completed; results have been obtained from different trials with different designs, endpoints and patient populations; results may not be comparable.

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire - Overall Summary Score

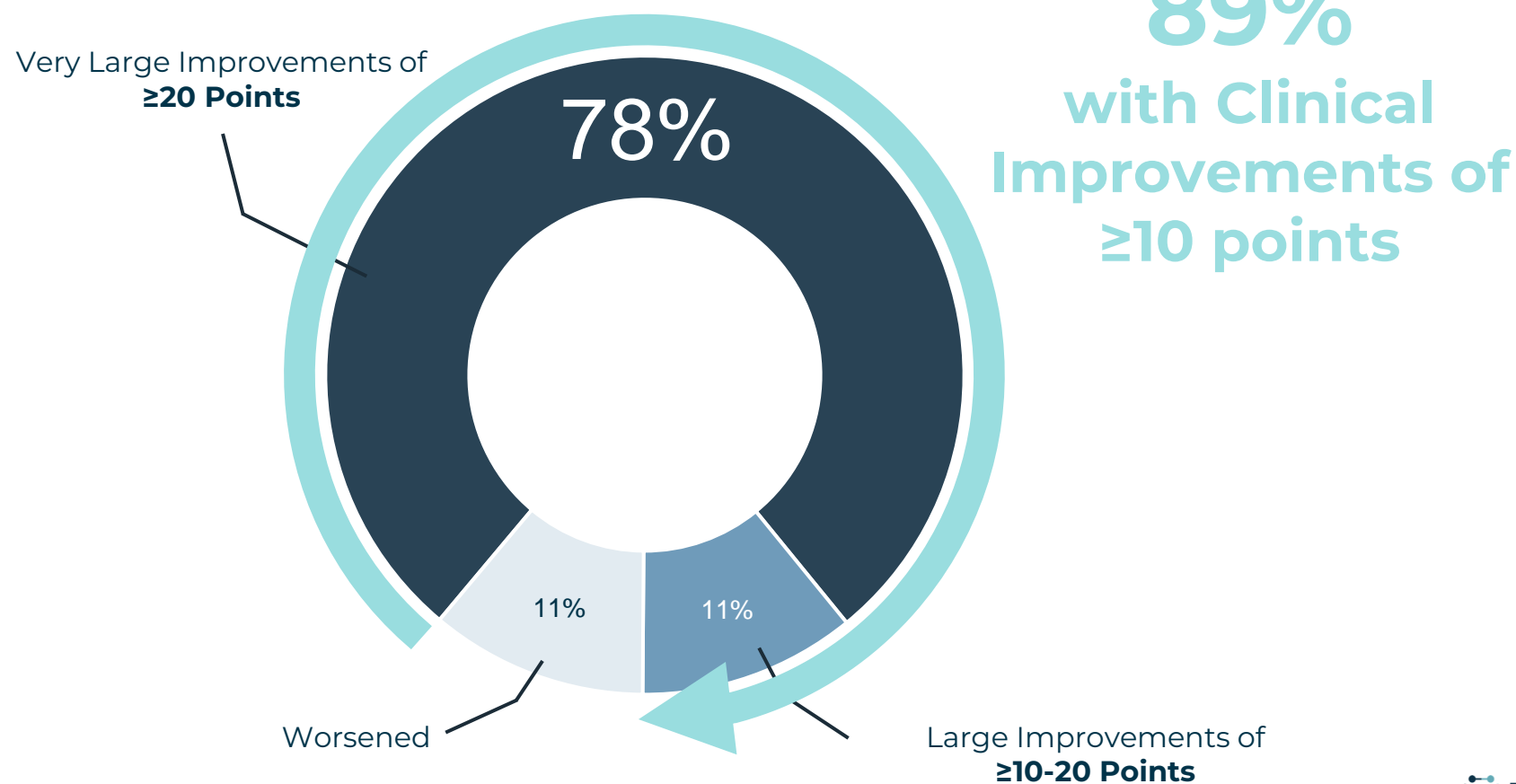
Maron M et al., N Engl J Med 2024;390:1849-1861; Maron M et al., JACC. 2024 Nov, 84 (19) 1821-1831; Sherrod CF et al., JACC. 2024; Spertus JA, Lancet, Volume 397, Issue 10293 p2467-2475 June 26, 2021

Edgewise Therapeutics – Data on file

# 78% of oHCM Patients Treated with 100 mg EDG-7500 Experienced Very Large Improvements in KCCQ-OSS

Safety Population

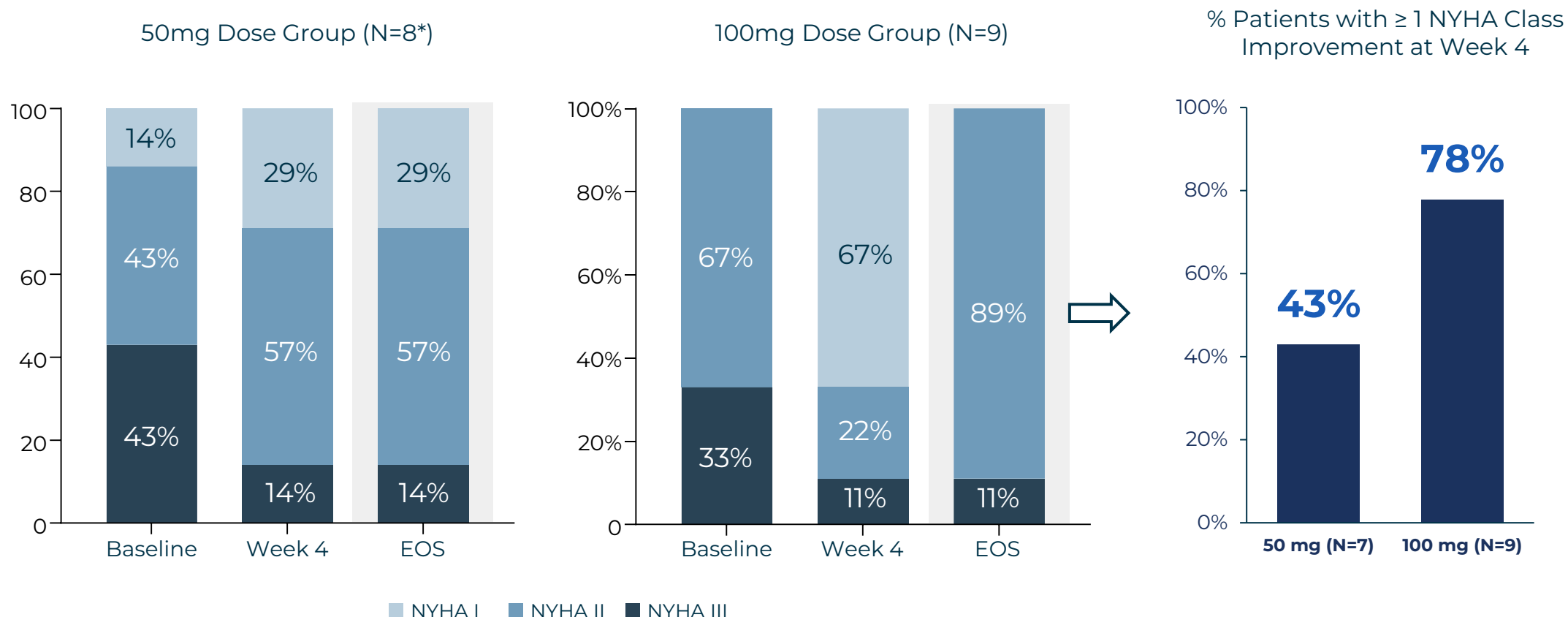
## KCCQ-OSS Changes with EDG-7500 in oHCM after 4 Weeks (100 mg) vs. Baseline



# 100 mg EDG-7500 Led to **78%** of Patients Achieving Improvements of $\geq 1$ NYHA Class; **67%** Achieved NYHA Class I

