Mechanism of EDG-7500

September 22, 2026



Edgewise® THERAPEUTICS

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 product candidates and programs, including EDG-7500, EDG-15400 and EDG-003; statements regarding Edgewise's expectations relating to its clinical trials; and statements regarding Edgewise's milestones, including Edgewise's initiation of a Phase 3 trial of EDG-7500 in HCM, timing of FDA feedback on Phase 3 design, a Phase 2 trial of EDG-15400 in participants with HFpEF, 48-week data in EDG-7500, a Phase 2 trial data of EDG-15400 in participants with HFpEF and candidate selection for EDG-003. 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 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 potential need for substantial additional capital to finance its operations; Edgewise's substantial dependence on the success of EDG-7500; Edgewise's ability to develop and commercialize EDG-7500 and EDG-15400, and discover, develop and commercialize product candidates in its cardiovascular, cardiometabolic and 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, top-line and preliminary data from Edgewise's clinical trials changing as more patient data becomes available; risks related to failure to develop a proprietary drug discovery platform; 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 regulatory approval processes of domestic and foreign authorities being lengthy, time consuming and inherently unpredictable; risks relating to disruptions at the FDA, the SEC and other government agencies; 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; risks related to future acquisitions or strategic partnerships; risks related to Edgewise's future operations following the sale of sevasemten; risks relating to Edgewise not receiving milestone payments related to the Transaction; risks related to general economic and market conditions; and other risks

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This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

