EDG-7500: Phase 1 & Phase 2 CIRRUS-HCM Development Program Update

September 19, 2024

Forward looking statement

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Agenda

Dr. Kevin Koch
Chief Executive Officer

Marc Evanchik
Vice President of Discovery

Dr. Anjali Owens
Center for Inherited Cardiac Disease, Hospital of the University of Pennsylvania

Dr. Marc Semigran
Chief Development Officer

1. Introduction to Edgewise Therapeutics
2. The unmet need in HCM
3. EDG-7500, a novel sarcomere regulator for the treatment of HCM
4. Topline results: Phase 1 trial in healthy volunteers and Phase 2 CIRRUS-HCM trial in oHCM
5. EDG-7500 future development plans
6. Closing remarks
7. Q & A

Focused on muscle science

- Global leader in muscle disease therapeutic development
- Deep knowledge of integrated muscle physiology
- Novel & holistic therapeutic approach to protect muscle

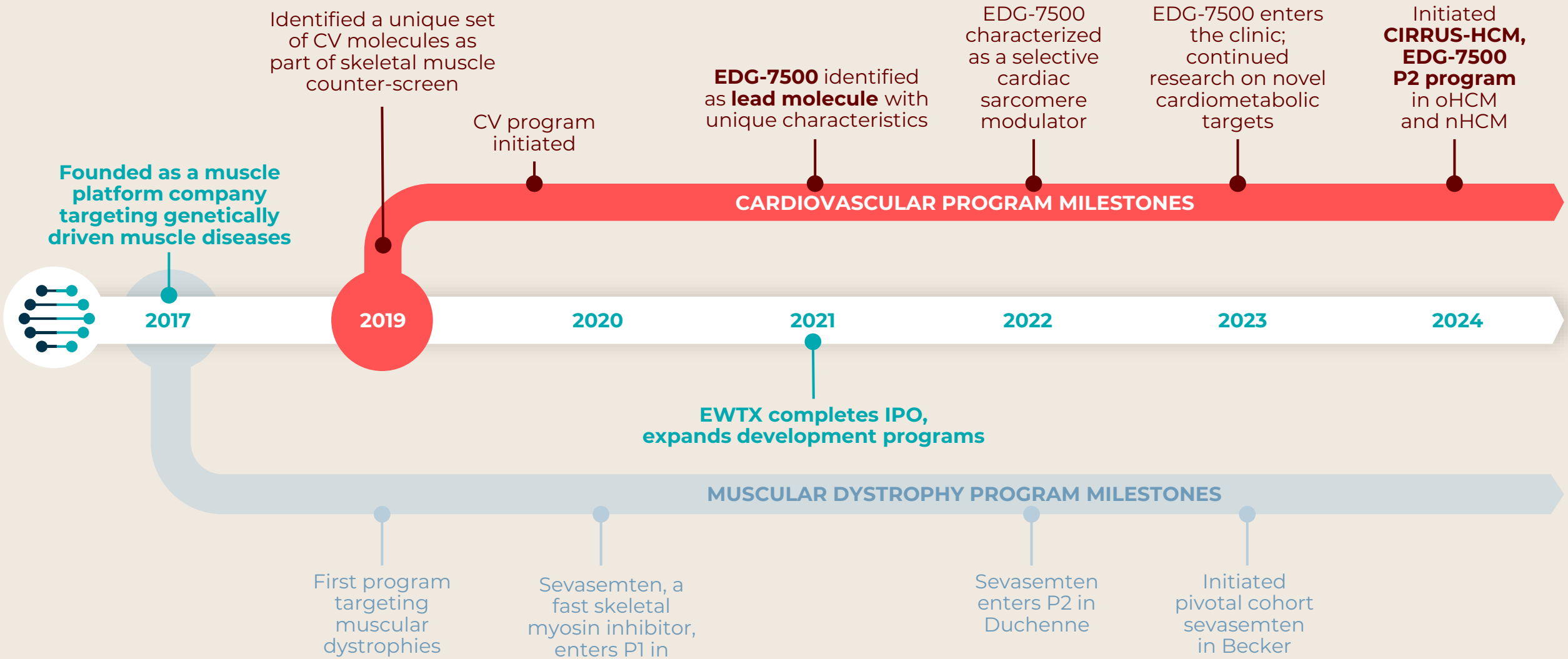
Rapidly advancing portfolio

- Advancing EDG-7500 in oHCM, nHCM, and other potential indications
- Pivotal trial of sevasemten as potential foundational therapy for muscular dystrophies
- 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

Edgewise Evolution into Cardiovascular Disease

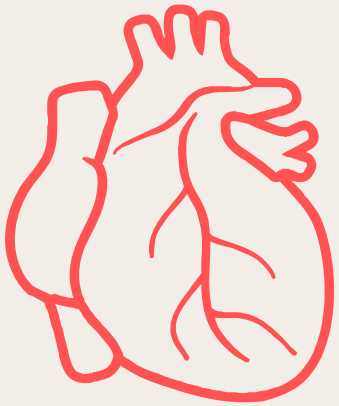


The Unmet Need in HCM

Dr. Marc Semigran

The Significance of Hypertrophic Cardiomyopathy (HCM)

Most common genetic cardiovascular disease
impacting ~1 in 500 people[1]



Can manifest at any age, important cause of sudden cardiac death, atrial fibrillation, stroke and of heart failure in all ages[1,2]

Prevalence of HCM gene carriers could be as high as 1:200 suggesting that

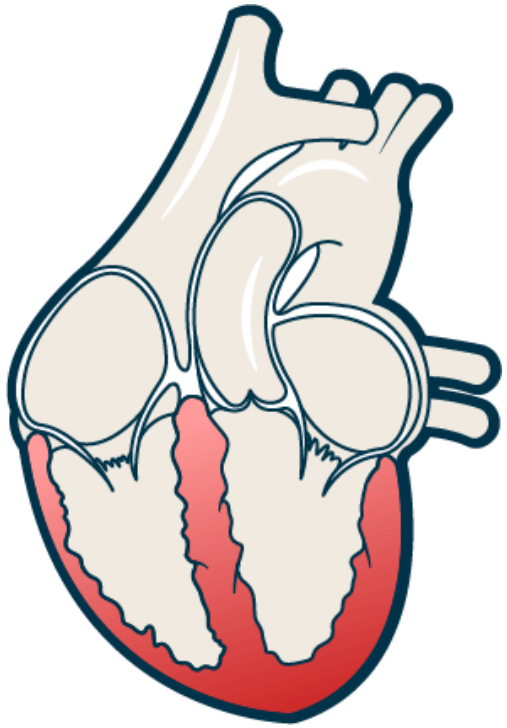
85% of individuals with HCM remain undiagnosed[3]

HCM dramatically impairs overall quality of life - **physical, emotional & financial**

HCM, hypertrophic cardiomyopathy; LV, left ventricle; LVOT-G, left ventricular outflow tract gradient; US, United States.
1. Maron BJ et al. *J Am Coll Cardiol.* 2022;79(4):390-414; 2. Geske JB et al. *JACC Heart Fail.* 2018;6(5):364-375; 3. Semsarian C et al. *J Am Coll Cardiol.* 2015;65(12):1249-1254.

HCM: Abnormalities in Heart Muscle Structure and Function Lead to Severe Abnormalities in Cardiac Performance

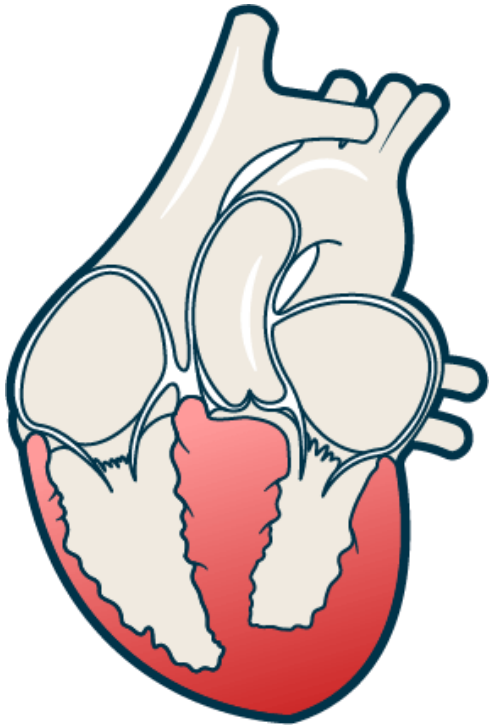
HEALTHY HEART



Normal contraction

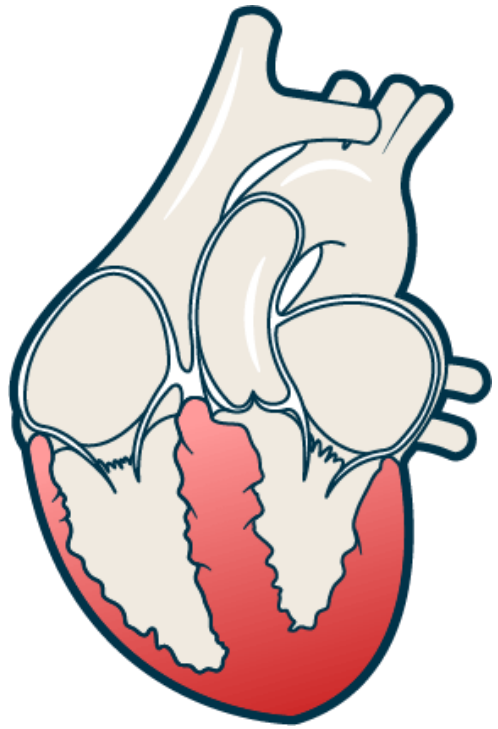
OBSTRUCTIVE HCM

(~65% OF PATIENT POPULATION)



NON-OBSTRUCTIVE HCM

(~35% OF PATIENT POPULATION)