Safety Population

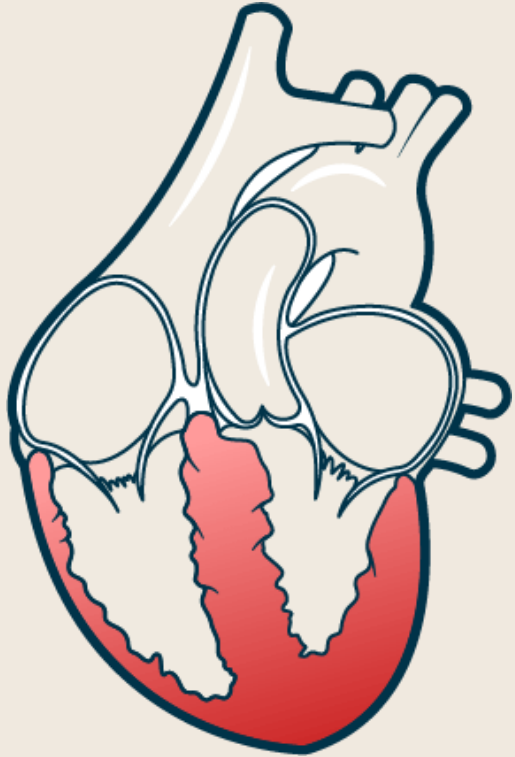
## NYHA Functional Class Improvements with EDG-7500 in oHCM at 4 Weeks



- ~40% of patients treated with a CMI in Ph 3 did not observe a  $\geq 1$  NYHA Class change end of study (at 6 mos.) when patients were on maximally efficacious doses
  - Percent of pts who did not experience a  $\geq 1$  NYHA functional class improvement with mavacamten and aficamten were 35% and 42%, respectively

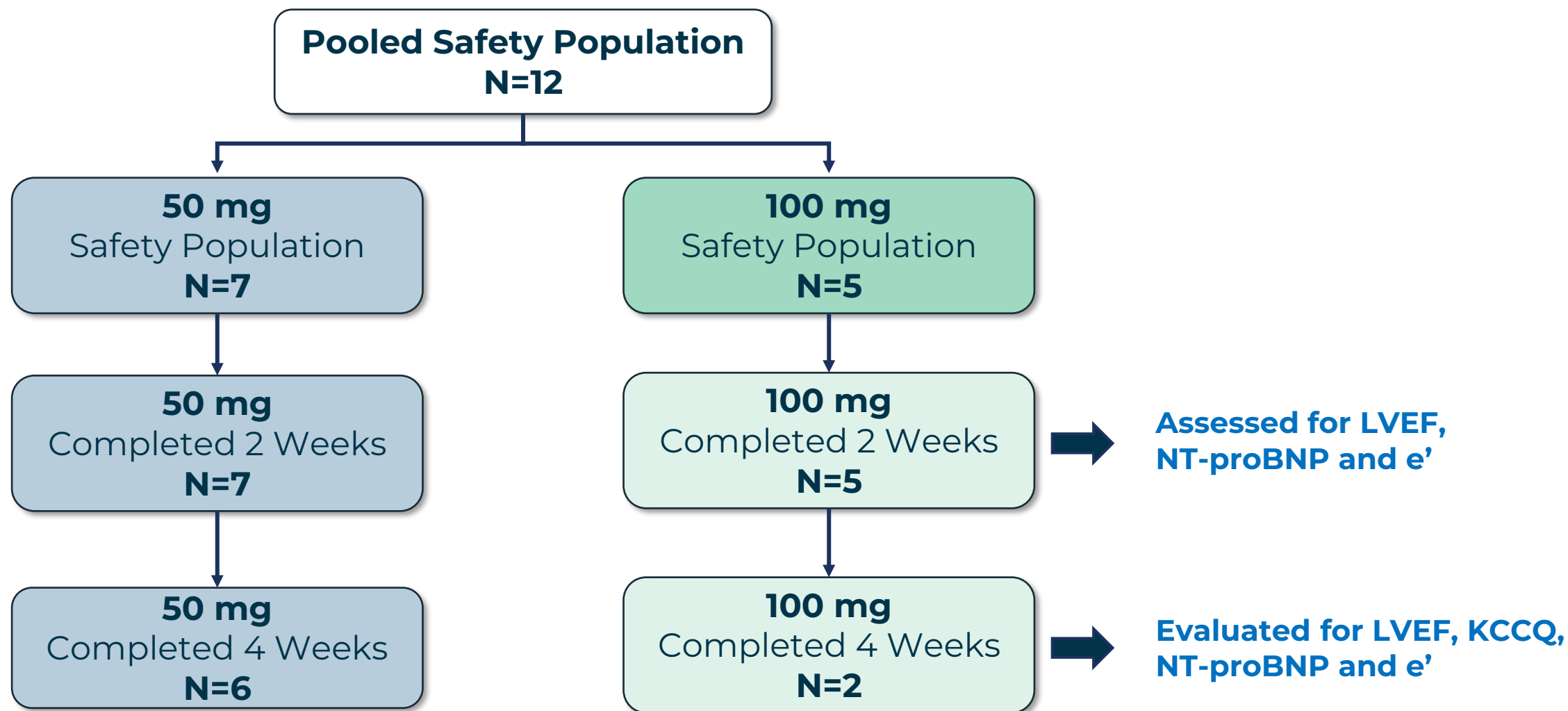
Abbreviation: NYHA, New York Heart Association Functional Classification  
Maron M et al., N Engl J Med 2024;390:1849-1861; Olivotto I. et al. The Lancet 2020; 396(10253), 759-769.  
Edgewise Therapeutics – Data on file