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Agenda

01

Introduction to Edgewise Therapeutics' Focused Cardiovascular Pipeline

02

EDG-7500 for HCM: Mechanism of Action

03

Near-term Program Milestones

04

Q & A

Speakers



Dr. Kevin Koch
Chief Executive Officer

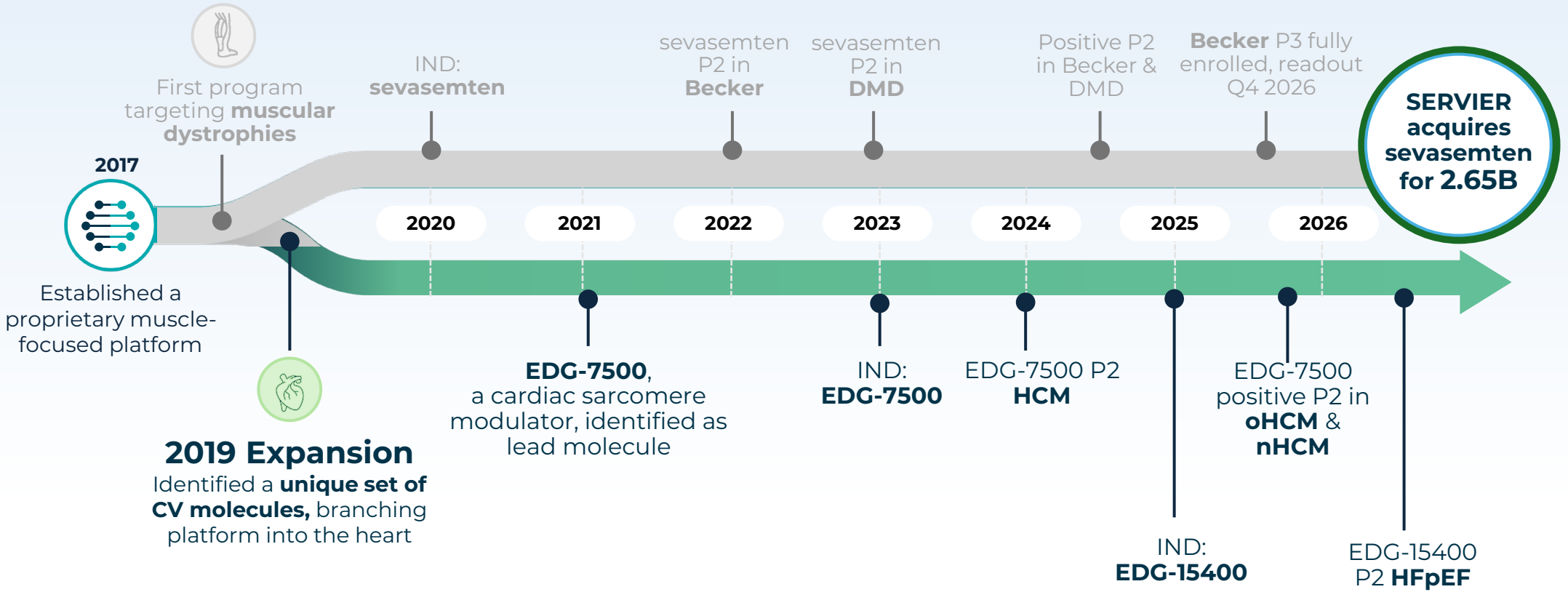


Dr. Alan Russell
Chief Scientific Officer

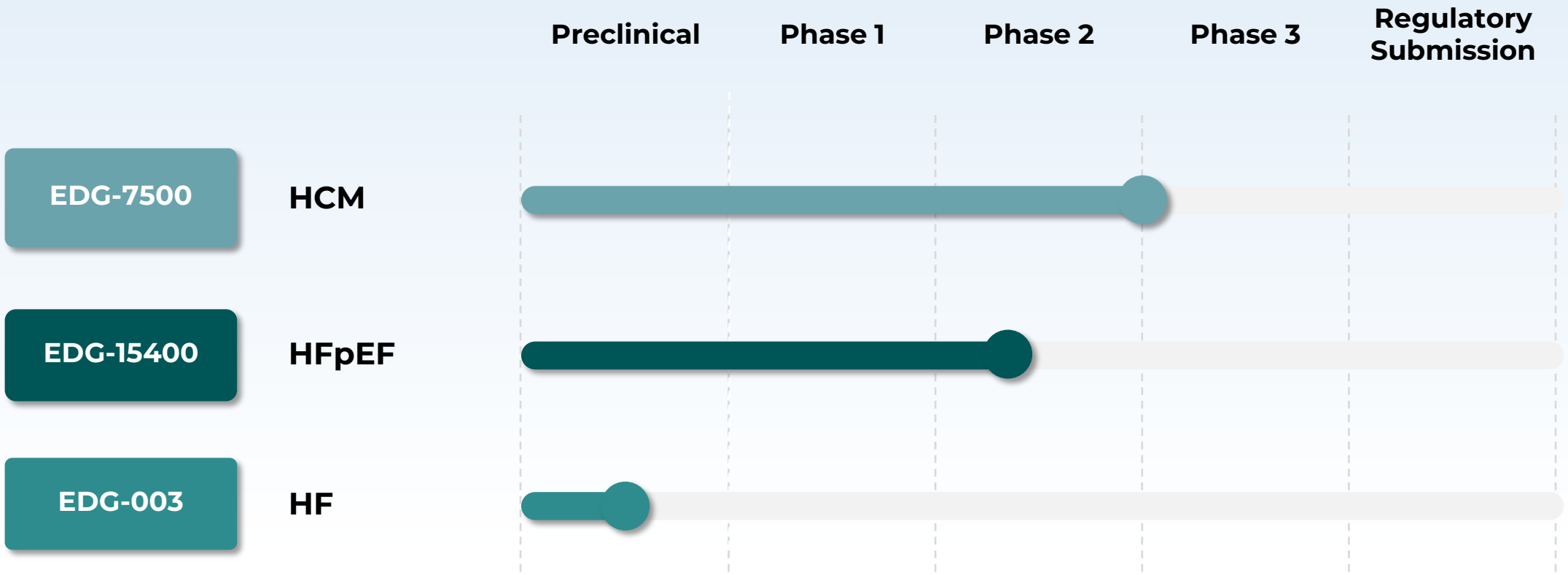


Dr. Michael Ayers
EDG-7500 Clinical Lead

Edgewise: Nine Years, Two Novel Targets and Three Clinical Programs



Edgewise Cardiovascular Portfolio



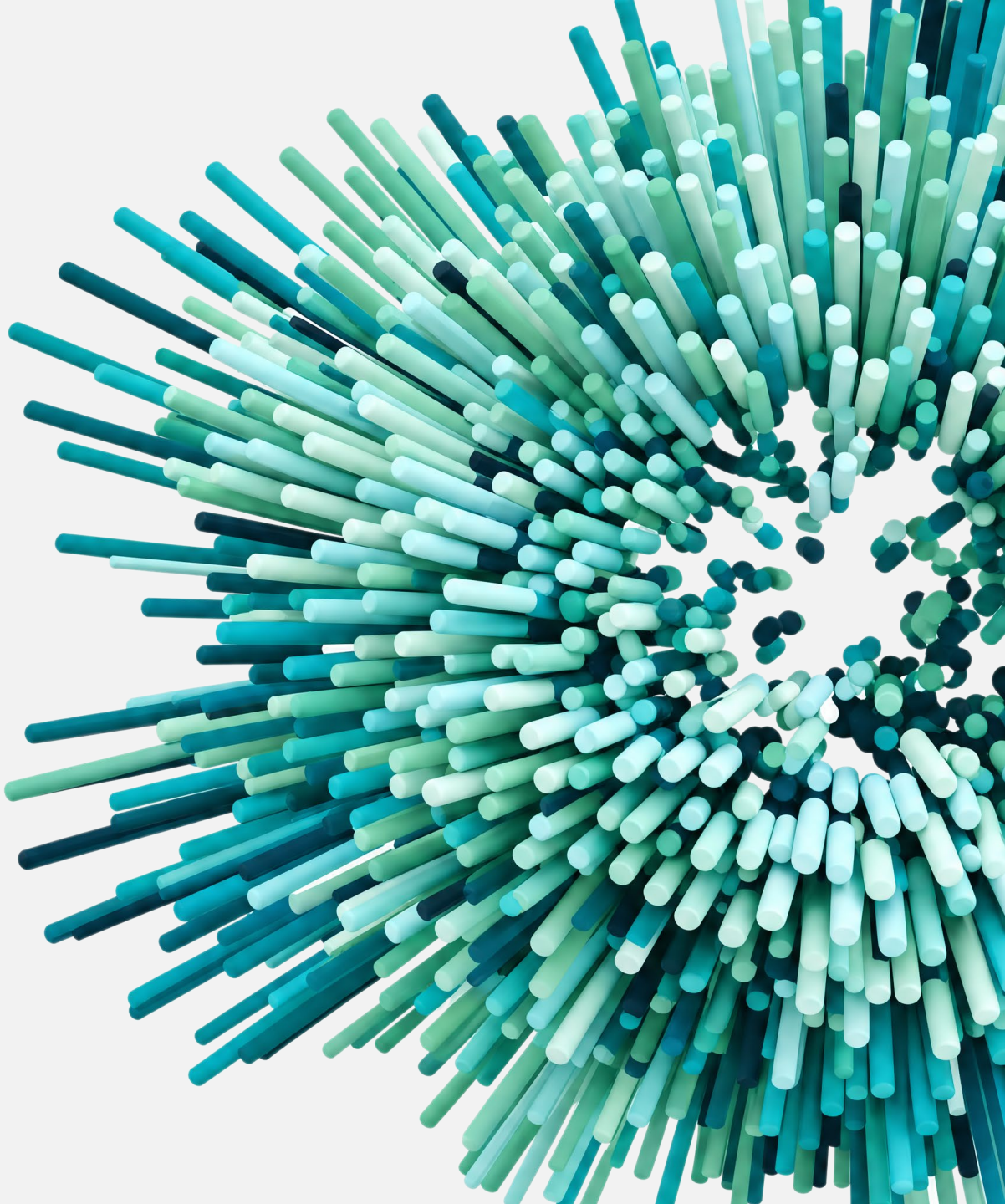
EDG-7500 and EDG-15400, and EDG-003 are investigational therapies that have not been approved by any regulatory authority, and their safety and efficacy have not been established
Abbreviations: HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HF, heart failure

Executive Summary

- EDG-7500 regulates the cardiac cycle through the Regulatory Light Chain (RLC)
- Targeting the RLC results in diverse profiles, from CMI-like negative inotropes to precision modulators
- EDG-7500 was selected to spare global systolic function and directly improve lusitropy
- Preclinically, EDG-7500 slows early systolic pressure, speeds up mid-to-late systole, and enhances early diastolic relaxation
- Clinical findings have been consistent with preclinical observations: EDG-7500 reduced gradients, preserved net systolic function, and improved diastolic relaxation
- Maintaining myosin availability may have differentiated exercise benefits in HCM patients

EDG-7500:

A Unique Mechanism Leading to Clinical Differentiation in HCM



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Four Questions That Have Defined the EDG-7500 Program

01 | RELIEVING OBSTRUCTION

How might EDG-7500 reduce LVOT gradients without suppressing contraction?

02 | PRESERVING SYSTOLIC FUNCTION

How might EDG-7500 modulate hypercontractility without suppressing LVEF?

03 | IMPROVING DIASTOLIC FUNCTION

How might EDG-7500 improve relaxation?

04 | IMPROVING FUNCTIONAL STATUS

How might EDG-7500 translate into meaningful improvements in symptoms and functional capacity?

A Mechanism that Acts Differently Across the Cardiac Cycle

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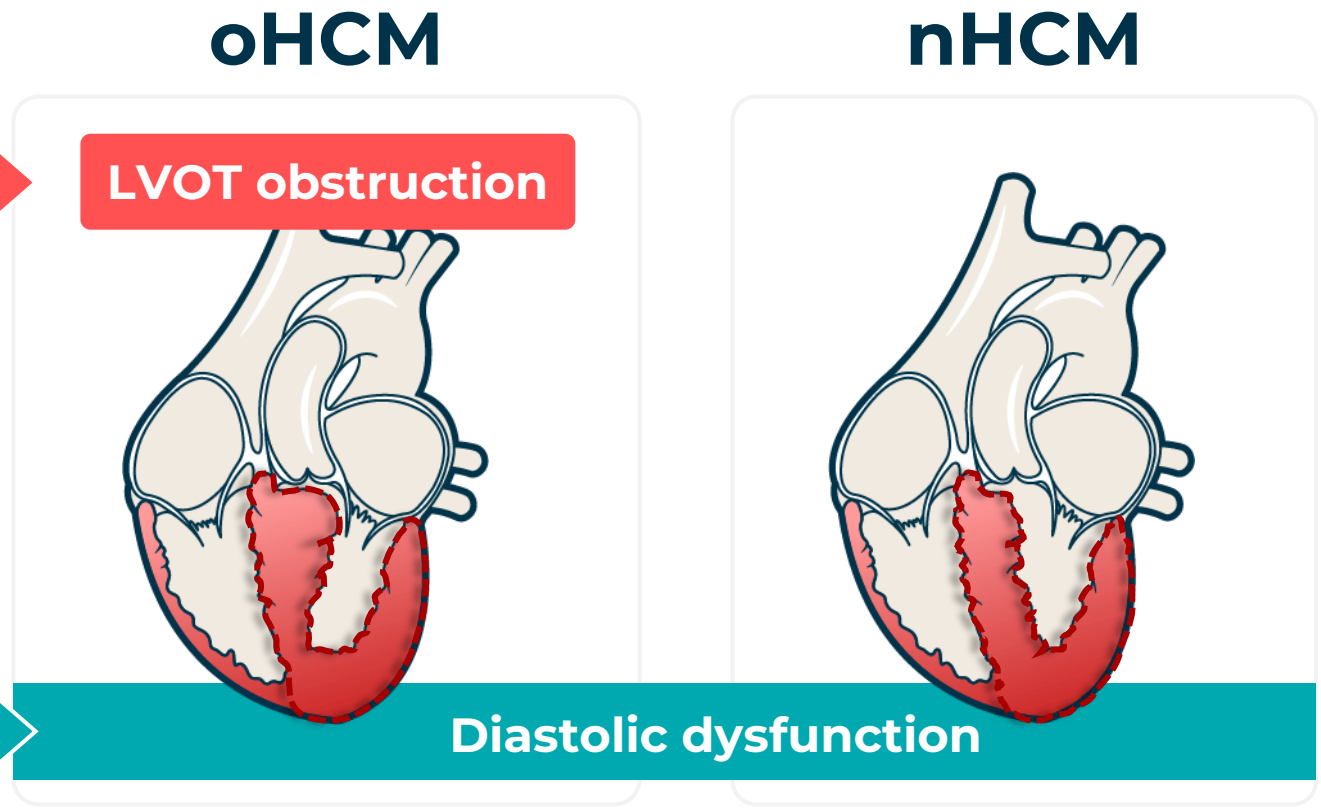
Abbreviation: LVOT, left ventricular outflow tract; LVEF, left ventricular ejection fraction