Excessive contraction & impaired relaxation

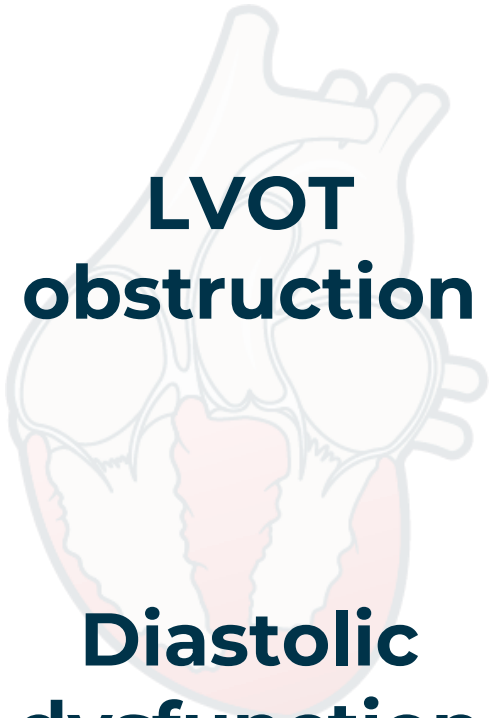
Abbreviations: LVOT, left ventricular outflow tract

LVOT Obstruction and Diastolic Dysfunction Contribute to the Development of Heart Failure in HCM[1–3]

Addressing LVOT obstruction alone will not resolve heart failure across the spectrum of HCM

Unmet need to resolve diastolic dysfunction

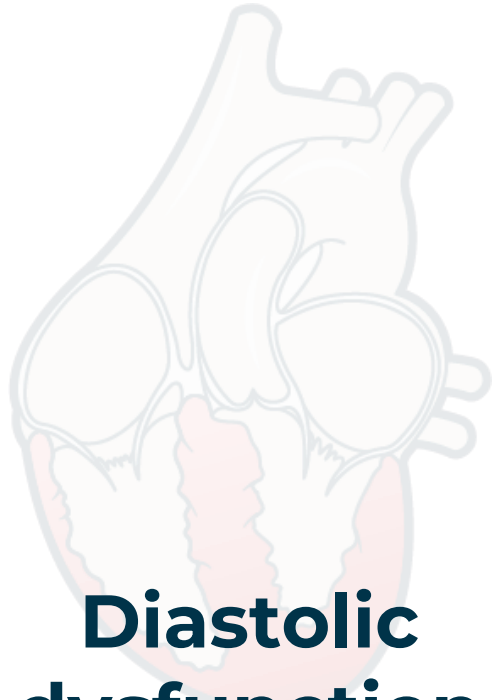
oHCM[1-3]



LVOT obstruction

Diastolic dysfunction

nHCM[4]



Diastolic dysfunction

HCM, hypertrophic cardiomyopathy; LVOT, left-ventricular outflow tract; nHCM, non-obstructive HCM; oHCM, obstructive HCM.

1. Maron MS et al. *N Engl J Med* 2003;348:4: 295-303; 2. Elliott PM et al. *Eur Heart J* 2006;27:16: 1933-1941.; 3. Lee HJ et al. *Korean Circ J.* 2022; 52(8) 563–575; 4. Rowin EJ et al. *Circ Heart Fail.* 2014;7(6):967-75

Treatments for HCM Have Key Limitations Leaving Substantial Unmet Needs for Patients

LIMITED BENEFIT ACROSS THE SPECTRUM OF HCM

Efficacy and safety limitations with interventions in oHCM[4]

- BB and CCBs have **limited efficacy** and associated side effects
- SRT interventions are **highly invasive**
- CMI efficacy may be **limited by intrinsic mechanism** tied to LVEF changes and are not recommended for patients with LVEF <55%

No approved therapies for nHCM

- SOC for nHCM includes the need for heart transplant
- Limited efficacy of off-label therapies

RISK OF HEART FAILURE[1,2]

Mavacamten black box warning for HF[3]

- The US prescribing information for mavacamten contains a boxed warning regarding heart failure

HF risk limits intervention[2]

- Guidelines recommend an **interruption in treatment** for patients who develop **LVEF <50%**

SUBOPTIMAL PATIENT EXPERIENCE

Safety-driven frequent echo monitoring[1-3]

- Treatment with mavacamten requires **echocardiography monitoring** for both the initiation and maintenance phases
- **Extensive titration and adjustment of dosage** needed to find a safe window of efficacy avoiding EF drop risk

CMI, cardiac myosin inhibitor; LVEF, left ventricular ejection fraction; LVOT, left ventricle outflow tract; oHCM, obstructive hypertrophic cardiomyopathy; SOC, standard of care.

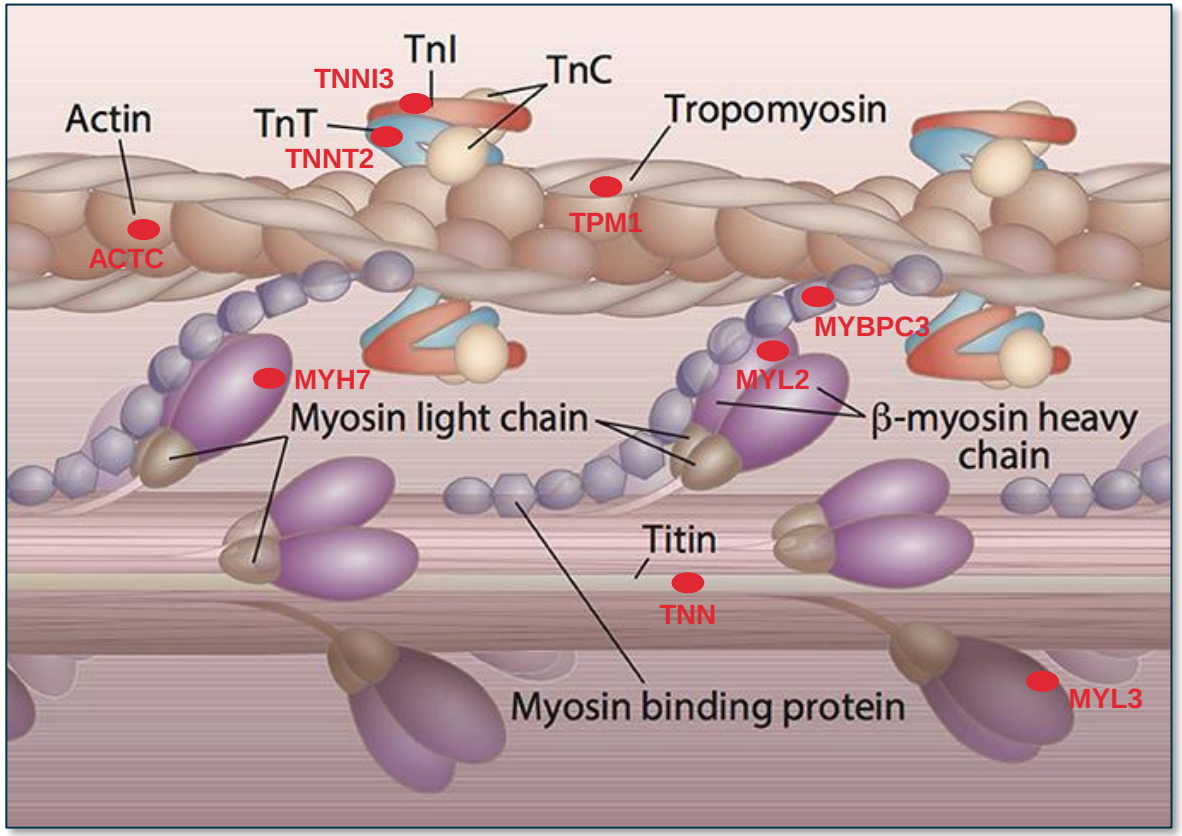
1. Ommen SR et al. *Circulation*. 2024;149(23):e1239-e1311; 2. Maron MS et al. *N Engl J Med.* 2024;390:1846-61; 3. CAMZYOS [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2023; 4. Olivotto I et al. *Lancet*. 2020;396(10253):759-769.

EDG-7500, a Novel Sarcomere Regulator for the Treatment of HCM

Marc Evanchik

EDG-7500: Designed to Slow Rate of Acto-Myosin Engagement and Speed Disengagement Without Inactivating Myosin Heads

The Sarcomere is the Molecular Unit in Cardiac Muscle Responsible for Heart Contraction and Relaxation



Protein	Gene Symbol	# of mutations to cause HCM
Cardiac β-MyHC	***MYH7***	**194**
Cardiac MyBP-C	***MYBPC3***	**197**
Cardiac TnT	*TNNT2*	31
Cardiac TnI	*TNNI3*	27
α-Tropomyosin	*TPM1*	11
Regulatory Light Chain	*MYL2*	10
Cardiac α-actin	*ACTC*	7
Essential Light Chain	*MYL3*	5
Titin	*TNN*	3

References: www.hypertrophiccardiomyopathy.com; https://sadayappanlab.org/hypertrophic_cardio.html; Kraker J, *et. al., Frontiers in Physiology*, 2016; Seidman CE & Seidman JG, *Circulation Research*, 2011

A Compelling Preclinical Package Supported Initiation of Clinical Studies of EDG-7500 as a Novel Therapy for HCM

Preclinical model	Key result
In vitro: Myofibril systems[1]	✓ Preserves myosin head motor function ✓ More potent at low calcium
oHCM *In vivo*: *MYBPC3* A31P feline validated oHCM model[3]	✓ Potent LVOT gradient reduction ✓ Well tolerated at supratherapeutic exposures
nHCM *In vivo*: *MYH7* R403Q porcine validated nHCM model[4]	✓ Improves diastolic function ✓ Positively impacts LA and LV remodeling ✓ Restores cardiac reserve
HFrEF *In vivo*: Dogs with pacing induced left-ventricular systolic dysfunction	✓ Improves diastolic performance in model of reduced systolic function ✓ No changes in systolic performance in a model of reduced LVEF
In vivo: Systolic and diastolic function assessed in healthy dogs[2]	✓ Increases ventricular diastolic compliance with limited effect on LVEF