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

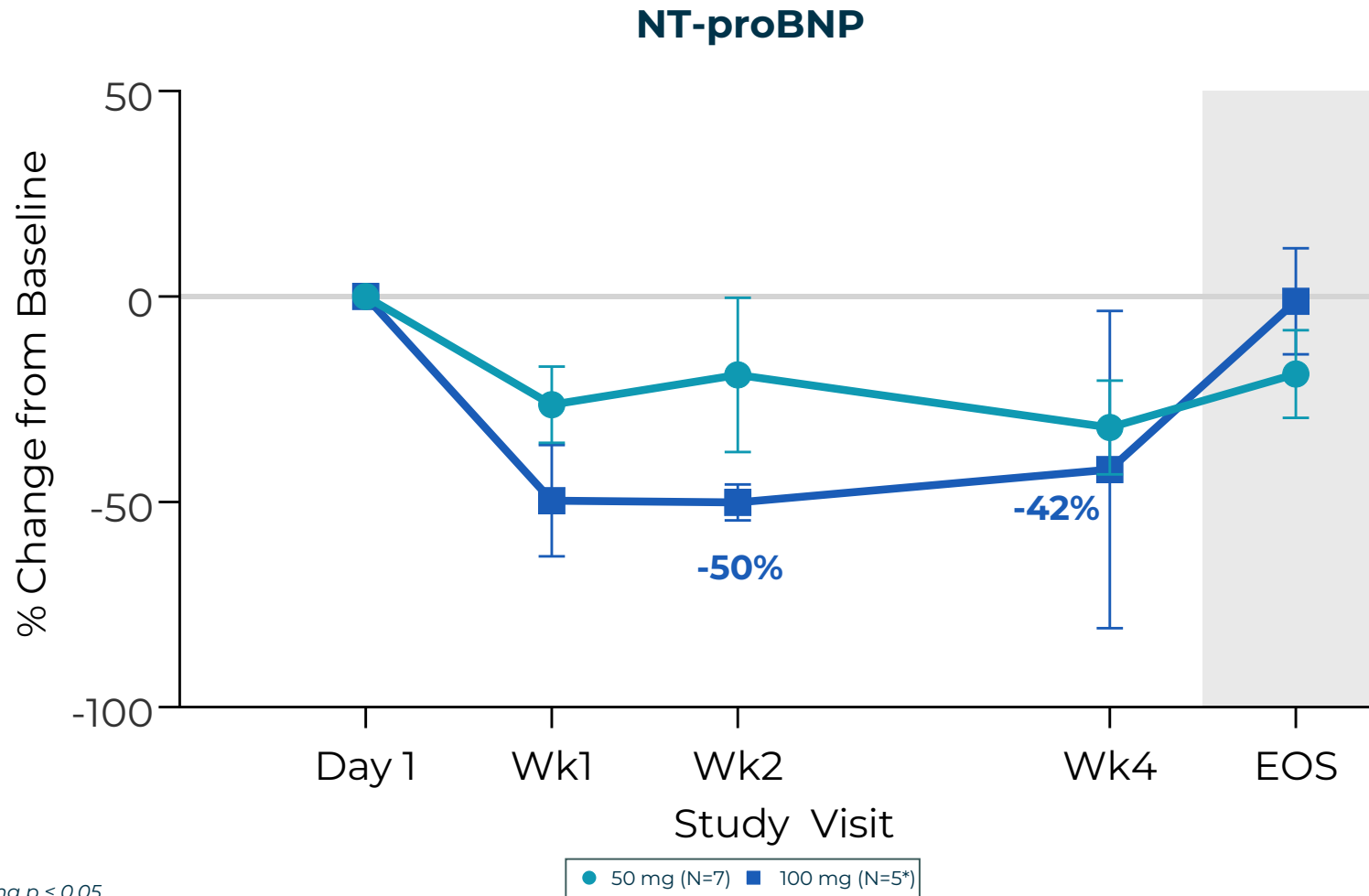


## Part C – Nonobstructive HCM

# Cohort C (nHCM): 12 Patients Evaluated as Part of the Safety Population; 8 Patients Completed All 4 Weeks of Treatment



# Like oHCM Patients, EDG-7500 Resulted in Rapid and Robust Reductions in NT-proBNP in Patients with nHCM



Wk2 vs Day 1: 50 mg  $p = NS$ ; 100 mg  $p \leq 0.05$

Wk4 vs Day 1: 50 mg  $p \leq 0.05$ ; 100 mg  $p = NS$

Means  $\pm$  Std Err presented

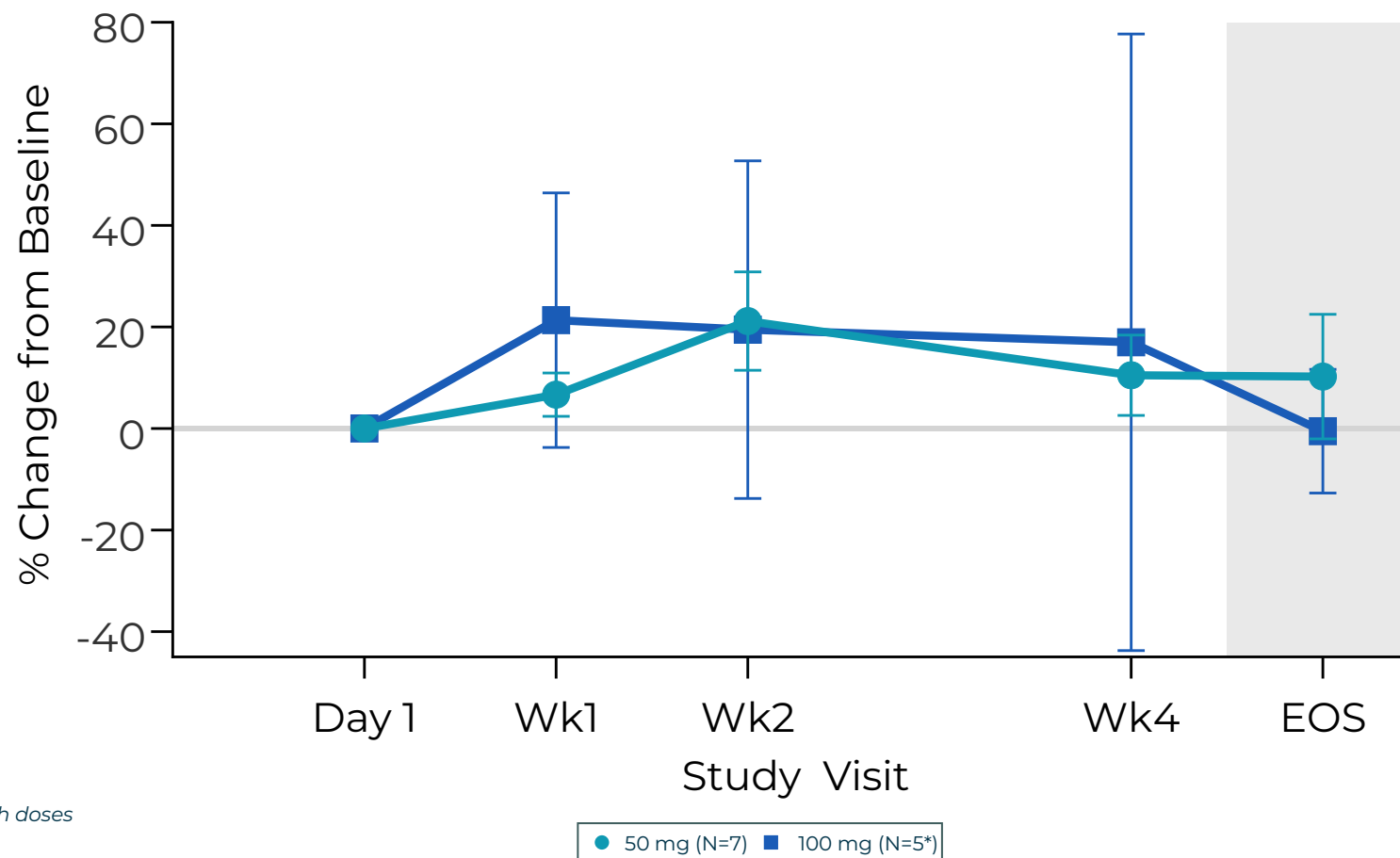
\* Two patients at week 4

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; nHCM, nonobstructive hypertrophic cardiomyopathy

Edgewise Therapeutics – Data on file

# EDG-7500 Led to Early and Rapid Signs of Diastolic Improvements in nHCM Participants after Only 4 Weeks

## Treatment with EDG-7500 Led to Mean e' Changes in nHCM Patients as Early as One Week Following Initiation of Dosing



Wk2/Wk4 vs Day 1:  $p = 0.05$  at both doses

Means  $\pm$  Std Err presented

\* Two patients at week 4

Abbreviations: nHCM, nonobstructive hypertrophic cardiomyopathy

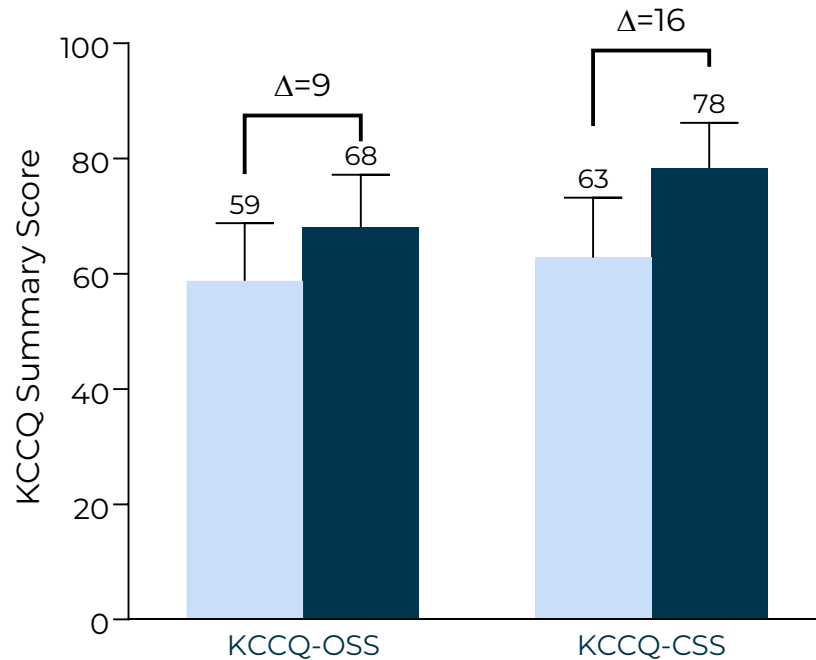
Edgewise Therapeutics – Data on file



# Preliminary KCCQ Observations with EDG-7500 in nHCM Suggest Improvements Beyond Those Observed with CMIs

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

50mg Dose Group (N=6)