Current HCM Therapies Leave Significant Unmet Need

HCM is an inherited thickening of the heart muscle disease

Current therapies relieve LVOT obstruction via negative inotropy

Any diastolic benefit comes at direct systolic cost

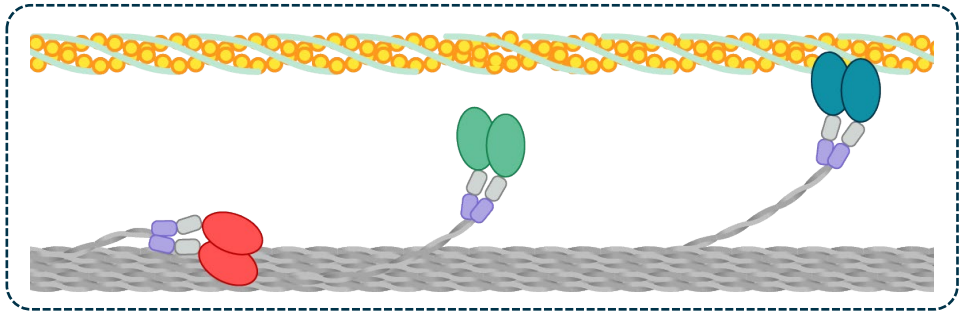


Abbreviations: LVOT, left ventricular outflow tract; HCM, hypertrophic cardiomyopathy; nHCM, nonobstructive HCM; oHCM, obstructive HCM

HCM Pathology is Caused by Myosin Overactivation

HEALTHY

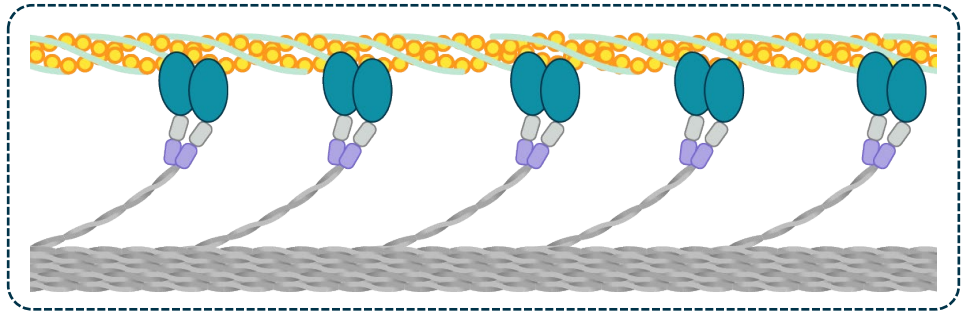
Sarcomere



- Active myosin heads
- Recruitable myosin heads
- Inhibited myosin heads

HCM

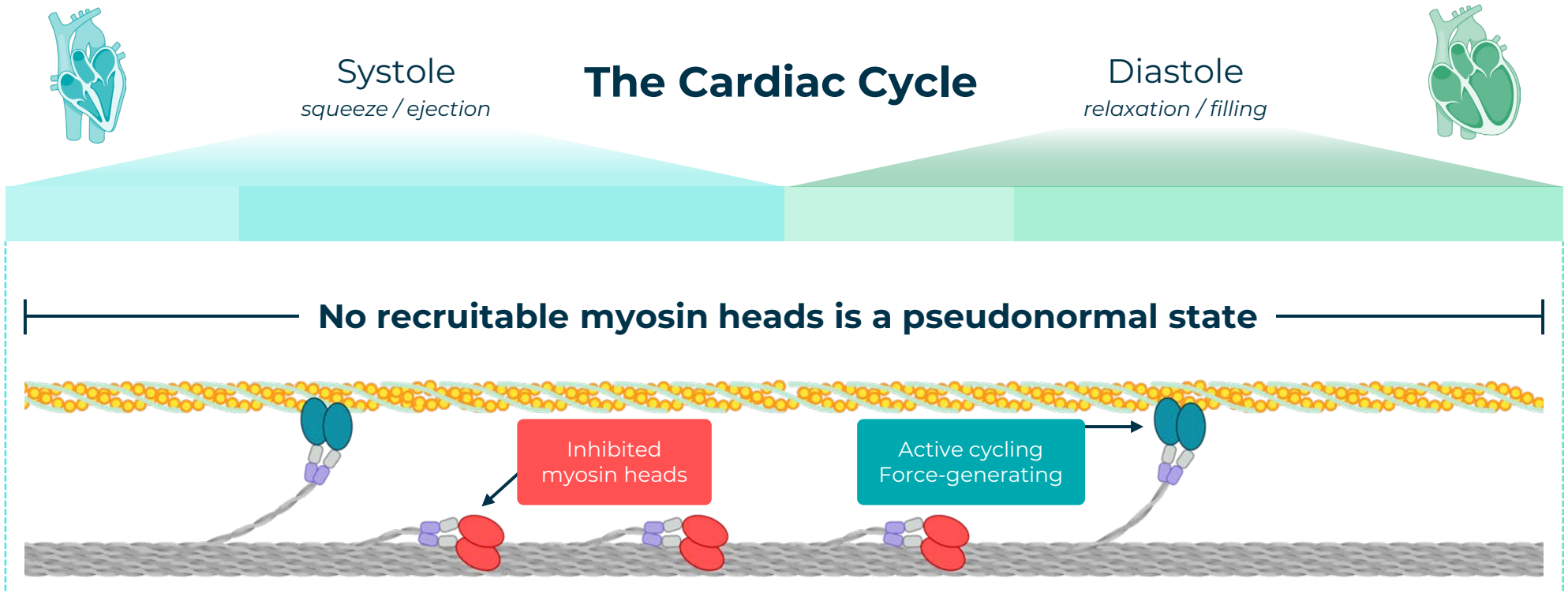
Sarcomere



- Hyperdynamic LVEF, hypertrophy and obstruction
- Diastolic dysfunction
- Impaired cardiac reserve

Abbreviations: HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction

CMIs Uniformly Inhibit Myosin Throughout the Cardiac Cycle



KEY TAKEAWAY: Diastolic benefit comes at a systolic cost with CMIs

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Abbreviations: CMIs, cardiac myosin inhibitors

Specific Phases of the Cardiac Cycle Drive Disease in HCM



Systole
squeeze / ejection

The Cardiac Cycle

Diastole
relaxation / filling



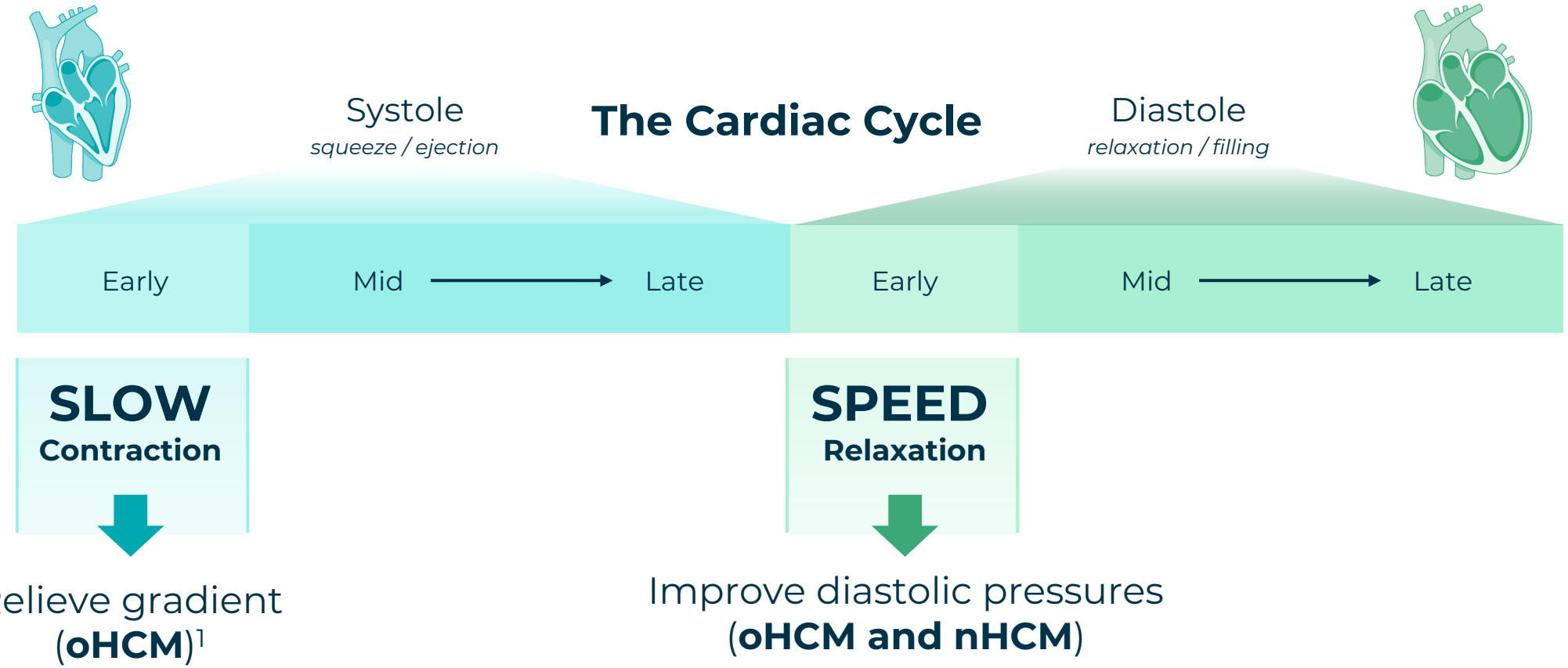
Early | Mid → Late | Early | Mid → Late

Gradient Initiation in oHCM

Diastolic Dysfunction in Both oHCM and nHCM

Abbreviations: HCM, hypertrophic cardiomyopathy; oHCM, obstructive HCM; nHCM, nonobstructive HCM