EDG-7500 has demonstrated potent LVOT gradient reduction and improvement in diastolic function with limited reduction in systolic performance, even at highest exposures, across multiple preclinical models

LA, left atrium; LV, left ventricle; LVEF, left ventricle ejection fraction, LVOT, left ventricle outflow tract; nHCM, non-obstructive hypertrophic cardiomyopathy; oHCM, obstructive hypertrophic cardiomyopathy.
1. Del Rio CL et al. 2023 American Heart Association Scientific Sessions. Philadelphia, PA. November 10–13, 2023. Abstract #15612; **2.** Del Rio CL et al. 2023 American Heart Association Scientific Sessions. Philadelphia, PA. November 10–13, 2023. Abstract #15822; **3.** Kaplan JL, et al. 2023 American College of Cardiology 72nd Annual Scientific Sessions. New Orleans LA. March 4–6, 2023. Poster #1066-13; **4.** Evanchik M et al. 2024 American College of Cardiology 73rd Annual Scientific Sessions. Atlanta, GA. March 6–8, 2024. Poster #1087-05; **5**. Evanchik M et. al., Poster Presentation at BCVS 2024

EDG-7500 is Positioned to Address Unmet Needs in HCM

Targeted MOA*

EDG-7500 is targeted to address both obstructive and non-obstructive HCM

Slows acto-myosin engagement & promotes faster disengagement

Efficacy disassociated from changes in LVEF*

EDG-7500 avoids excessive drops in systolic performance manifesting as reduced ejection fraction

Potential ease of administration

EDG-7500's novel MOA supports investigating fixed dose regimens, potentially eliminates any need for cumbersome up-titration and frequent echocardiographic assessments

* Based on preclinical data with EDG-7500
Abbreviations: HCM, hypertrophic cardiomyopathy; oHCM, obstructive HCM; nHCM, non-obstructive HCM; LVEF, left ventricular ejection fraction; MOA, mechanism of action
References: Edgewise ACC presentation (https://edgewisetx.com/application/files/1616/7812/1221/EDG-7500_Cat_HCM_ACC23-WCC_Final.pdf)

Phase 1 Trial in Healthy Subjects

Study Overview of EDG-7500 in Healthy Adults

PRIMARY OBJECTIVE

Safety & tolerability in healthy volunteers

KEY INCLUSION CRITERIA

Healthy male, non-pregnant female 18 to <60 years of age

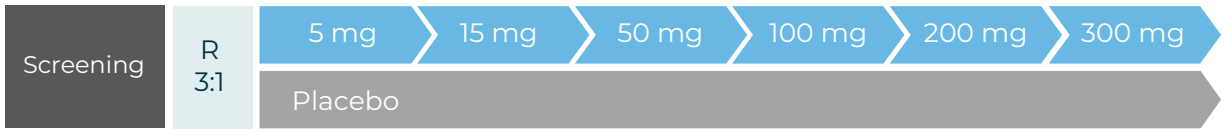
ENROLLMENT

72

KEY OUTCOME MEASURES

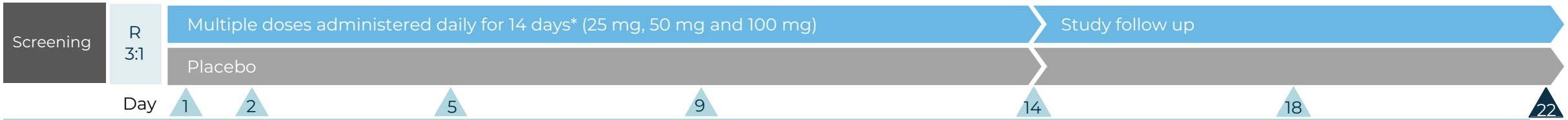
PK, LVEF

Part A (n=48)
Single Ascending Dose (SAD)



5 day follow up, EOS visit at day 9; 96-hour PK profile, echocardiography at 1.5, 6, 24, 96, and 192 hours post-dose

Part B (n=24)
Multiple Ascending Dose (MAD)



Once-daily dose for 14 days, 18-day follow-up, EOS visit at day 22;
24-hour PK profile on days 1 and 14; echocardiography at days 2, 5, 9, 15, 18 and 22

Abbreviations: EOS, end of study; LVEF, left ventricle ejection fraction; PK, pharmacokinetics
ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06011317

EDG-7500 was Well Tolerated Across All Doses in Both the SAD and MAD HV Cohorts

TEAEs by body system and treatment after single ascending doses of EDG-7500 (n=6 per cohort on active)

System Organ Class	Pooled Placebo (N=12)	EDG-7500						
		Overall (N=36)	5 mg	15 mg	50 mg	100 mg	200 mg	300 mg
Any TEAE	**3 (25%)**	**9 (25%)**	0	1	4	2	0	2
Eye disorders	0	1 (3%)	0	0	0	0	0	1
Gastrointestinal disorders	1 (8%)	2 (6%)	0	0	1	1	0	0
General disorders and administration site conditions[1]	1 (8%)	3 (8%)	0	1	0	2	0	0
Infections and infestations	0	2 (6%)	0	0	1	0	0	1
Injury, poisoning and procedural complications	1 (8%)	0	0	0	0	0	0	0
Nervous system disorders	0	3 (8%)	0	0	1	1	0	1
Respiratory, thoracic and mediastinal disorders	0	1 (3%)	0	0	1	0	0	0

TEAEs by body system and treatment after 3 ascending doses of daily EDG-7500 for 14 days (n=6 per cohort on active)

System Organ Class	Pooled Placebo (N=6)	EDG-7500			
		Overall (N=18)	25 mg QD	50 mg QD	100 mg QD
Any TEAE	**2 (33%)**	**6 (33%)**	3	3	0
General disorders and administration site conditions	1 (17%)	1 (6%)	1	0	0
Injury, poisoning and procedural complications	0	1 (6%)	1	0	0
Musculoskeletal and connective tissue disorders	0	3 (17%)	3	0	0
Nervous system disorders	1 (17%)	1 (6%)	1	0	0
Reproductive system and breast disorders	0	1 (6%)	1	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (6%)	1	0	0
Skin and subcutaneous tissue disorders	0	3 (17%)	0	3	0

[1] ECG tab site irritation.
Source: Edgewise Therapeutics Data on File

EDG-7500 was Well Tolerated Across All Doses in Both the SAD and MAD HV Cohorts *(continued)*

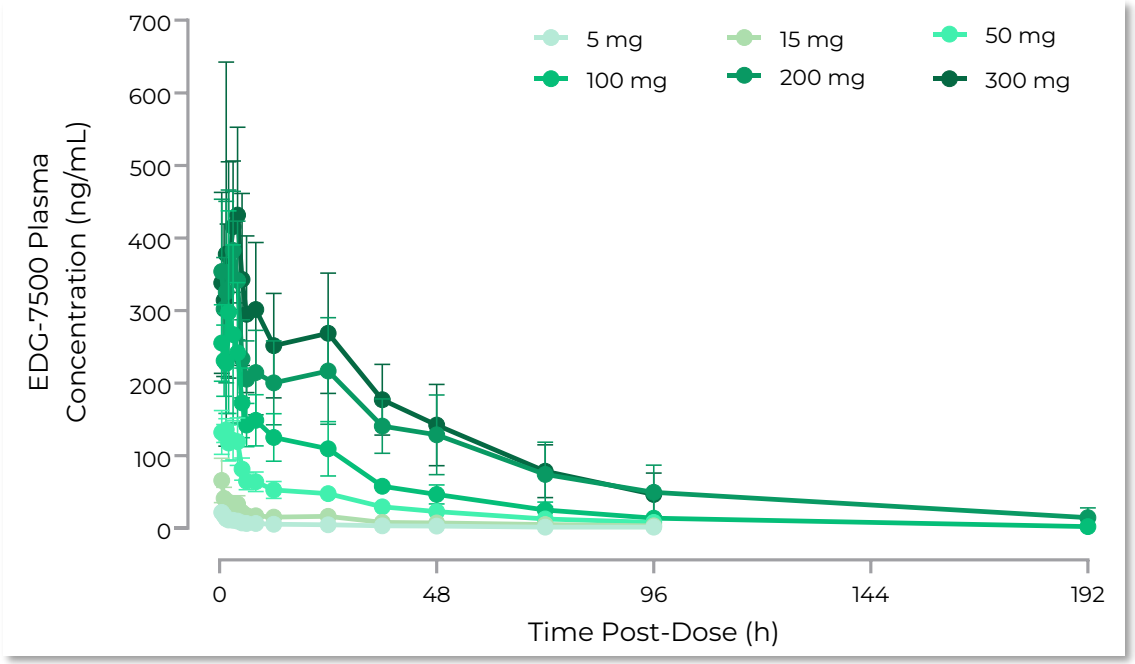
Across both the SAD and MAD cohorts:

- No significant changes in vital signs were observed
- Well-tolerated with no clinically significant changes or trends in clinical chemistry, hematology, or ECGs
- Incidence of treatment-emergent adverse events was similar compared to placebo
- LVEF remained within the normal range for all subjects at all time points; importantly, **none of the subjects** experienced a decrease in LVEF <50%

Source: Edgewise Therapeutics Data on File

SAD: EDG-7500 Mean Plasma Elimination Half-Life ($T_{1/2}$) Ranged from 25 to 39 Hours

SAD: EDG-7500 Plasma Concentration Over Time (mean ± SD)