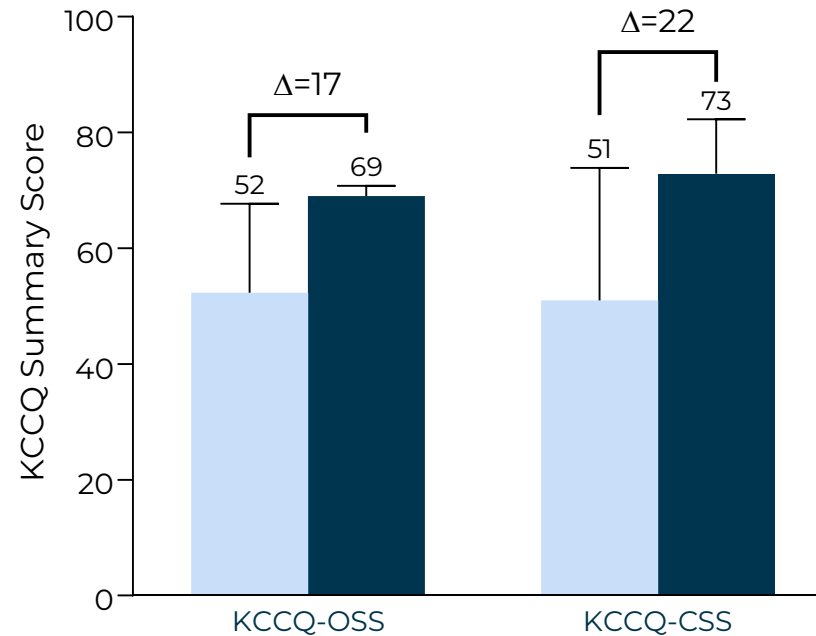


Median KCCQ Improvement:

**12 points**

**11 points**

100mg Dose Group (N=2)



**17 points**

**22 points**

Baseline Week 4

Wk4 vs Day 1:  $p = NS$  at both doses across both KCCQ measures

- **No meaningful improvement in KCCQ with CMIs:**

- MAVERICK (**16-week** study; placebo controlled) and REDWOOD Cohort 4 (**10-week** study; no placebo) showed KCCQ-OSS and KCCQ-CSS improvements of **+6 point** and **+10.6 points**, respectively in nHCM (both Phase 2 studies)

Means  $\pm$  Std Err presented

Note: To-date, no head-to-head comparisons of any other products to any of our product candidates in any clinical trial have been completed; results have been obtained from different trials with different designs, endpoints and patient populations; results may not be comparable.

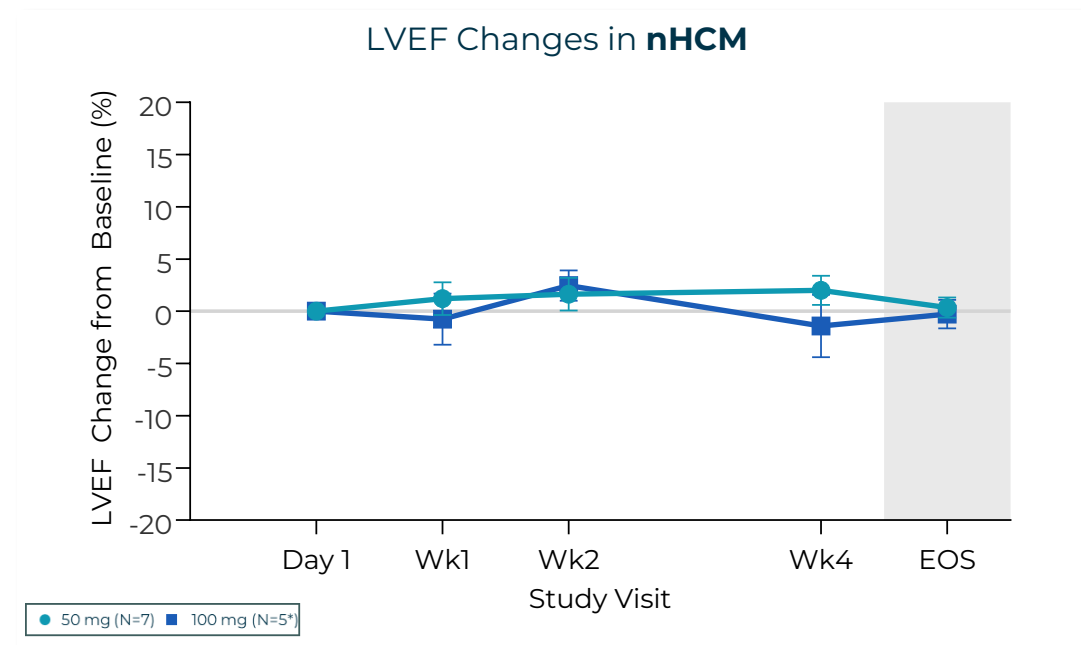
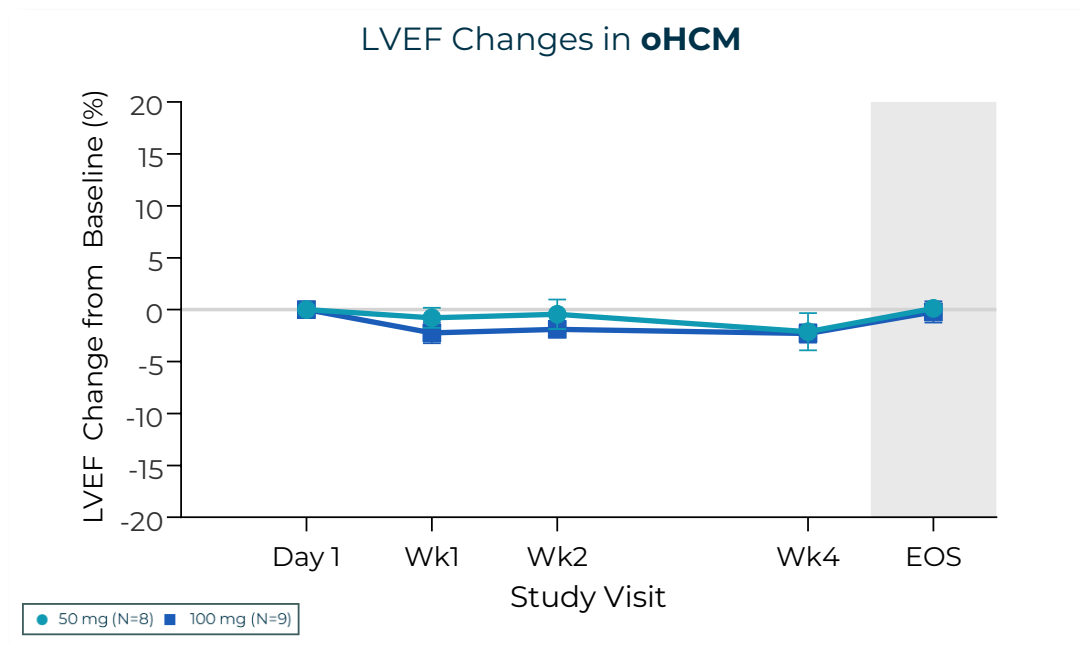
Ahmad Masri Presentation at World Congress on Acute Heart Failure, 20 May 2023: Evaluation of Aficamten in Patients with Symptomatic N on obstructive Hypertrophic Cardiomyopathy: REDWOOD HCM Cohort 4; Ho C et al., JACC, Volume 75, Issue 21, 2 June 2020, Pages 2649-2660

Edgewise Therapeutics – Data on file

# **EDG-7500 Safety in Parts B and C**

# EDG-7500 Continues to Demonstrate **No Meaningful Reductions in LVEF**; **No Participants had LVEF Drops <50%**

## No Correlation Between EDG-7500 Plasma Concentration and LVEF Change



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

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%

# EDG-7500 was Generally Well Tolerated in oHCM Participants in Part B and nHCM Participants in Part C

## Safety Summary for EDG-7500 in CIRRUS Parts B (oHCM) and C (nHCM)

Treatment Emergent Adverse Events (TEAE)	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 Part B and Part C.