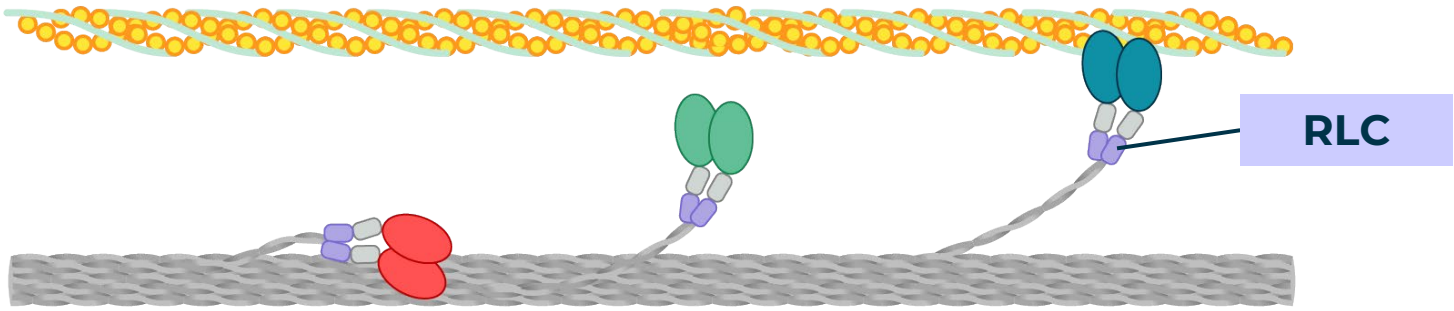
The Ideal Therapeutic Profile Relieves Gradients, Preserves LVEF, Improves Diastolic Function and Cardiac Reserve



1. Sherrid MV. Curr Cardiol Rev 2016; 12: 52-65

Abbreviations: LVEF, left ventricular ejection fraction; HCM, hypertrophic cardiomyopathy; oHCM, obstructive HCM; nHCM, nonobstructive HCM.

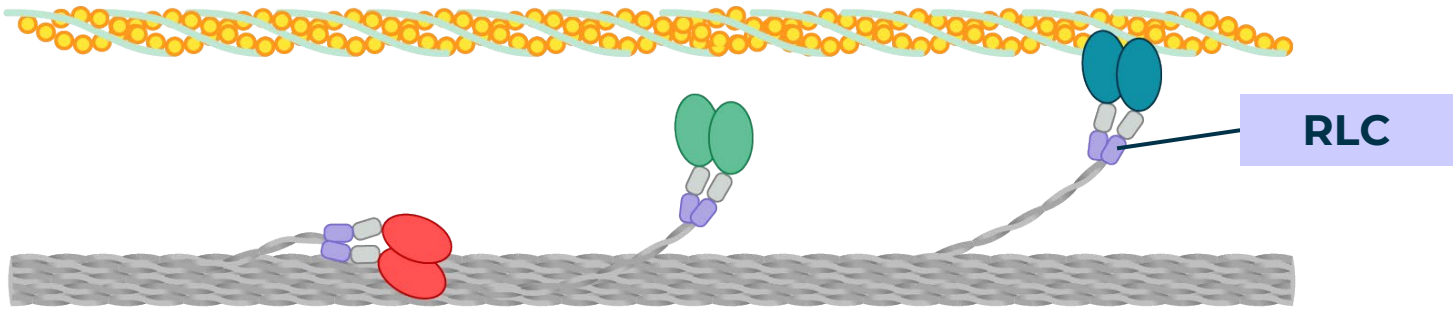
Myosin Regulatory Light Chain (RLC) Fine-Tunes the Cardiac Cycle



Two main functions of the RLC

1. Adjusting the stiffness of the lever arm to modify the efficiency of force development and relaxation
2. Adjusting the position of myosin heads relative to actin

EDG-7500 Alters Both Roles of the RLC to Adjust Contraction



EDG-7500 alters both functions of the RLC

1

EDG-7500 **reduces the stiffness** of the lever arm

- Slowing early contraction, speeding relaxation

2

EDG-7500 moves myosin heads **towards** actin

- Speeding of late systolic contraction

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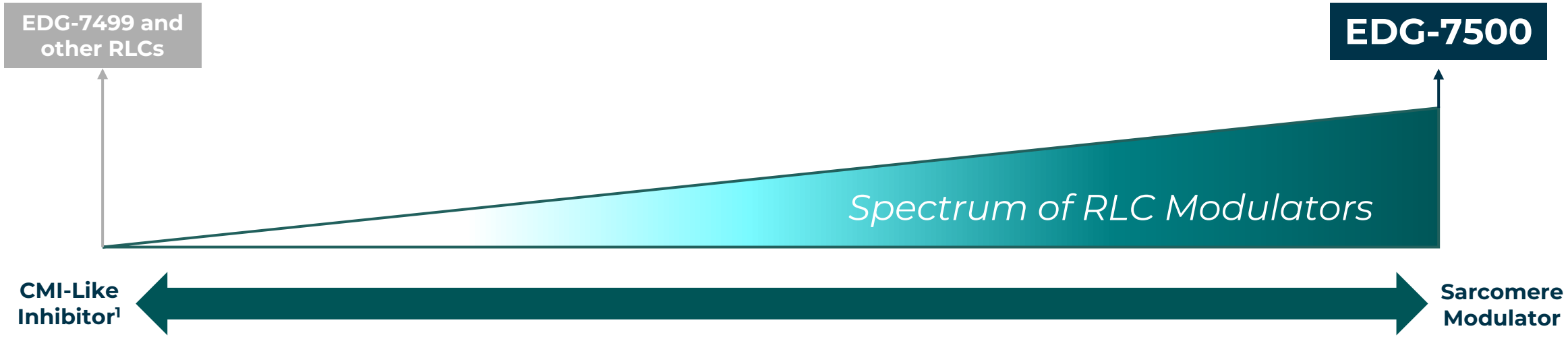
Emter et al. JCI Insight. 2026
Abbreviations: RLC, regulatory light chain

Not all RLC Modulators Behave Like EDG-7500

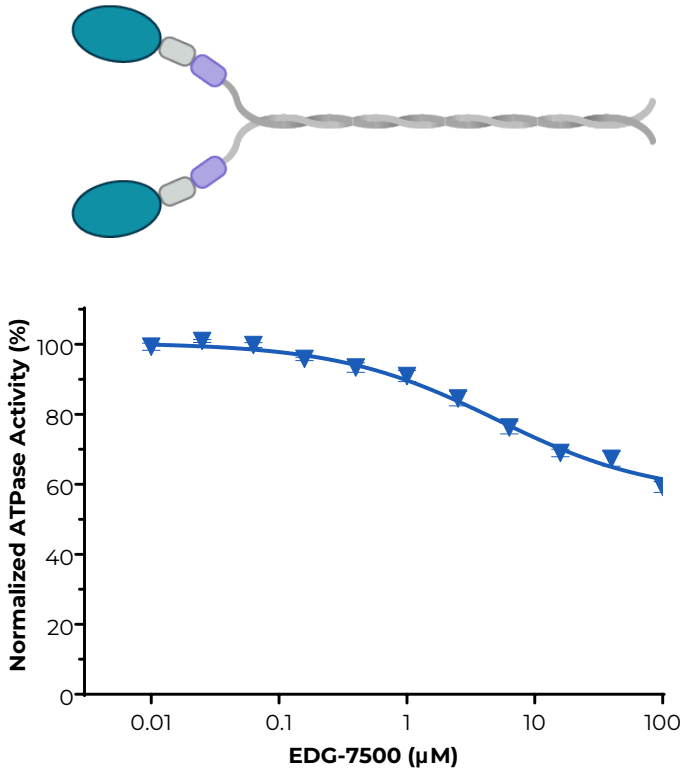


- Our discovery process revealed extensive mechanistic diversity across RLC modulators
- At the extreme are compounds that act like cardiac myosin inhibitors (CMIs)
  - **Strong negative inotropy** under all conditions
  - **Narrow therapeutic index** due to liability of systolic heart failure