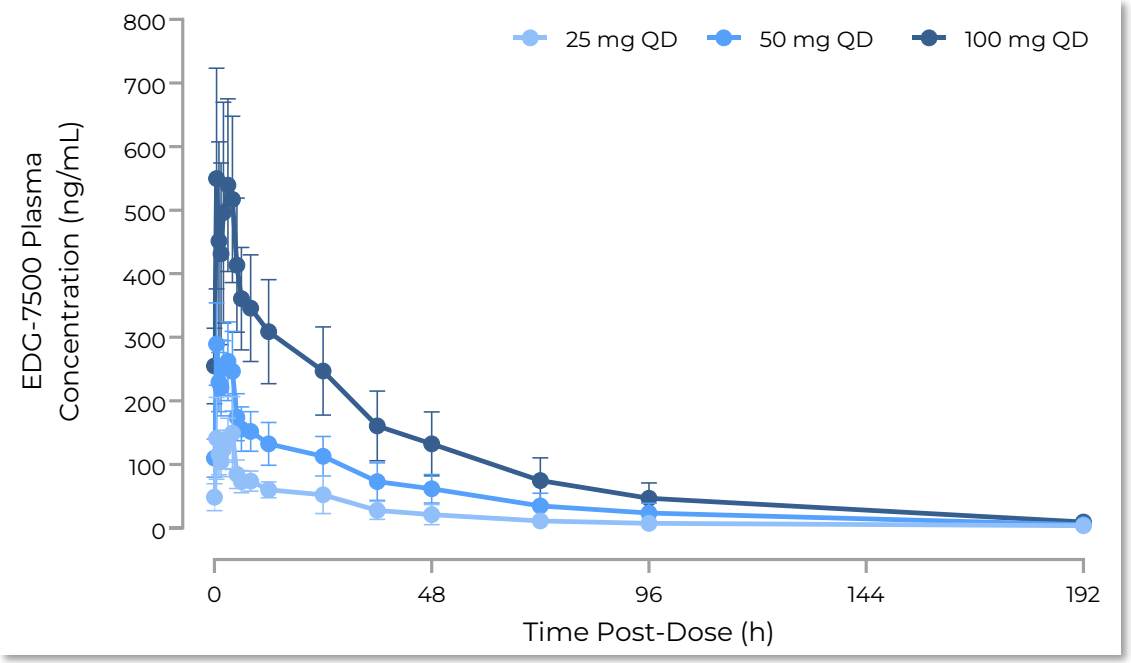
EDG-7500 Dose	C_{max} (ng/mL)	$T_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (h*ng/mL)	AUC_{INF} (h*ng/mL)
5 mg	22.7 ± 6.41 (28.2%)	27.4 ± 9.07 (33.1%)	168 ± 28.3 (16.9%)	363 ± 140 (38.6%)
15 mg	69.8 ± 25.4 (36.3%)	31.5 ± 12.8 (40.8%)	489 ± 107 (22.0%)	1,140 ± 460 (40.4%)
50 mg	157 ± 16.3 (10.4%)	31.5 ± 7.67 (24.3%)	1,610 ± 236 (14.7%)	3,490 ± 782 (22.4%)
100 mg	334 ± 126 (37.8%)	25.1 ± 7.20 (28.7%)	3,580 ± 997 (27.8%)	7,010 ± 1,720 (24.6%)
200 mg	464 ± 50.2 (10.8%)	38.7 ± 14.7 (38.1%)	5,570 ± 1,380 (24.8%)	17,100 ± 8,330 (48.8%)
300 mg	512 ± 198 (38.6%)	29.5 ± 9.78 (33.1%)	6,950 ± 1,960 (28.2%)	18,000 ± 6,850 (38.0%)
Data are presented as arithmetic mean ± standard deviation (CV%)				

- EDG-7500 was readily absorbed with a T_{max} of 1.5 to 2 hours
- Exposure was generally linear and dose proportional for C_{max} and AUC; exposure was slightly less than dose proportional from the 200 mg to 300 mg dose in the SAD
- Mean terminal half-life was ~30 hours (range: 25 to 39 hours)

Source: Edgewise Therapeutics Data on File

MAD: Consistent Observations to SAD with a 2-Fold Accumulation Ratio Consistent with a ~30 Hour $T_{1/2}$

MAD: EDG-7500 Plasma Concentration Over Time (mean ± SD)



EDG-7500 Dose	C_{max} (ng/mL)	$T_{1/2}$ (h)	AUC_{0-24h} (h*ng/mL)	AUC_{0-24h} AR
25 mg QD	176 ± 61.8 (35.1%)	23.0 ± 9.62 (41.8%)	1,780 ± 492 (27.6%)	1.80
50 mg QD	315 ± 50.4 (16.0%)	34.3 ± 14.9 (43.4%)	3,690 ± 801 (21.7%)	2.00
100 mg QD	574 ± 160 (28.0%)	30.6 ± 5.52 (18.0%)	8,150 ± 2,100 (25.8%)	2.30

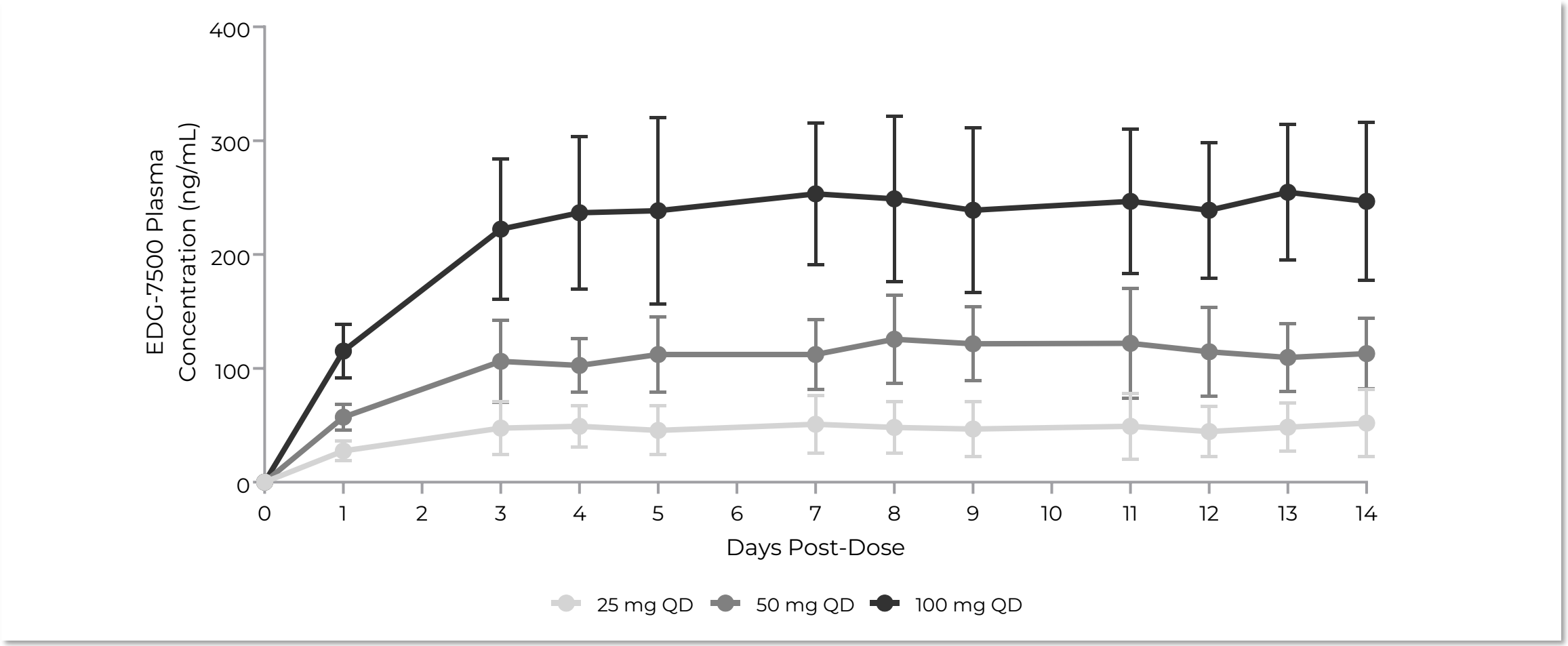
Day 14 data are presented as arithmetic mean ± SD (CV%)
AR = Accumulation ratio (Day 14 PK compared to Day 1 PK)

- EDG-7500 was readily absorbed with a T_{max} of 1.5 to 2 hours
- Exposure was generally linear and dose proportional
- ~2-fold accumulation following 14 days of administration
- Mean terminal half-life was ~30 hours (range: 23 to 34 hours)

Source: Edgewise Therapeutics Data on File

Steady-State was Achieved ~4 Days After Start of Once-Daily Dosing with EDG-7500

Plasma Concentration Over Time (mean ± SD) After 3 Ascending Doses of Daily EDG-7500 for 14 Days

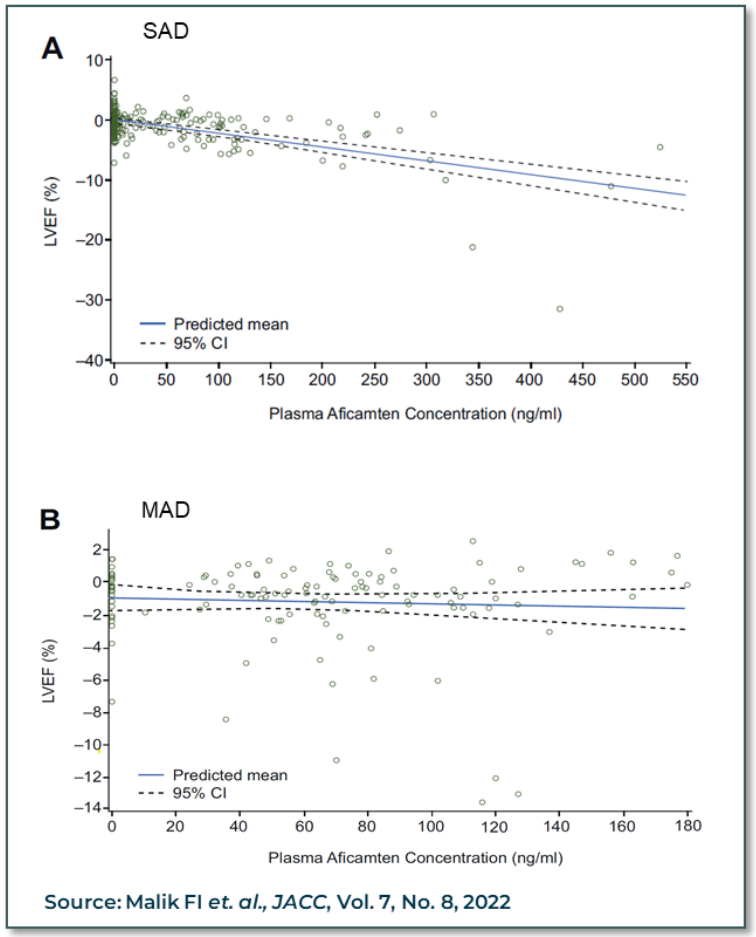


Source: Edgewise Therapeutics Data on File

Data with CMIs, Both Approved and in Development, Show a Decrease in LVEF as a Mechanistic Component