\* A total of 3 oHCM patients and 1 nHCM patient had new onset atrial fibrillation; two of these events were considered SAEs

- Two oHCM patients were determined to have not met entry criteria on post-hoc review by two non-Sponsor echo reviewers (one blinded); these patients would be excluded in Phase 3 since both patients would not meet criteria for HCM diagnosis based on wall thickness in addition to:
  - Significant mitral annular calcification with mild/moderate mitral stenosis (one patient at 50 mg)
  - Hypertension, thyroid disease, diabetes, and obstructive lung disease (one patient at 100 mg)
- One oHCM (100 mg) patient had significant baseline mitral regurgitation and an enlarged left atrium
- One nHCM (100 mg) patient had a markedly large left atrial volume index (50.2 ml/m<sup>2</sup>) and a left atrial diameter (60 mm) with a significantly reduced left atrial reservoir strain, all well-established predictors of new onset atrial fibrillation
- None of the patients who had atrial fibrillation experienced LVEF <50% at any time
- One participant discontinued treatment due to moderate dizziness

# Atrial Fibrillation Rates Observed in the HCM Patients in CIRRUS are Similar to Rates Observed in CMI Trials

## Summary of Atrial Fibrillation Rates in HCM Clinical Trials

Mavacamten	PIONEER <sup>1</sup>	EXPLORER <sup>2</sup>	VALOR <sup>3</sup>	VALOR BL-128w <sup>4</sup>	MAVERICK (nHCM) <sup>16</sup>	MAVA-LTE (oHCM) <sup>11</sup>	Integrated Safety - PIONEER, EXPLORER, VALOR, and MAVA-LTE <sup>14</sup>
	Coh A / Coh B	Mava / pbo	Mava / pbo	Mava	Gr1 / Gr2 / pbo	Median time 166.1 wks.	
Reported AF (%)	3 (27%) / 1 (10%)	10 (8.1%) / 10 (7.8%)	4 (7.1%) / 0 (0%)	11 (10.2%)	0 (0%) / 3 (14.3%) / 1 (5.3%)	33 (14.3%)	58 (15.8%)

Aficamten	REDWOOD <sup>5</sup>	REDWOOD <sup>6</sup>	SEQUOIA <sup>7</sup>	Integrated Safety Analysis <sup>8</sup>		FOREST-HCM (SoC withdrawal) <sup>9</sup>	FOREST-OLE <sup>10</sup>
	C1 / C2 / C3	C4 (nHCM)	Afi / pbo	Cumulative Afi	Afi / pbo	Yes attempt/No attempt	nHCM
Reported AF (%)	2 (5.2%)	1 (2.4%)	4 (2.8%) / 4 (2.9%)	12 (4.2%)	4 (2.4%) / 5 (3.3%)	5 (7.8%) / 3 (4.2%)	2 (5.9%)

EDG-7500	CIRRUS HCM
	Cumulative Part B & C
Reported AF (%)	4 (13.8%)



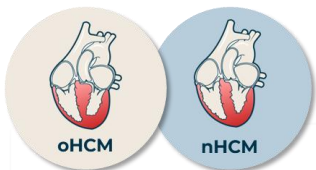
Exclusion of the two oHCM patients who were determined to have **not met entry criteria** on post-hoc review, results in a rate of **7.4%**

- AF prevalence of approximately 25% in patients with HCM; >40% among HCM pts with severe LV dysfunction or >70 yrs<sup>15-18</sup>
- The overall incidence of post-operative atrial fibrillation after septal myectomy for HCM was reported to be 30-35%<sup>12-13</sup>

**HYPOTHESIS:** AF rates tend to go down from Ph 2 to Ph 3 in CMI trials in part driven by **more rigorous patient selection**, exemplified with CAMZYOS™ in PIONEER (16% screen fail rate) vs EXPLORER (41% screen fail rate) and **individualized dose optimization** for efficacy

<sup>1</sup> Heitner S. et al. *Ann. Intern. Med.* 2019; 170:741-748; <sup>2</sup> CAMZYOS FDA Clinical and Statistical Review(s) document. Treatment-emergent serious adverse events of AF recorded in EXPLORER (Olivotto et al., 2020) were 2 (2%) in the mavacamten arm and 4 (3%) in the placebo arm, while 8 (6.5%) in the mavacamten arm and 9 (7.0%) in placebo arm had AF recorded as cardiovascular treatment-emergent adverse events occurring in ≥1% of patients in any group (Olivotto et al., 2020 Appendix Table S1 pg 6); <sup>3</sup> Desai M. et al. *JACC* 2022; 80(2): 95-108. AF recorded as serious on-treatment adverse event in 2 (3.6%) subjects on mavacamten and 0 (0%) on placebo, and an additional 2 (3.6%) recorded AF as nonserious on-treatment adverse event in the mavacamten arm and 0 (0%) in the placebo arm; <sup>4</sup> Desai M. et al. *Circulation*. 2024; 150. New onset AF events were recorded; <sup>5</sup> Masri et al., Poster #352 HFSA'2022 REDWOOD C1-C3 OLE; <sup>6</sup> Masri et al., ACC'2023 Poster, Heart Failure presentation 2023 (SAE of new onset AF), Masri A. et al. 2024; <sup>7</sup> Maron et al., NEJM 2024; 390:1849-61; <sup>8</sup> Cytokinetics Corporate press release September 1, 2024; <sup>9</sup> Masri et al., 2024 JACC. AF or flutter requiring medical intervention; <sup>10</sup> Masri et al., 2024 E J of HF; <sup>11</sup> Garcia-Pavia et al., European Heart Journal (2024) 45, 5071-5083; Sun D et al., Ann Thorac Surg. 2022 Jun;113(6):1918-1924; <sup>12</sup> Canadian Journal of Cardiology, Volume 39, Issue 12, December 2023; <sup>13</sup> Kharbanda R et al., International Journal of Cardiology 328 (2021) 63-68; <sup>14</sup> Dr. Anjali Owens Presentation at AHA 2024; <sup>15</sup> Ho C. et al. *JACC* 2020; 75(21): 2649-60; <sup>16</sup> Fumagalli C. et al. *Cad J Cardiol*. 2024; 40(5):876-886; <sup>17</sup> Rowin J. et al. *Circulation*. 2017; 136(25); <sup>18</sup> Falasconi G. et al. *Am J Cardiovasc Dis*. 2020; 10(4):409-418; <sup>19</sup> Garg L. et al. *Heart Fail Rev*. 2019; 24:189-197

# Summary Remarks



- EDG-7500 is emerging as an **exciting potential new therapeutic** option for both oHCM and nHCM
- The prospect of using EDG-7500 to improve LVOT-G, NT-proBNP, e', KCCQ and NYHA **without reductions in LVEF** could allow treatment of a broader pool of HCM patients **without the need for safety echoes**
- EDG-7500 appears to be **generally well tolerated** across a broad exposure range
- Dose optimization for efficacy in CIRRUS Part D, may lead to **deepening of clinical and feel-and-function responses** observed in Parts B and C
- Refinements to Part D's patient selection criteria and dose optimization should **continue to strengthen EDG-7500's profile** heading into Phase 3 trials next year