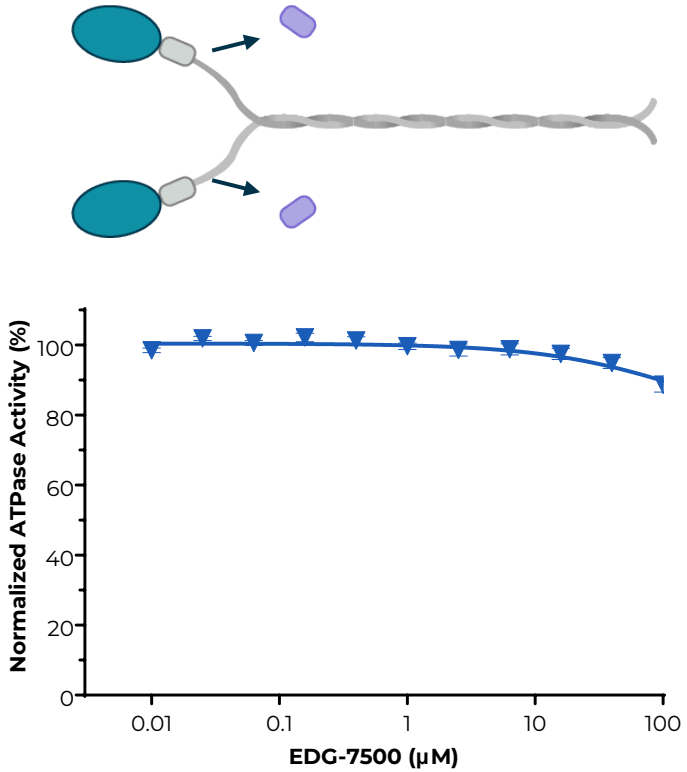
1. Lutz JD et al. *A First-in-Human Study of Ulacamten, a Novel Cardiac Myosin Inhibitor*. Clin Pharmacokinet. 2026.
Abbreviations: RLC, regulatory light chain

EDG-7500 is Inactive When Myosin RLC is Removed

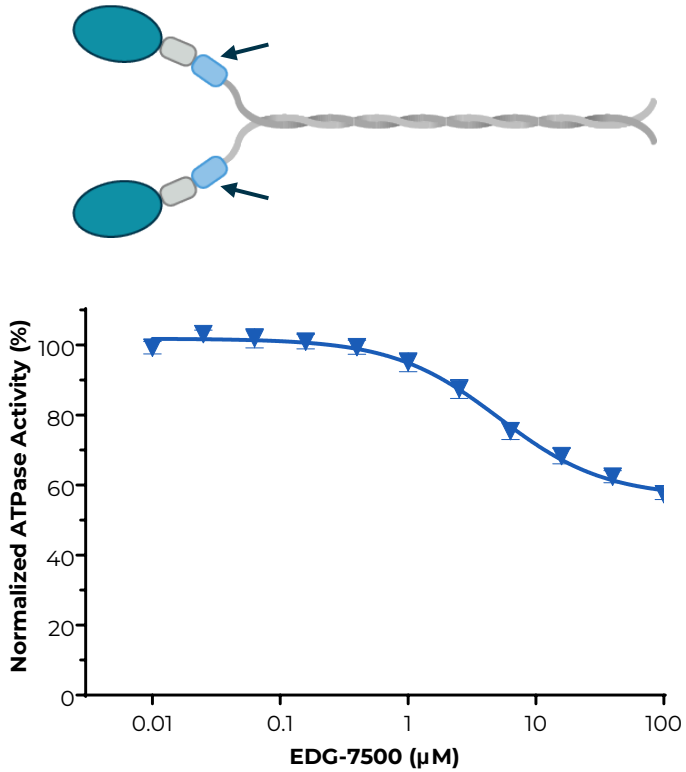
"Native Full-length Myosin" containing **RLC and ELC**