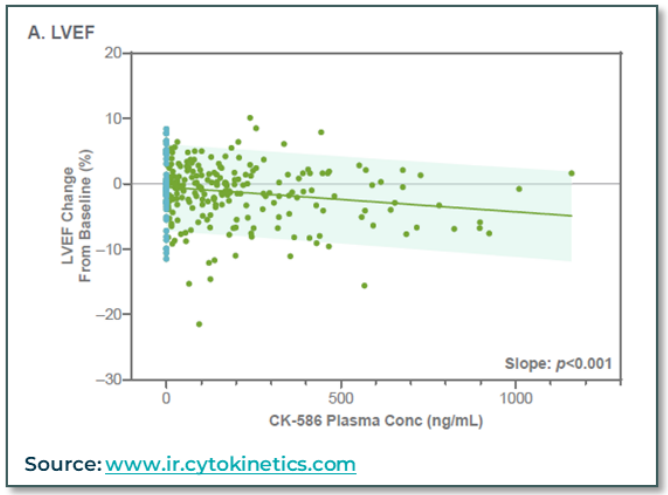
PD Active Doses of CMIs Decreased LVEF in a Concentration Dependent Manner

Aficamten SAD and MAD HV Data



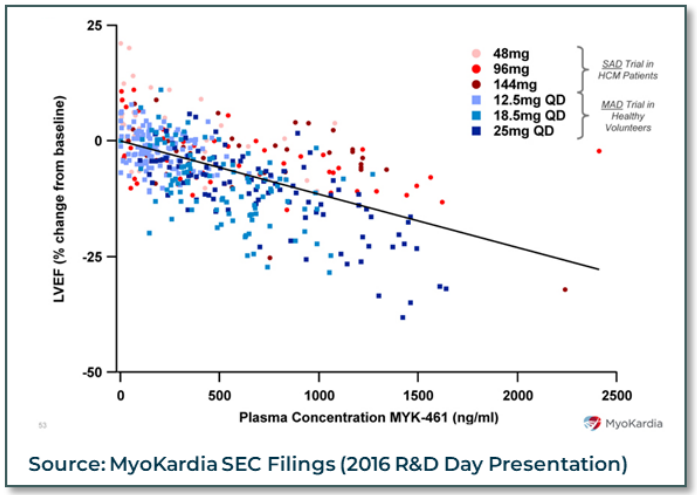
Source: Malik FI *et. al.*, *JACC*, Vol. 7, No. 8, 2022

CK-586 Pooled SAD/MAD HV Data



Source: www.ir.cytokinetics.com

Mavacamten (CAMYZOS®) Data

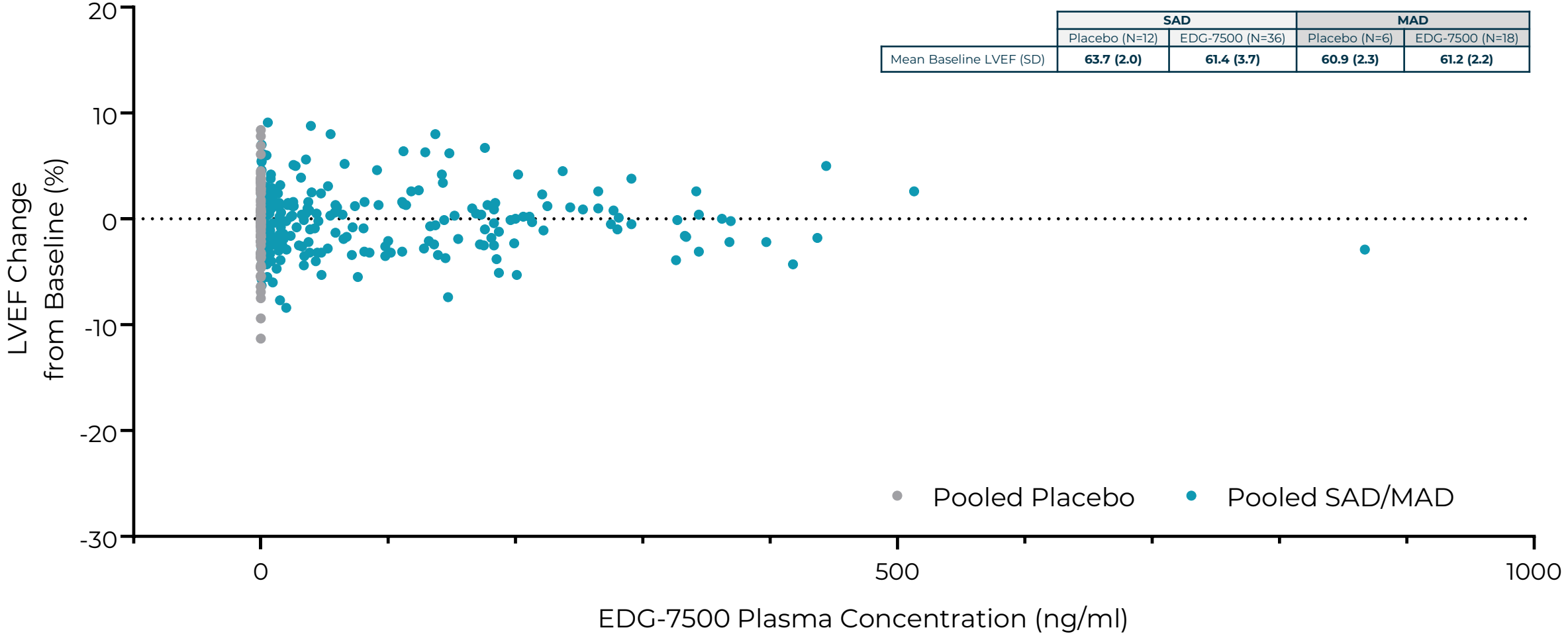


Source: MyoKardia SEC Filings (2016 R&D Day Presentation)

EWTX prioritized candidates that preserved LVEF as part of the clinical candidate selection criteria

There Was **No Change in Contractility** Versus Placebo and Baseline With Increasing Doses of EDG-7500

	SAD		MAD	
	Placebo (N=12)	EDG-7500 (N=36)	Placebo (N=6)	EDG-7500 (N=18)
Mean Baseline LVEF (SD)	**63.7 (2.0)**	**61.4 (3.7)**	**60.9 (2.3)**	**61.2 (2.2)**



SAD: # Subjects = 48, # Observations = 238; MAD: # Subjects = 24, # Observations = 95
Source: Edgewise Therapeutics Data on File

Observations with EDG-7500 Highlight a Potentially Unique Mechanism to Target HCM without **Risk of Reducing LVEF**

- EDG-7500 was **well-tolerated** with no clinically significant changes or trends in clinical chemistry, hematology or ECGs
- EDG-7500 showed optimal PK properties supporting **once-daily fixed-dose** administration, **reaching steady state ~4 days** after start of dosing
- **None of the subjects experienced a LVEF <50%** across both the SAD and MAD healthy subjects
- No meaningful drops in LVEF were observed within **a range of EDG-7500 plasma concentrations of up to 874 ng/ml**, above our predicted target therapeutic exposures

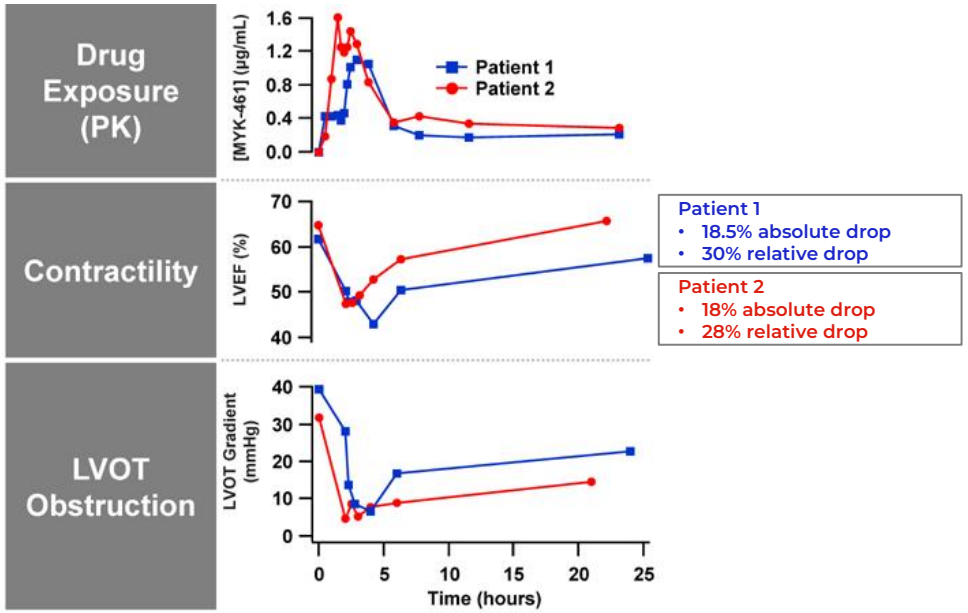
Healthy Subject Data With EDG-7500 Support a Differentiated MoA that Does Not Rely on Reductions in Systolic Performance

Phase 2 CIRRUS-HCM Trial in oHCM

Dr. Semigran and Dr. Owens

Results of Mavacamten Single Dose Administration in oHCM Patients

Treatment of 2 oHCM patients with a single dose of mavacamten (MYK-461), a cardiac myosin inhibitor, led to relief of LVOT obstruction at expense of a reduction in contractility (LVEF drops)