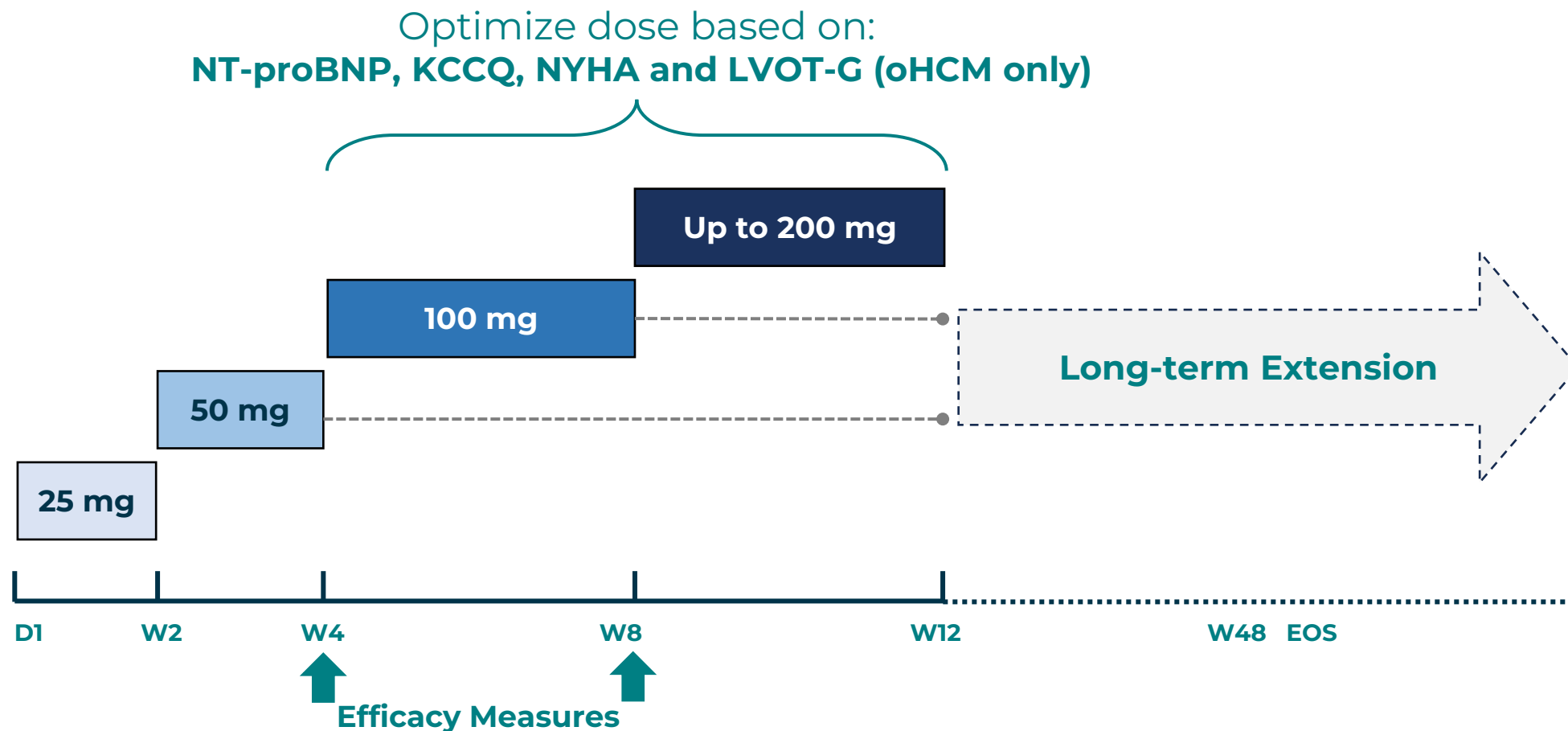
# EDG-7500 Future Development Plans

Dr. Robert Blaustein

*Chief Development Officer*

# CIRRUS-HCM Part D: Updated Design in oHCM and nHCM on Path to Phase 3 Start in 1H2026

## Positive Observations from CIRRUS Part B and C Inform Intra-Patient Dose Optimization in CIRRUS Part D



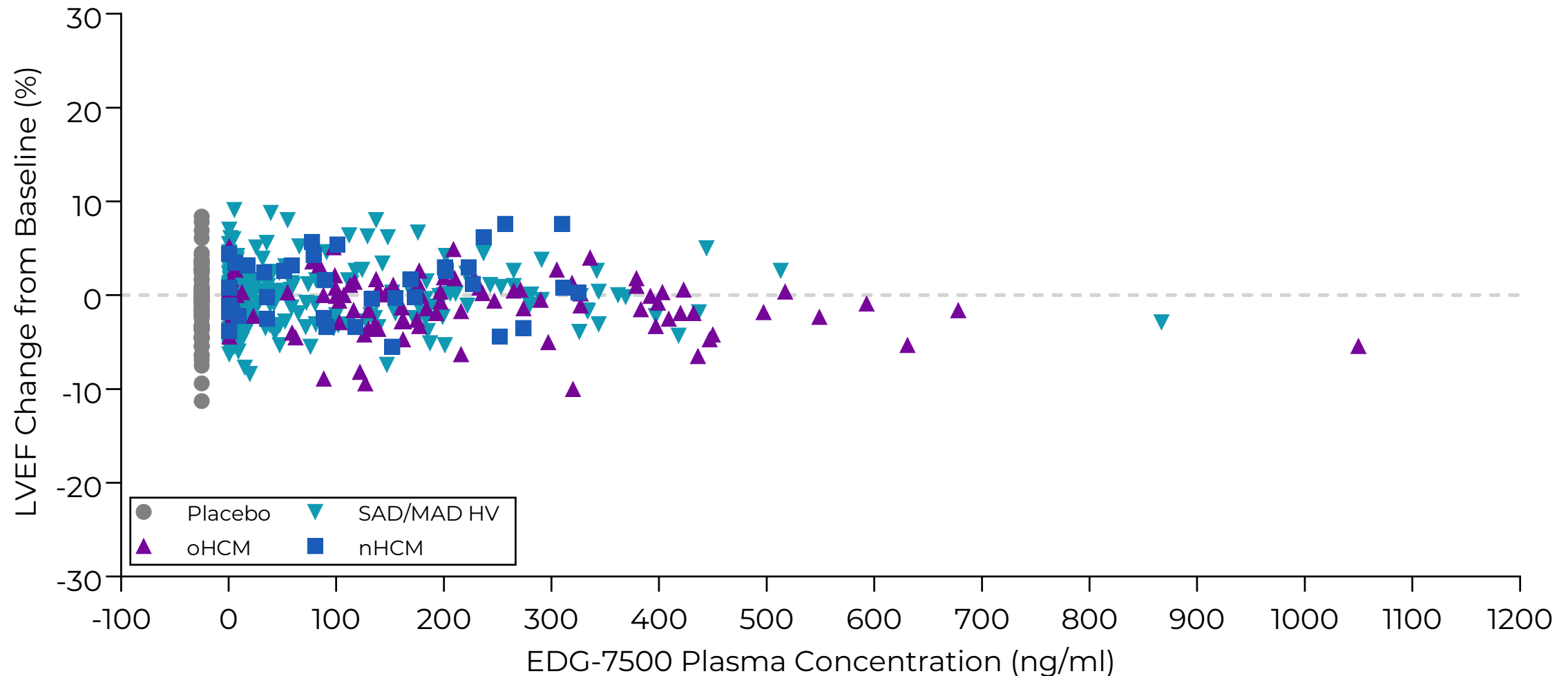


A photograph of a smiling couple standing outdoors. The woman on the left has curly hair and is wearing a black puffer jacket. The man on the right is wearing a dark beanie and a green jacket. They are both smiling and looking towards the right. The background features a large, colorful geometric shape with teal, red, and dark blue sections.