Full-length Myosin **depleted of RLC**

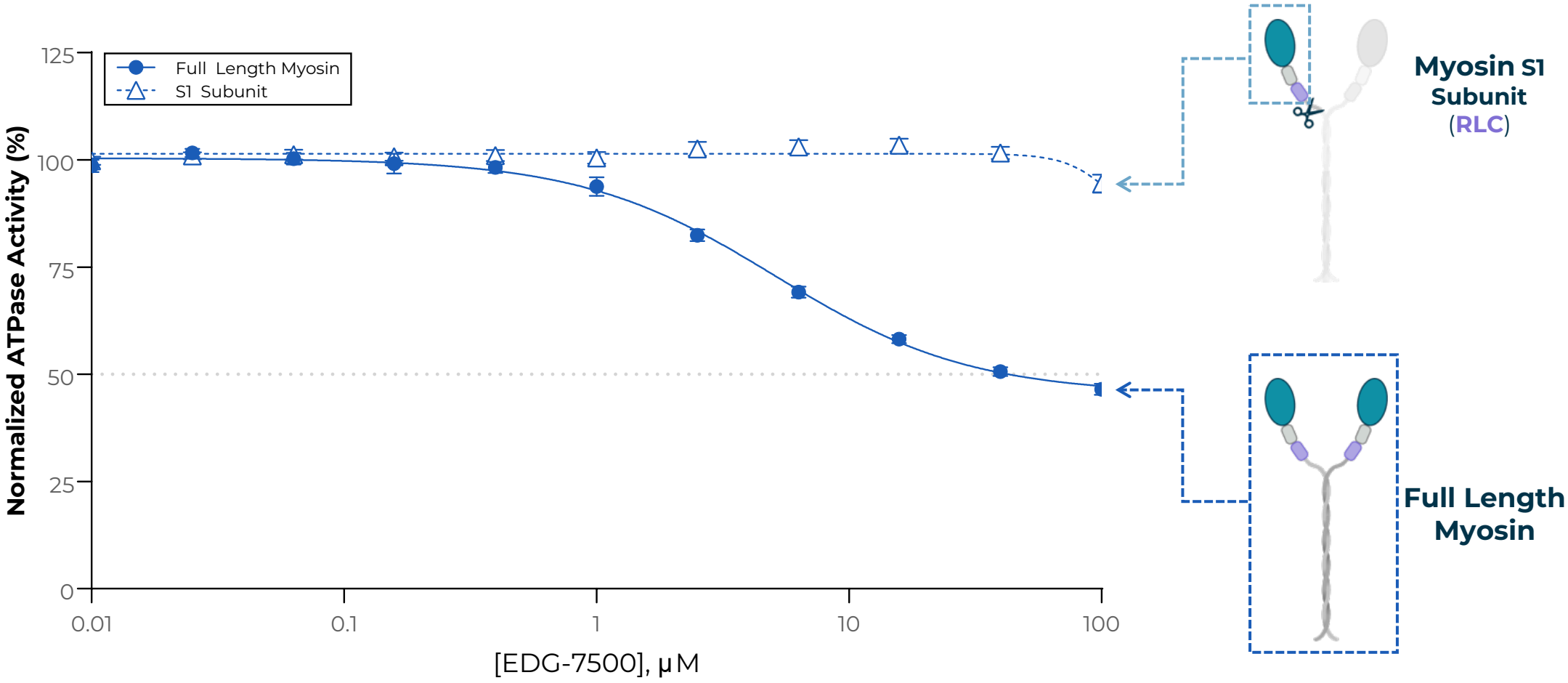


Full-length Myosin **exchanged with human ventricle RLC**



Abbreviations: RLC, regulatory light chain; ELC, essential light chain

EDG-7500 Does Not Inhibit Myosin Enzymatic Activity



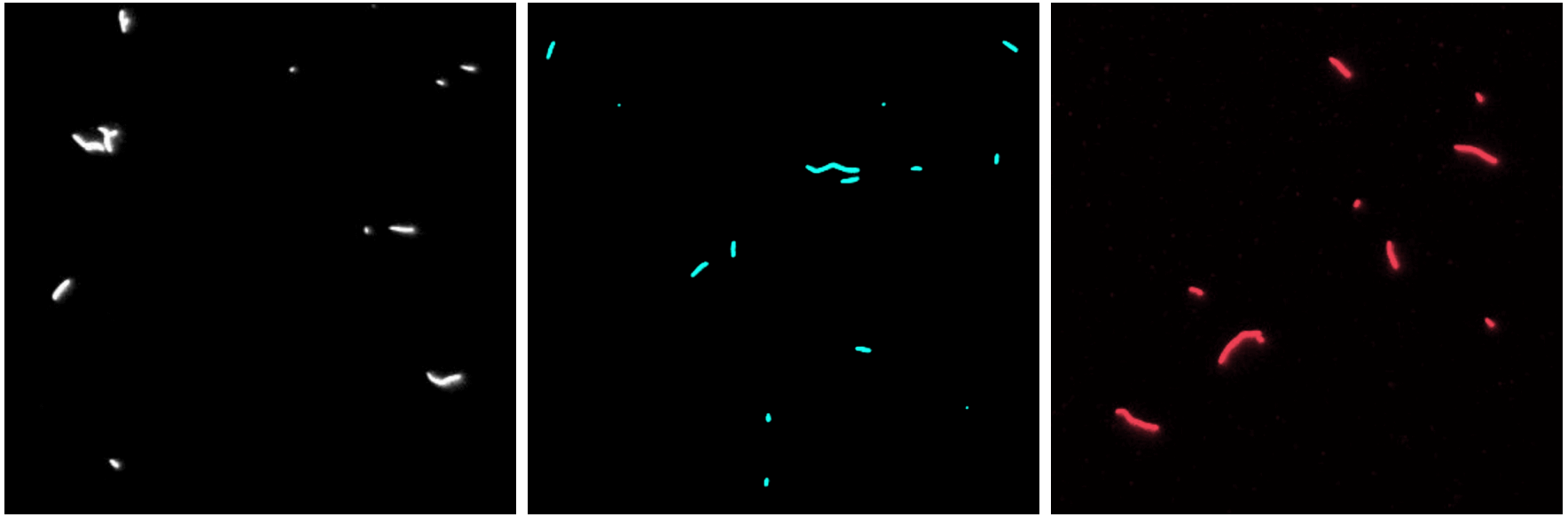
Abbreviations: RLC, regulatory light chain

How might EDG-7500 reduce LVOT gradients without suppressing contraction?

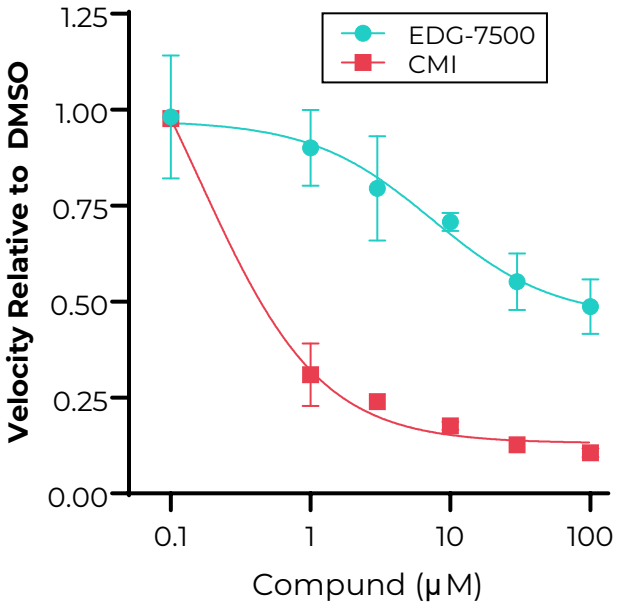
EDG-7500 Slows but Does Not Inactivate Myosin

In Vitro Motility Assay Measures the Sliding Velocity of Fluorescent Actin Filaments Propelled by Surface-Bound Myosin

DMSO **EDG-7500** **CMI**

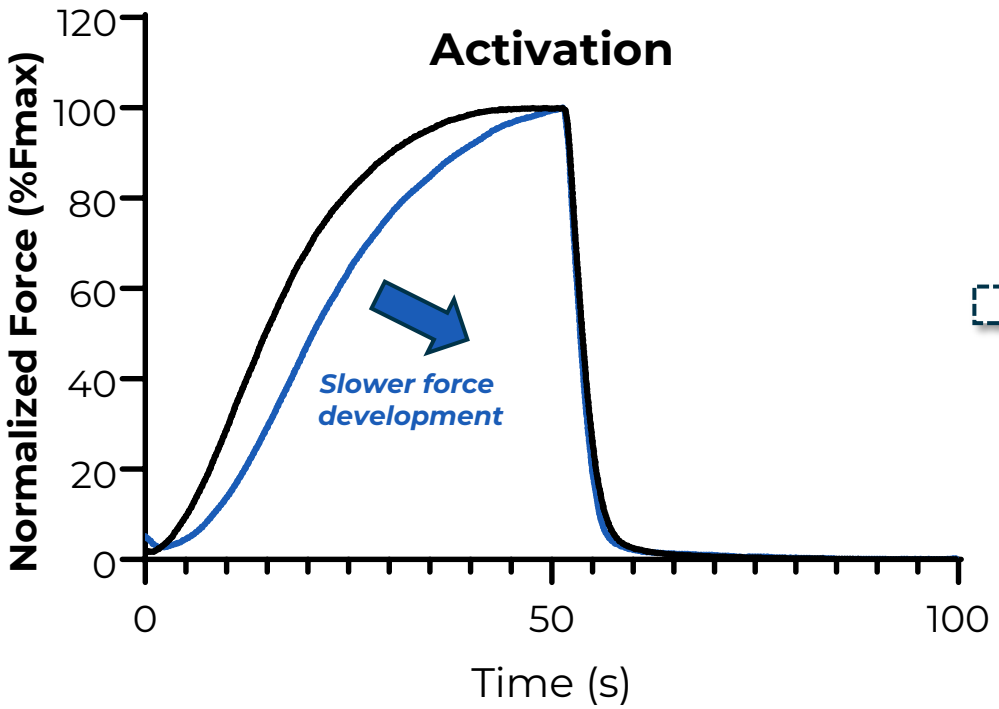


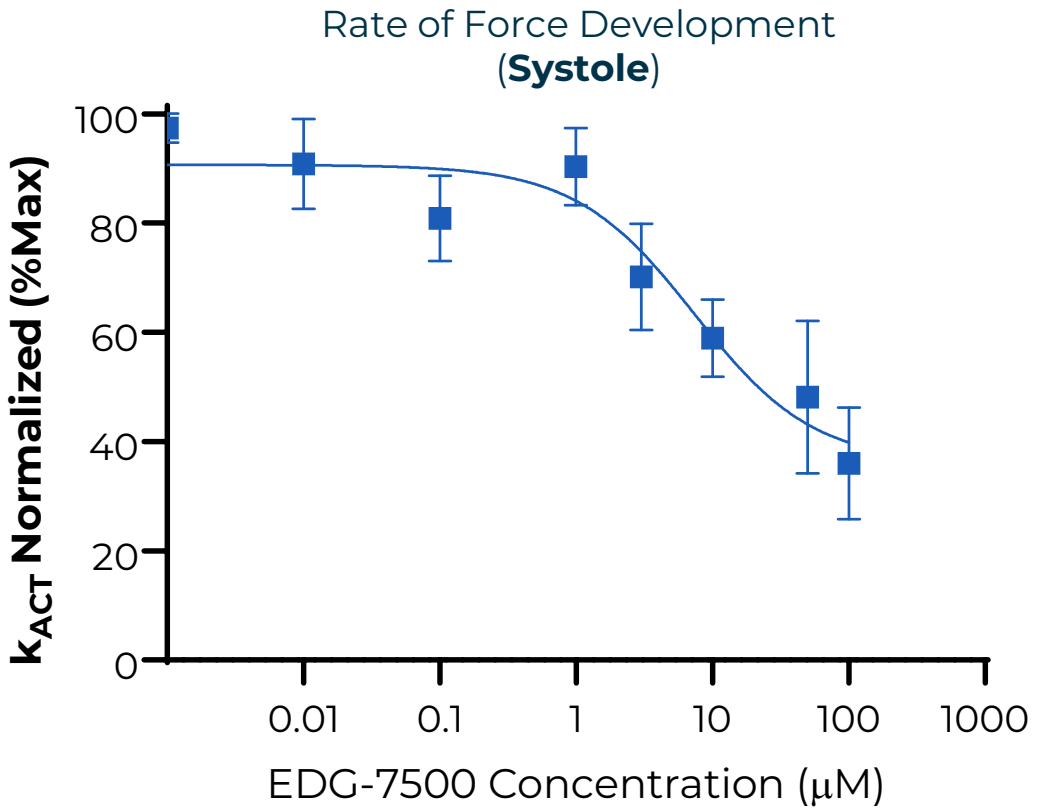
Video playback is at 15 frames per second