Patient 1
- 18.5% absolute drop
- 30% relative drop

Patient 2
- 18% absolute drop
- 28% relative drop

Conclusions

- Both patients' gradients reduced following single dose of MYK-461
- Time course of drug exposure corresponds to temporal pattern of reduction in contractility (LVEF) and LVOT gradient
- Consistent with literature and MYOK pre-clinical experiments that **reduction in contractility leads to reducing outflow tract gradients**
- Further exploration of relationship among contractility, LVOT gradient and other measures in PIONEER-HCM and beyond

Source: MyoKardia SEC filings: https://www.sec.gov/Archives/edgar/data/1552451/000119312516715379/d264412dex992.htm
MyoKardia AHA Presentation 2016: A Novel Oral Myosin Modulator (MYK-461) for the Treatment of Obstructive Hypertrophic Cardiomyopathy: Initial Single Ascending Dose Data in Healthy Volunteers and Patients

CIRRUS-HCM: Clinical Trial Design

PRIMARY OBJECTIVE

Safety & tolerability in adults with HCM

KEY INCLUSION CRITERIA

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

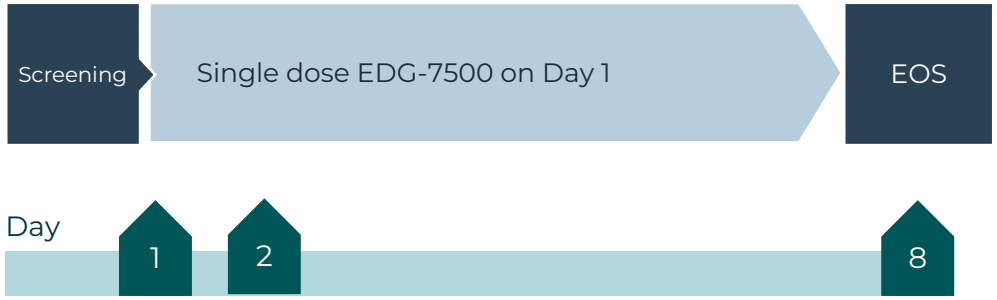
TARGET ENROLLMENT

~55

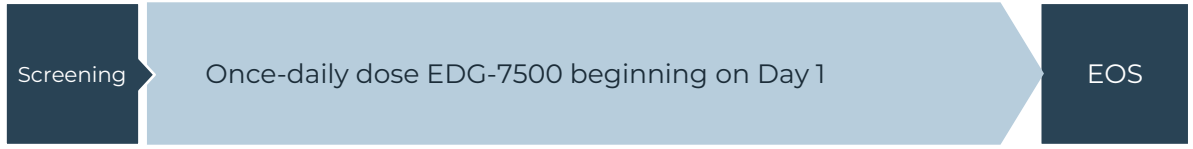
KEY OUTCOME MEASURES

Cardiovascular PD, LVEF, Biomarkers, PK

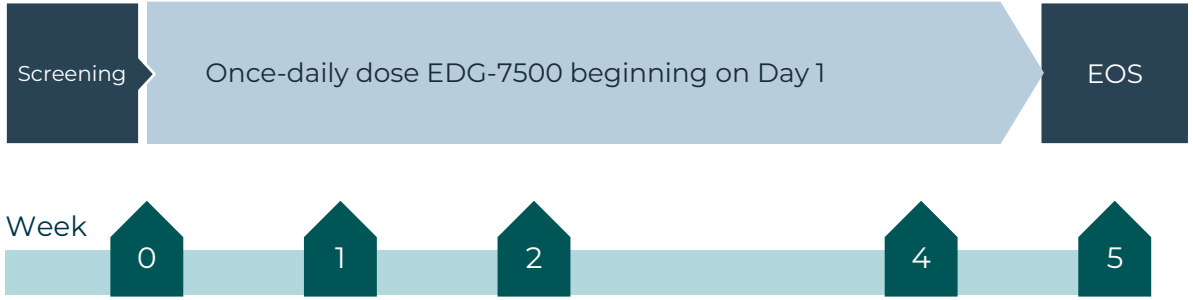
PART A (oHCM): Single Dose Administration (n=11)



PART B (oHCM): Multiple Dose Administration (n=~20)



PART C (nHCM): Multiple Dose Administration (n=~20)



Abbreviations: PK, pharmacokinetics; PD, pharmacodynamics; EOS, end of study

Today's Focus will be on the CIRRUS Part A Cohort of oHCM Patients Treated with a Single Dose of EDG-7500

CIRRUS HCM

PRIMARY OBJECTIVE

Safety & tolerability in adults with oHCM

KEY INCLUSION CRITERIA

- Healthy male, non-pregnant female ≥ 18 diagnosed with oHCM
- Resting LVOT-G ≥ 30 mmHg **AND** Valsalva LVOT-G ≥ 50 mmHg
  LVEF ≥ 60%
- NYHA I-III
- No previous CMI exposure

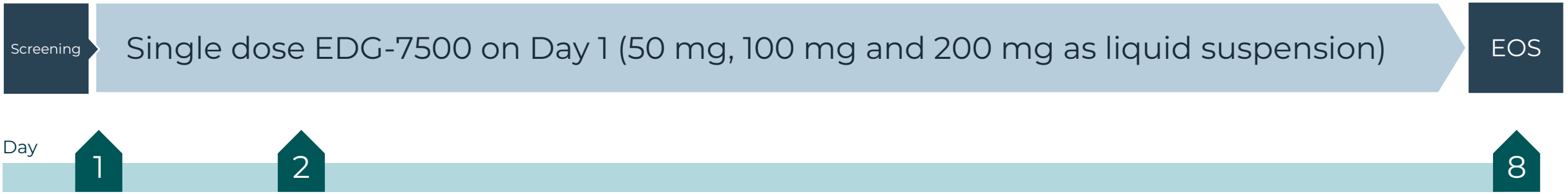
ENROLLMENT

11

KEY OUTCOME MEASURES

- Safety and tolerability
- LVOT-G (rest and during Valsalva)
- Cardiac biomarkers
- PK of EDG-7500

PART A (oHCM): Single Dose Administration (N=11)



Abbreviations: PK, pharmacokinetics; PD, pharmacodynamics; EOS, end of study

Pre-Specified Efficacy Evaluable Population

- 11 patients were eligible at screening and constituted the safety population
- 7 patients met the following criteria at baseline qualifying for efficacy evaluation:
  - Resting left ventricular outflow tract gradient (LVOT-G) ≥ 30 mmHg and Valsalva LVOT-G ≥ 50 mmHg determined by echocardiography
  - Good acoustic window and ability to obtain a high-quality transthoracic echocardiogram
  - No clinically significant cardiac structural abnormalities
- 4 patients did not meet the gradient eligibility at baseline but were evaluable for safety

Source: Edgewise Therapeutics Data on File

CIRRUS-HCM Part A: Baseline oHCM Patient Demographics and Characteristics

CHARACTERISTIC	oHCM PARTICIPANTS (n=11)
Age (Years), Mean (SD)	59 (15)
Sex – Female (%)	73
Race – Black/White (%)	9 / 91
BMI (kg/m^2)	28 (4)
NYHA Class (%)	
Class I	27
Class II	45
Class III	27
Time from HCM Diagnosis (years), Mean (SD)	5 (6)
Max End-Diastolic LV Wall Thickness (mm), Mean (SD)	20 (6)
LVOT-G Rest (mmHg), Mean (SD)*	60 (28)
LVOT-G Valsalva (mmHg), Mean (SD)*	88 (32)
LVEF (%), Mean (SD)*	68 (4)
Background Beta Blockers (%)	64

* Core read of Day 1 pre-dose baseline echocardiogram

Single Doses of EDG-7500 Were Well Tolerated Across All 3 Doses Studied in oHCM Patients

- EDG-7500 was well-tolerated by all oHCM patients
- No treatment emergent abnormalities in clinical hematology or chemistry laboratories
- No patients experienced a decrease in LVEF <50%