# Closing Remarks

Kevin Koch, CEO

## Pooled Healthy Volunteer and CIRRUUS Data

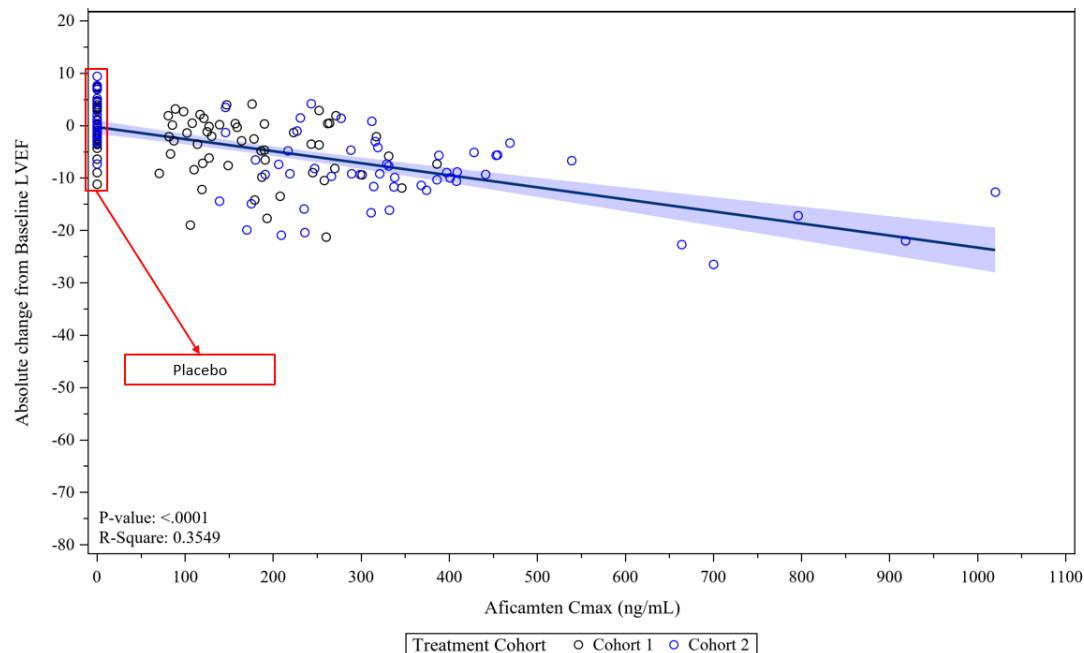


Abbreviations: LVEF, left ventricular ejection fraction

# Conversely, Treatment with Aficamten in REDWOOD Demonstrated an **Exposure Dependent Decrease in LVEF**

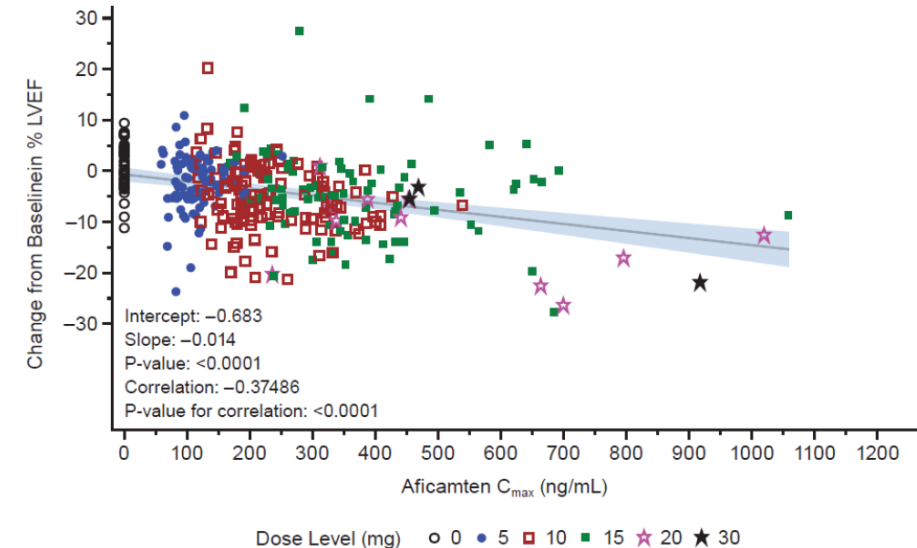
## REDWOOD Phase 2 Studies of Aficamten: As much as a 25% Absolute LVEF Reduction Observed with Aficamten Even at Low Plasma Exposures

REDWOOD Cohorts 1 and 2 (oHCM)



REDWOOD Cohort 1-4

Fig. S4. Relationship of plasma *aficamten* concentration to left ventricular ejection fraction<sup>a</sup>



<sup>a</sup> Intercept slopes were estimated from a MMRM model with LVEF change from baseline as dependent variable, baseline by group (Cohorts 1, 2, 3, or 4), and maximal day match post-baseline PK concentration by group as explanatory variables. Random participant effect was specified. Regression line from simple regression of LVEF change over log-transformed max day post-baseline PK concentration is plotted.

LVEF, left ventricular ejection fraction; MMRM, mixed-model repeated measures; PK, pharmacokinetic.

Abbreviations: LVEF, left ventricular ejection fraction

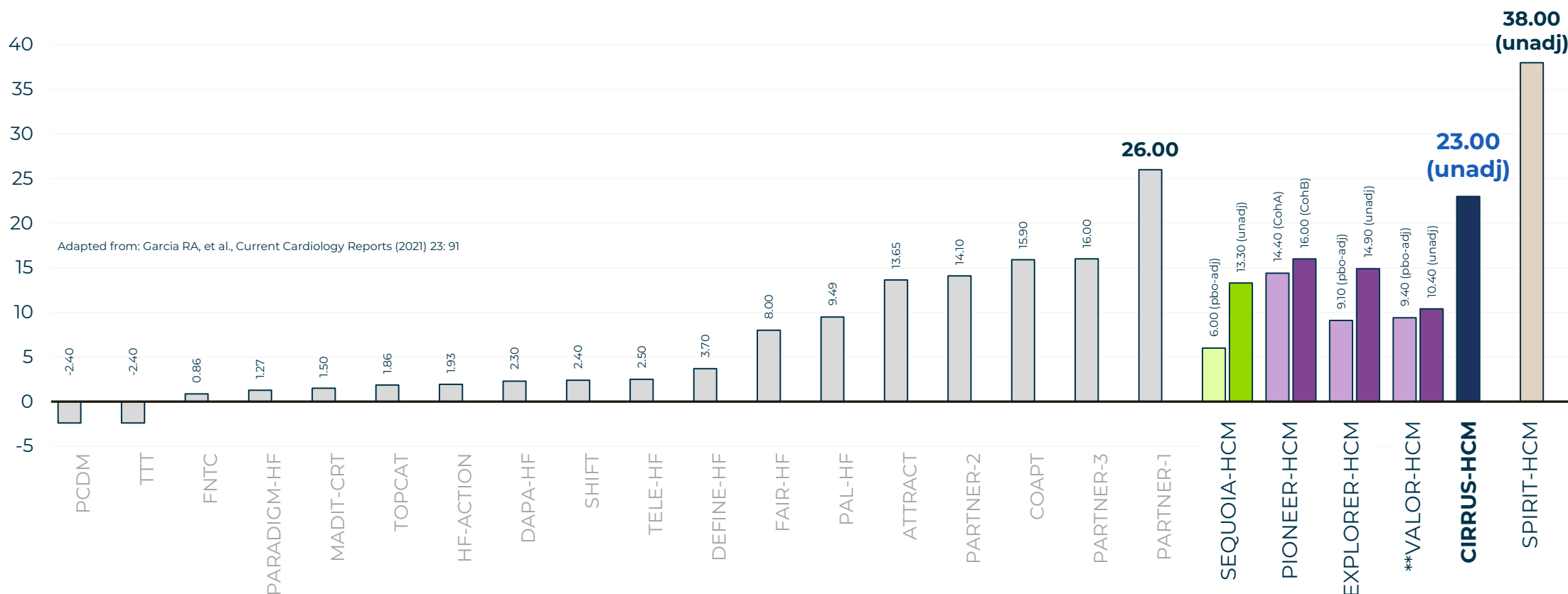
Note: To-date, no head-to-head comparisons of any other products to any of our product candidates in any clinical trial have been completed; results have been obtained from different trials with different designs, endpoints and patient populations; results may not be comparable.

Masri A et al., Journal of Cardiac Failure 30 (2024) 1439 1448; Maron M et al., Journal of the American College of Cardiology vol. 81, no.1, 2023

# EDG-7500 Led to KCCQ Improvements that **Compare Favorably to Efficacy-Optimized oHCM Patients on CMIs**

**Despite Being Medically More Complex, oHCM Patients Treated with 100 mg EDG-7500 Demonstrated a 23 Point KCCQ-OSS Improvement, Greater than That Observed in Any CMI Trial to Date**

KCCQ Mean Difference Changes in Clinical Trials Including CMIs and EDG-7500\*



Note: To-date, no head-to-head comparisons of any other products to any of our product candidates in any clinical trial have been completed; results have been obtained from different trials with different designs, endpoints and patient populations; results may not be comparable.