Abbreviations: CMI, cardiac myosin inhibitor

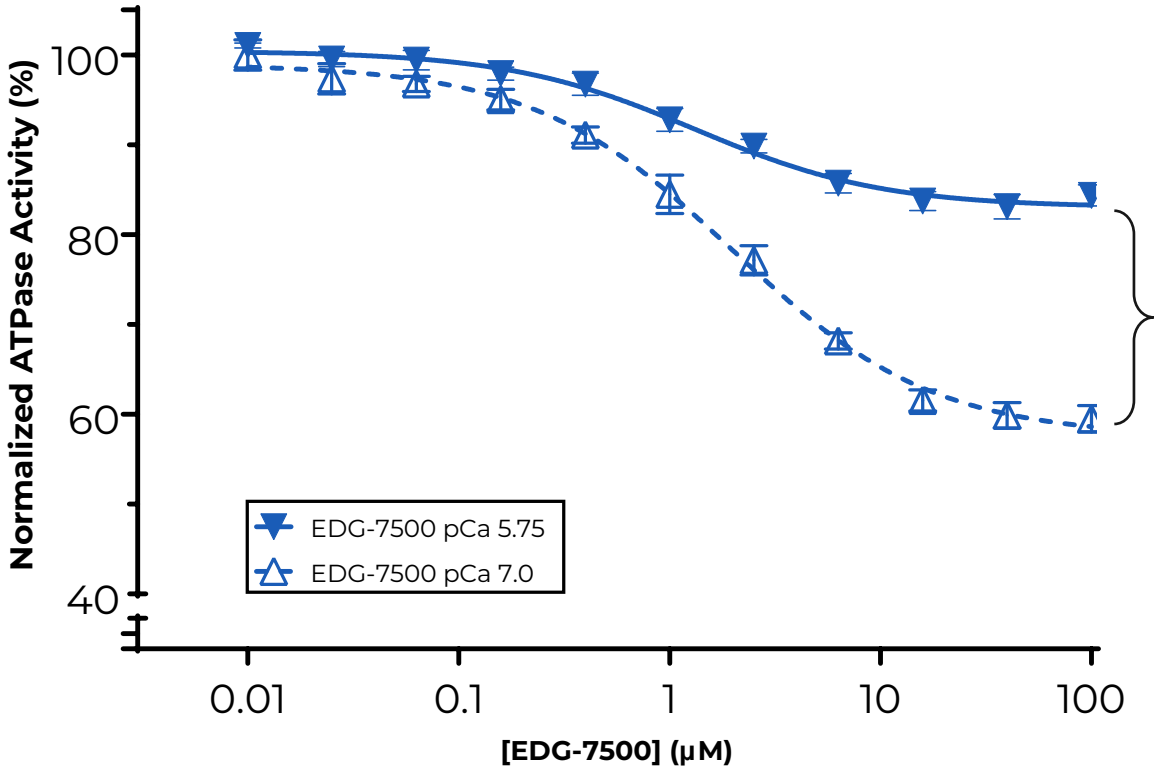
EDG-7500 Slows Early Force Development





Abbreviations: k_{ACT}, normalized rate of activation

EDG-7500 Slows Myosin Preferentially During Early Systole



Big shift in inhibitory activity between **high calcium (top)** and **low calcium (bottom)**

Abbreviations: pCa, negative logarithm of the free calcium ion concentrations (lower pCa = higher Ca^{2+})

EDG-7500 Administration Slowed Early Systolic Pressure in HCM

CIRRUS HCM



Systole
squeeze / ejection

The Cardiac Cycle

Diastole
relaxation / filling



Early | Mid → Late | Early | Mid → Late

SLOW Contraction
Pre-ET
+17.3%

Relieve Gradient (**oHCM**)[1]

1. Sherrid MV. Curr Cardiol Rev 2016; 12: 52-65
Abbreviations: oHCM, obstructive hypertrophic cardiomyopathy; Pre-ET, pre-ejection time
Pre-ET: Echocardiographic Measure of Early Systolic Pressure Decrease (Pre-ejection time) in CIRRUS-HCM 12-week Part D

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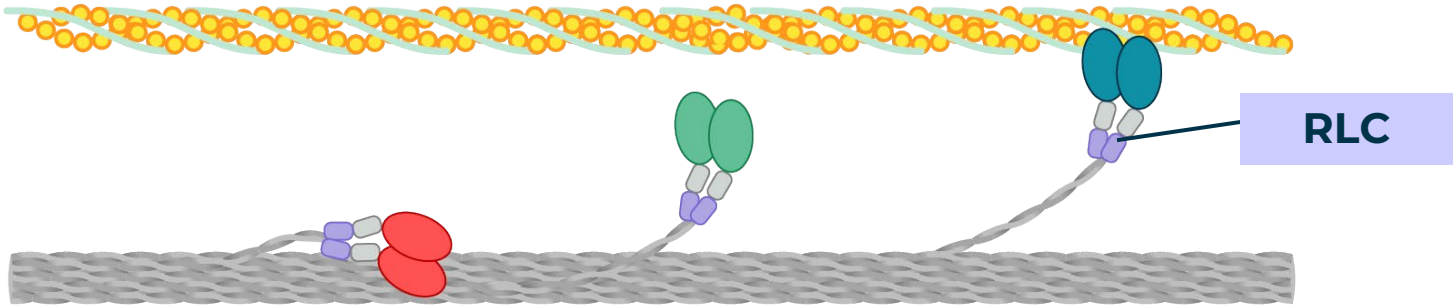
How might EDG-7500 modulate hypercontractility without suppressing LVEF?