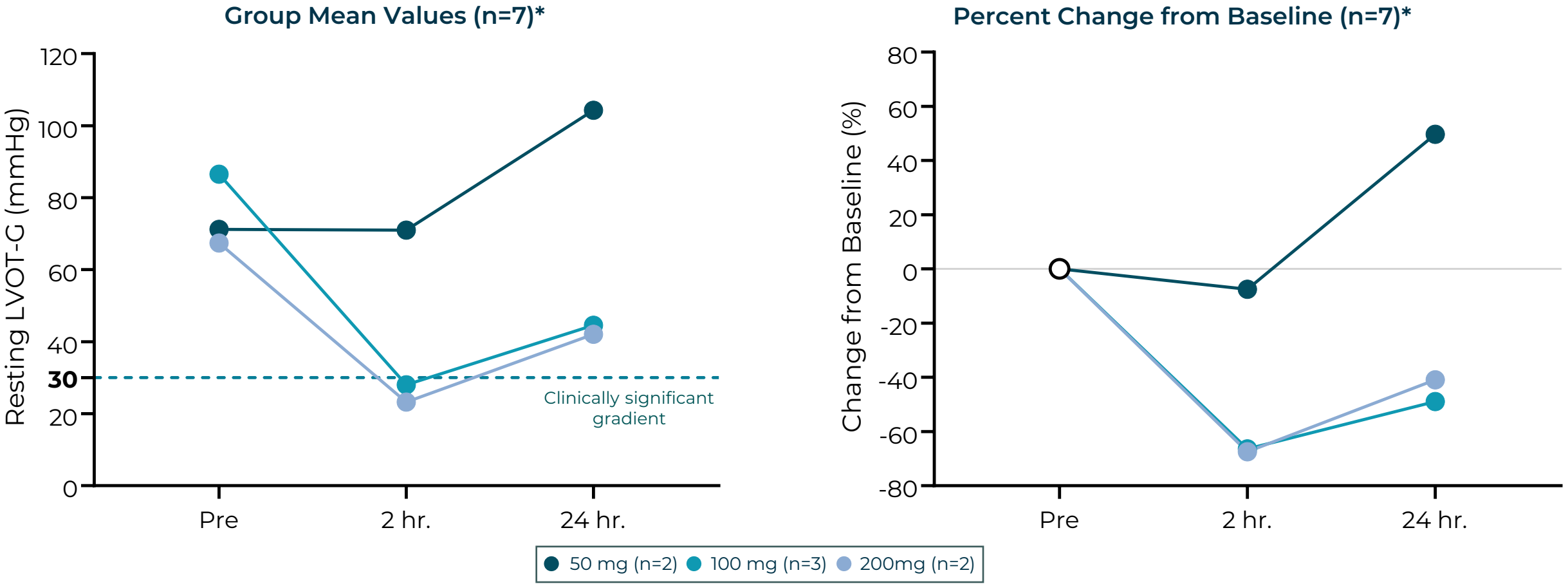
Summary of AEs

Dose	Term	Severity	Relatedness	Outcome	Serious	Comment
200 mg	Atrial Fibrillation (asymptomatic)	Mild	Not Related	Resolved	No	History of Paroxysmal AF; Patient on BB and NOAC
100 mg	Hypotension	Mild	Not Related	Resolved	No	History of Lightheadedness
50 mg	Parasomnia (nightmares)	Mild	Not Related	Ongoing	No	History of PTSD, anxiety, depression
50 mg	Hypokalemia	Mild	Not Related	Ongoing	No	3.9 → 3.1 mmol/L (LLN = 3.6)

Source: Edgewise Therapeutics Data on File

EDG-7500 Led to a Meaningful Reduction in **Resting** LVOT-G of **67%** for the Combined 100/200 mg Cohorts

CIRRUS HCM



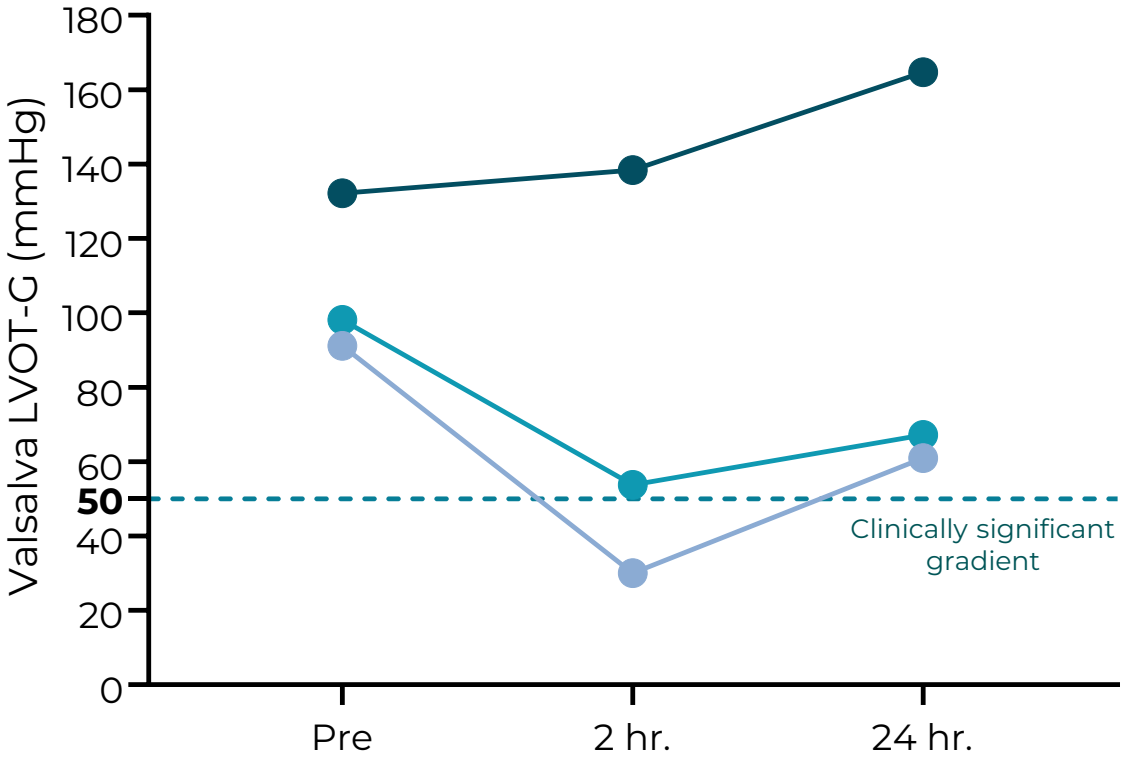
3 of 5 Patients (100 mg and 200 mg Cohorts) Had a Resting LVOT-G of <30 mmHg After a Single Dose of EDG-7500

* Efficacy evaluable population
Source: Edgewise Therapeutics Data on File

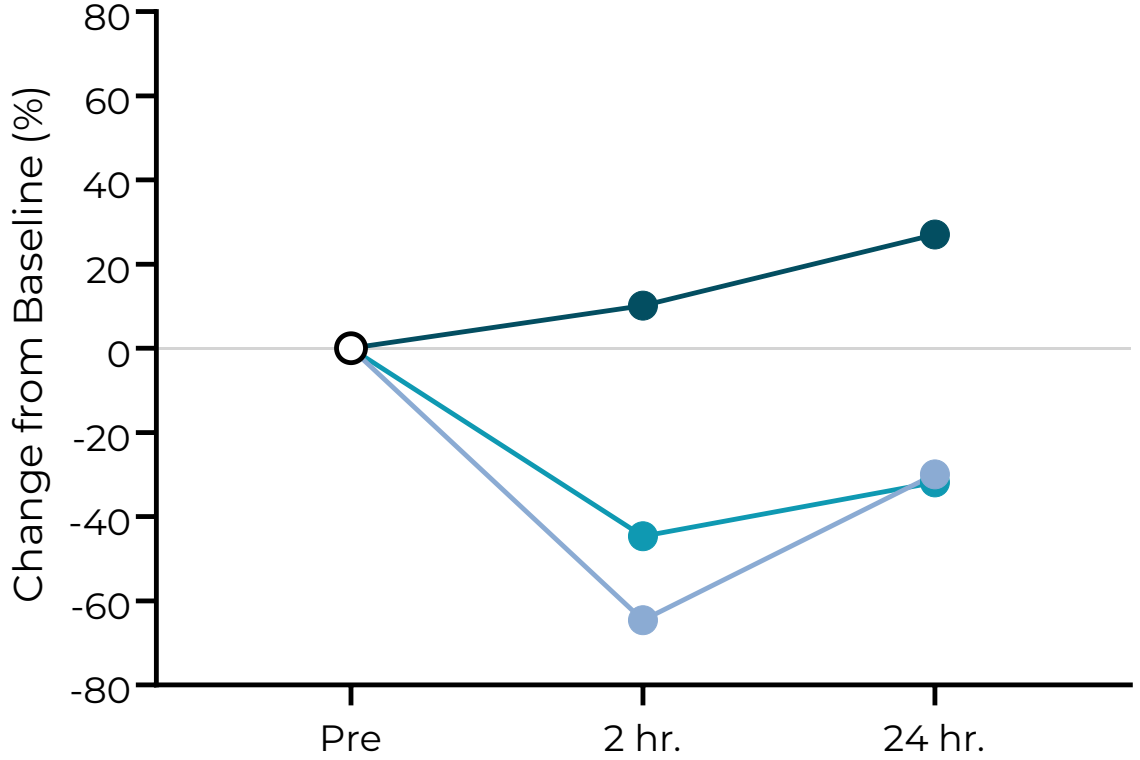
EDG-7500 Led to a Meaningful Reduction of **Valsalva** LVOT-G of **55%** for the Combined 100/200 mg Cohorts