Speratus J. et al. The Lancet 2021; 397(10293), 2467-2475; Sherrod C. et al. JACC 2024; 84(19); Desai M. et al. JACC 2022; 80(2), 95-108; Heitner S. et al. Ann. Intern Med. 2019; 170:741-748; Desai M. et al. JAMA Netw Open. 2022; 5(4):e227293

\* Data for CMIs and EDG-7500 in obstructive HCM

\*\* VALOR-HCM figures are KCCQ-CSS vs all other trials are KCCQ-OSS

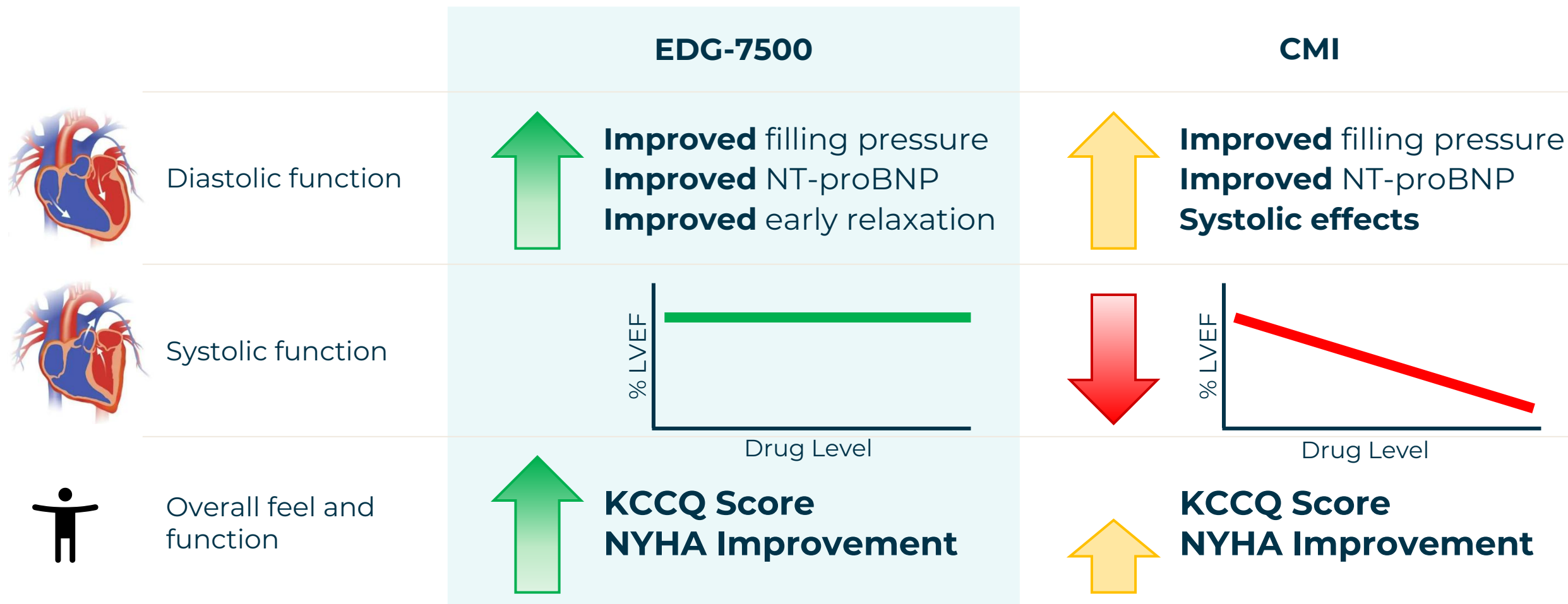
# CIRRUS Part B and Part C Outcomes are Especially Impressive Considering More **Medically Complex Patients** were Enrolled

Observations from CIRRUS Part A Demonstrating EDG-7500's Lack of Reductions in Systolic Performance Allowed Us to Also Treat More Medically Complex oHCM Patients

Baseline Characteristics	CIRRUS nHCM (Safety; n=12)	CIRRUS oHCM (Safety; n=17)	EXPLORER-HCM (n=251)	SEQUOIA-HCM (n=282)
Age (yrs.)	54	61	59	59
Sex, % females	58%	71%	46%	39%
BMI (kg/m <sup>2</sup> )	27	28	30	28
History of AF	8%	6%	10%	16%
ICD	50%	12%	22%	16%
➡ Prior SRT	0%	6%	9%	-
➡ Hypertension	17%	65%	46%	53%
Diabetes	17%	6%	5%	10%
NYHA I	0%	6%	0%	0%
NYHA II	50%	59%	72%	76%
➡ NYHA III	50%	35%	28%	24%
KCCQ-OSS	57	63	67	69
➡ LVEF	61%	65%	74%	75%
➡ LVOT-G (resting; mmHg)	9	59	52	55
➡ LVOT-G (Valsalva; mmHg)	14	93	72	83
NT-proBNP (geometric mean/median; pg/ml)	782 / 715	724 / 710	777	735

Abbreviations: nHCM, nonobstructive hypertrophic cardiomyopathy; oHCM, obstructive hypertrophic cardiomyopathy; HCM, hypertrophic cardiomyopathy; SRT, stereotactic radiotherapy; NYHA, New York Heart Association Classification; LVEF, left ventricular ejection fraction; LVOT-G, left ventricle outflow tract gradient







# EDG-7500 has the Potential to **Revolutionize HCM Care**, Where Unmet Needs and Persistent Challenges Remain





# Edgewise is Committed to Delivering a Novel and Differentiated Therapy for Patients with HCM

## Aspirational Target Product Profile for EDG-7500 in the Treatment of HCM

	<b>Safety</b>	Based on Observations to Date, No Concerns of LVEF Drops; Potential to Eliminate Safety Echoes
	<b>Efficacy</b>	Ability to Deepen Functional, Symptom and QoL Improvements Without Concerns of LVEF Drops < 50%
	<b>Monitoring</b>	No Excessive Monitoring Requirements Outside of Standard of Care in HCM; Opens Potential for Use Outside of CoEs
	<b>Superior Patient Experience</b>	Overcomes the Need for Cumbersome Safety Echoes, Easing the Burden on Patients
	<b>Diastolic Effect</b>	Ability to Resolve Diastolic Dysfunction in Patients with Non-Obstructive HCM
	<b>Dosing</b>	Intra-Patient Dose Optimization Using SOC assessments (Biomarkers, Feel-and-Function and Echo at Physician's Discretion)

# Edgewise Upcoming Value-Generating Milestones

**H1 2025**

**H2 2025**

**H1 2026**

## Muscular Dystrophy

Sevasemten

**Duchenne**

P2 LYNX & FOX  
Controlled dose-ranging data

P3 trial  
Initiation

CANYON EOP2 Feedback  
Path to Sevasemten Approval

**Becker**



GRAND CANYON  
Recruitment complete

GRAND CANYON  
Results **4Q2026**

## Cardiac

**Hypertrophic  
Cardiomyopathy**



P2 CIRRUS-HCM 28-day  
EDG-7500 initial readout  
in oHCM & nHCM

P2 CIRRUS-HCM 12-week  
EDG-7500 initial readout  
in oHCM & nHCM

EDG-7500 P3 initiation  
oHCM & nHCM

**Heart Failure &  
Cardiometabolic**

EDG-CV candidate  
IND in Heart Failure

Cardiometabolic  
Candidate  
*In vivo* POC

EDG-CV P2 Data  
NHV/Heart Failure



# Well-Capitalized to Execute Important Milestones Across Both Sevasemten and EDG-7500

CASH, CASH EQUIVALENTS &  
MARKETABLE SECURITIES\*

~\$660M

DEBT

\$0

COMMON SHARES OUTSTANDING  
(NASDAQ: EWTX)

~105M

CASH RUNWAY THROUGH 2028\*

\* Takes into account the expected proceeds from the recently announced registered direct offering, together with existing cash, cash equivalents and marketable securities as of December 31, 2024



# Thank You