CIRRUS HCM

Group Mean Values (n=7)*



Percent Change from Baseline (n=7)*

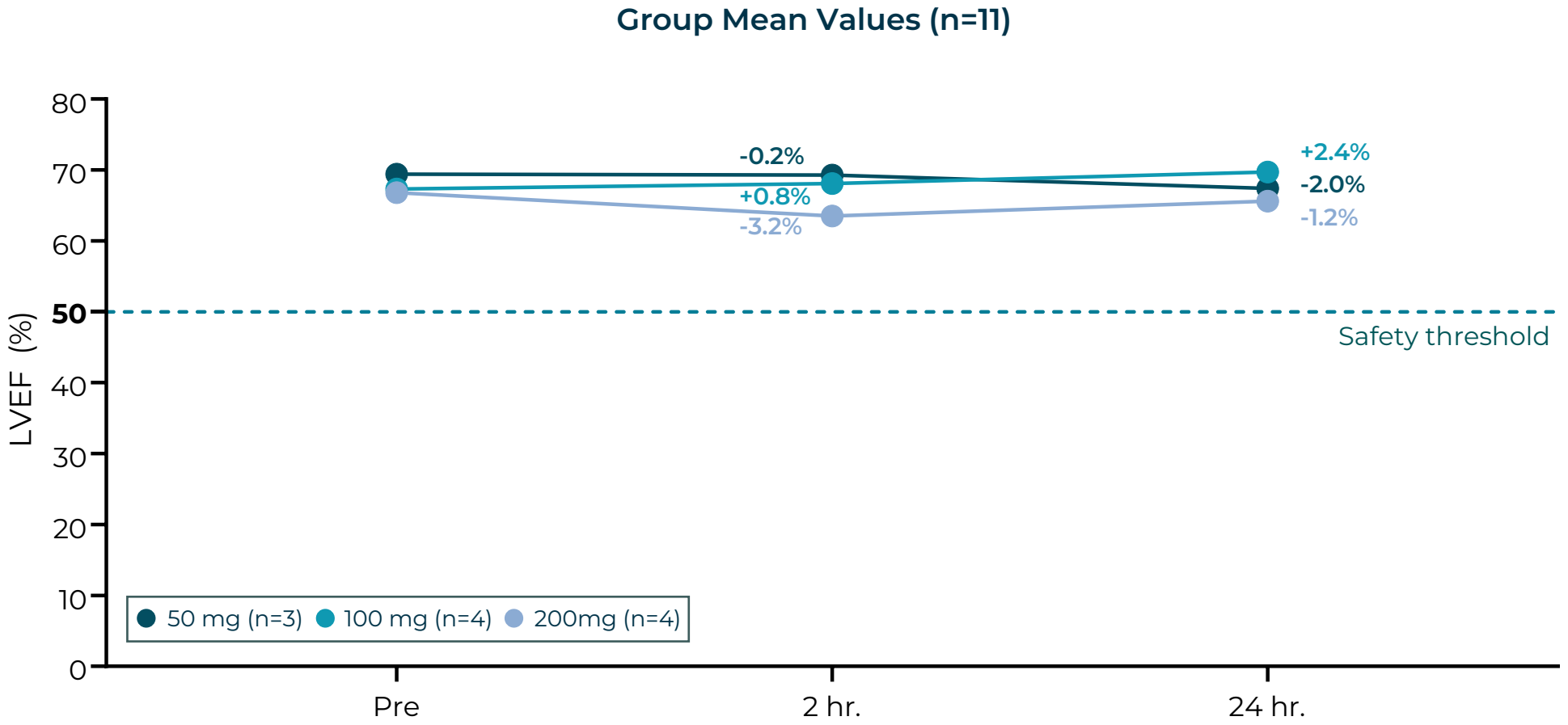


50 mg (n=2) 100 mg (n=3) 200mg (n=2)

3 of 5 Patients (100 mg and 200 mg Cohorts) Had a Valsalva LVOT-G of <50 mmHg After a Single Dose of EDG-7500

* Efficacy evaluable population
Source: Edgewise Therapeutics Data on File

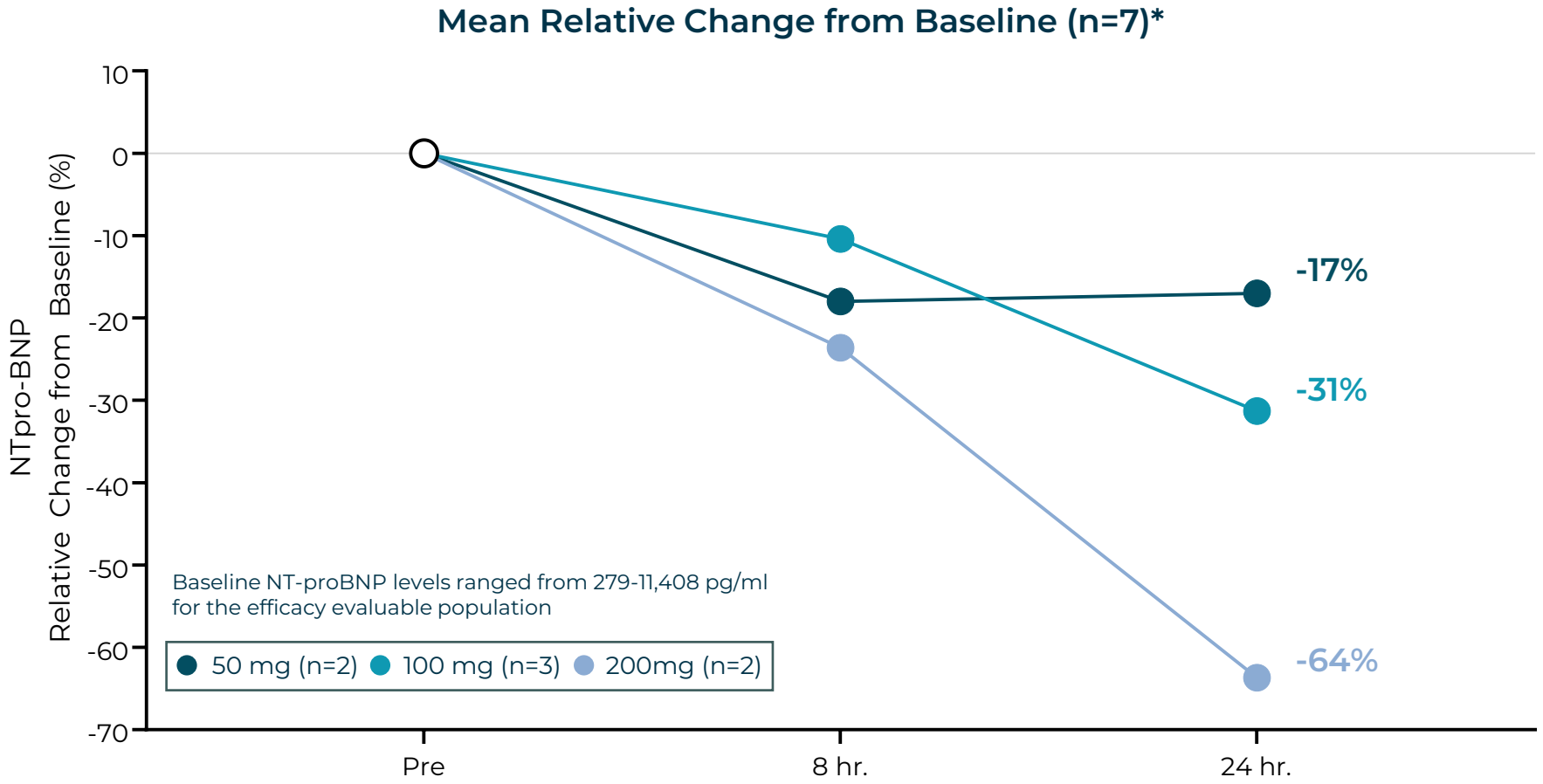
Gradient Relief in oHCM Patients was Achieved Without a Meaningful Reduction in LVEF



There was No Correlation Between EDG-7500 Plasma Concentration and LVEF Change

Source: Edgewise Therapeutics Data on File

EDG-7500 Administration Resulted in Robust Reductions in NT-proBNP, a Key Marker of Heart Failure in HCM[1]



NT-proBNP is a Marker of Diastolic Function, and Reductions Have Been Associated with Increased *p*Vo_2 the Primary Endpoint in oHCM Phase 3 Trials

* Efficacy evaluable population
Source: Edgewise Therapeutics Data on File
[1]Coats C.J. et al. European Heart Journal. 2013; 34(32), 2529–2537

EDG-7500 in oHCM patients **Relieved LVOT-G Without Reductions in LVEF**

CIRRUS HCM

- EDG-7500 was **well tolerated** across all doses studied in oHCM patients
- EDG-7500 administration led to a reduction in **resting LVOT-G of 67%** for the 100/200 mg cohorts combined with multiple individuals achieving gradients <30 mmHg
- EDG-7500 administration led to a reduction in **Valsalva LVOT-G of 55%** for the 100/200 mg cohorts combined with multiple individuals achieving gradients <50 mm Hg
- LVOT-G relief was achieved without reductions in LVEF
- EDG-7500 administration also led to a mean **31%** (100 mg) and **64%** (200 mg) drop in NT-proBNP, an independent predictor of heart failure

Encouraging Observations from the Single Dose Study Highlight EDG-7500's Potential as a Novel Therapy for Patients with HCM

EDG-7500 Future Development Plans

Dr. Marc Semigran

Positive Data from CIRRUS-HCM Part A Supported the Initiation of Parts B and C in oHCM and nHCM, respectively

- **Edgewise has initiated enrollment of patients in the 28 Day study** of EDG-7500 for both obstructive and non-obstructive HCM
  - *Part B*: designed to demonstrate continued safety and deepening of efficacy response after 28-days of dosing with EDG-7500 in patients with **obstructive HCM**
  - *Part C*: designed to demonstrate improvements in diastolic function after 28-days of dosing with EDG-7500 in patients with **non-obstructive HCM**
  - Solid dosage form enables **outpatient administration** of EDG-7500
- Upon completion of CIRRUS-HCM, patients may be eligible for enrollment in a long-term extension study
  - Long term evaluation of tolerability and effects on patient feel and function to be studied

Closing Remarks

Kevin Koch, CEO

Early Observations from the CIRRUS-HCM Single Dose Study Highlight EDG-7500's Potentially Differentiated Profile in HCM

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

Safety	Based on Observations to Date, No Concerns of LVEF Drops
Efficacy	Ability to Deepen Functional, Symptom and QoL Improvements Without Concerns of LVEF Drops < 50%
Monitoring	No Excessive Monitoring Requirements Outside of Standard of Care in HCM
Diastolic Effect	Ability to Resolve Diastolic Dysfunction in Patients with Non-Obstructive HCM
Dosing	Fixed Once-Daily Dosing Without the Need for a Complicated Titration

What's Next? Edgewise Upcoming Value-Generating Milestones

		H1 2024	H2 2024	H1 2025
Cardiac EDG-7500	Hypertrophic Cardiomyopathy	Phase 2 CIRRUS-HCM Initiation ✓	Phase 1/Phase 2 EDG-7500 data in HVs & oHCM** ✓	
			Phase 2 28-day study Initiate in oHCM & nHCM** ✓	Phase 2 28-day study Initial Data readout
Skeletal Sevasemten	Becker	ARCH 24-month data ✓	Phase 2 CANYON 1-year placebo-controlled data	GRAND CANYON Recruitment complete (Q1)
	Duchenne	Phase 2 DUNE Exercise challenge data* ✓	Phase 2 LYNX & FOX Controlled dose-ranging data	Phase 3 trial Initiation

*includes Limb-Girdle & McArdle
**HV, healthy volunteers, oHCM, obstructive hypertrophic cardiomyopathy nHCM, non obstructive hypertrophic cardiomyopathy

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

CASH, CASH EQUIVALENTS & MARKETABLE SECURITIES

~$512M

DEBT

$0

COMMON SHARES OUTSTANDING (NASDAQ: EWTX)

~94M

CASH RUNWAY THROUGH 2027

As o June 30, 2024

Q & A