EDG-7500 Alters Both Roles of the RLC to Adjust Contraction



EDG-7500 alters both functions of the RLC

1

EDG-7500 **reduces the stiffness** of the lever arm

- Slowing early contraction, speeding relaxation

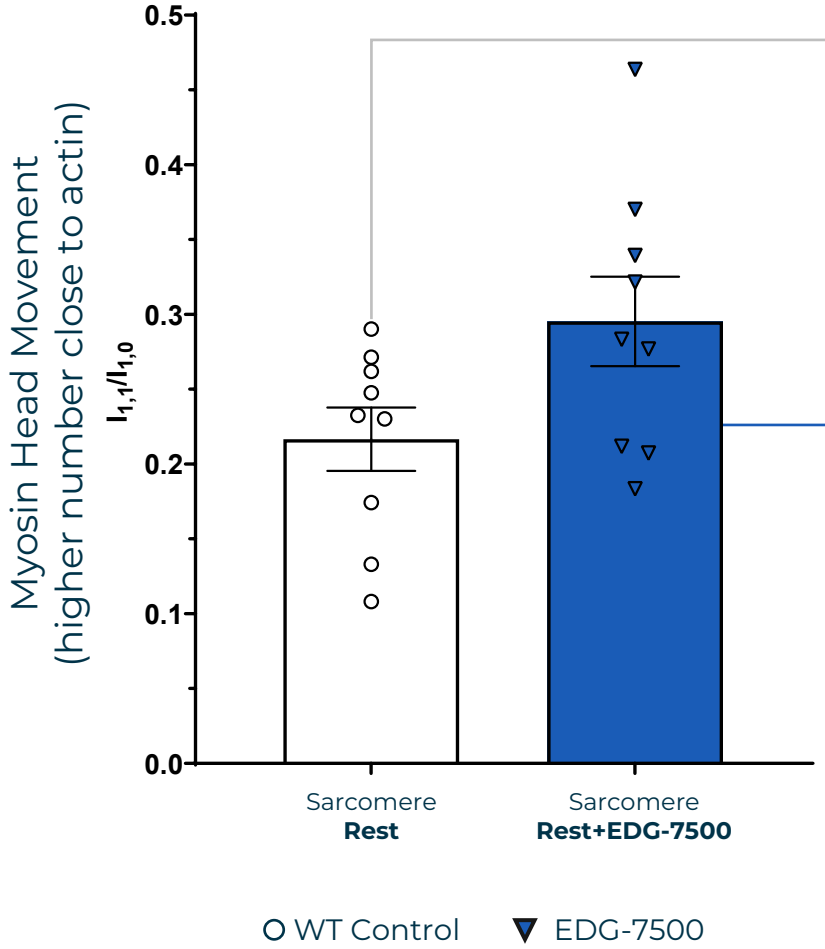
2

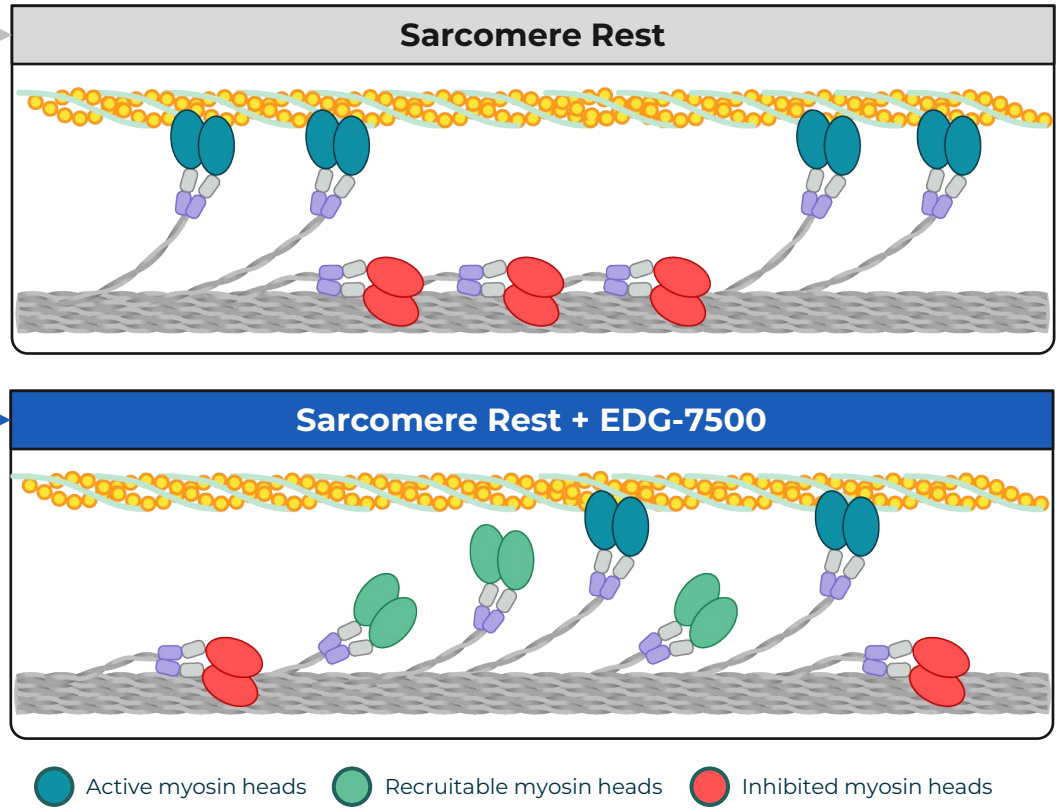
EDG-7500 moves myosin heads **towards** actin

- Speeding of late systolic contraction

Abbreviations: RLC, regulatory light chain

EDG-7500 Shifts Myosin Closer to Actin

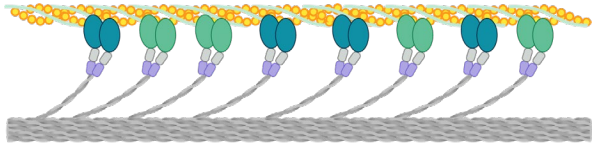




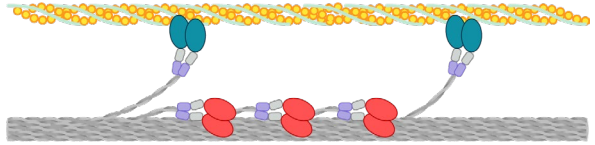
X-ray diffraction measures patterns reflective of sarcomeric protein organization in muscle. The I1,1/I1.0 ratio measures the position of myosin heads relative to the actin filament (higher = closer to actin)

In Late Systole, EDG-7500 Speeds Force Development

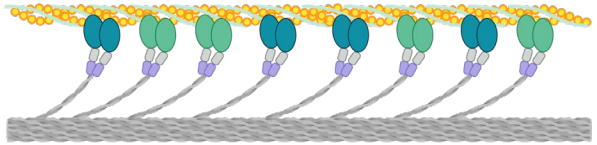
Fiber bundle fully activated

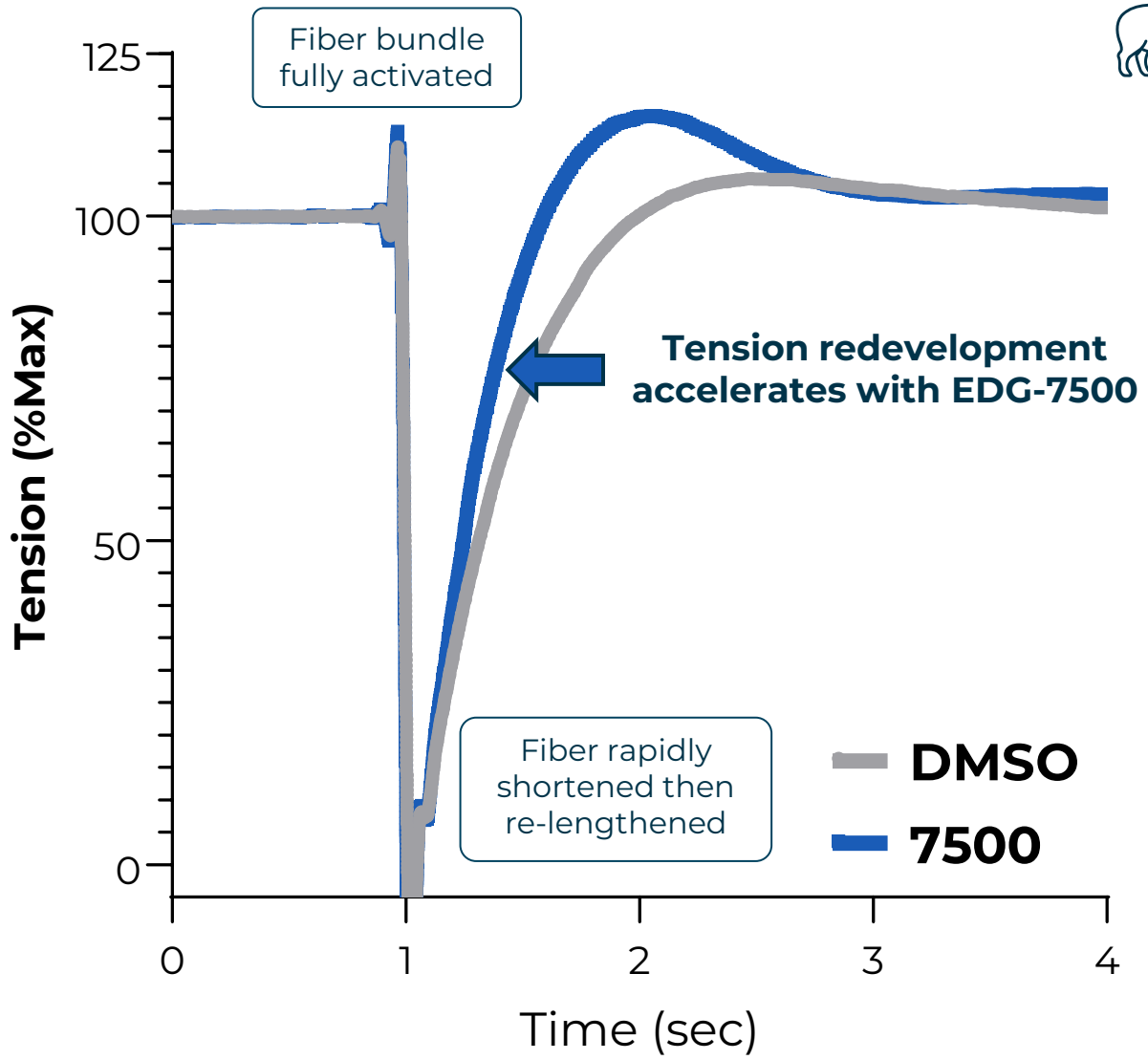


Rapidly shorten ***myosin heads disengage***

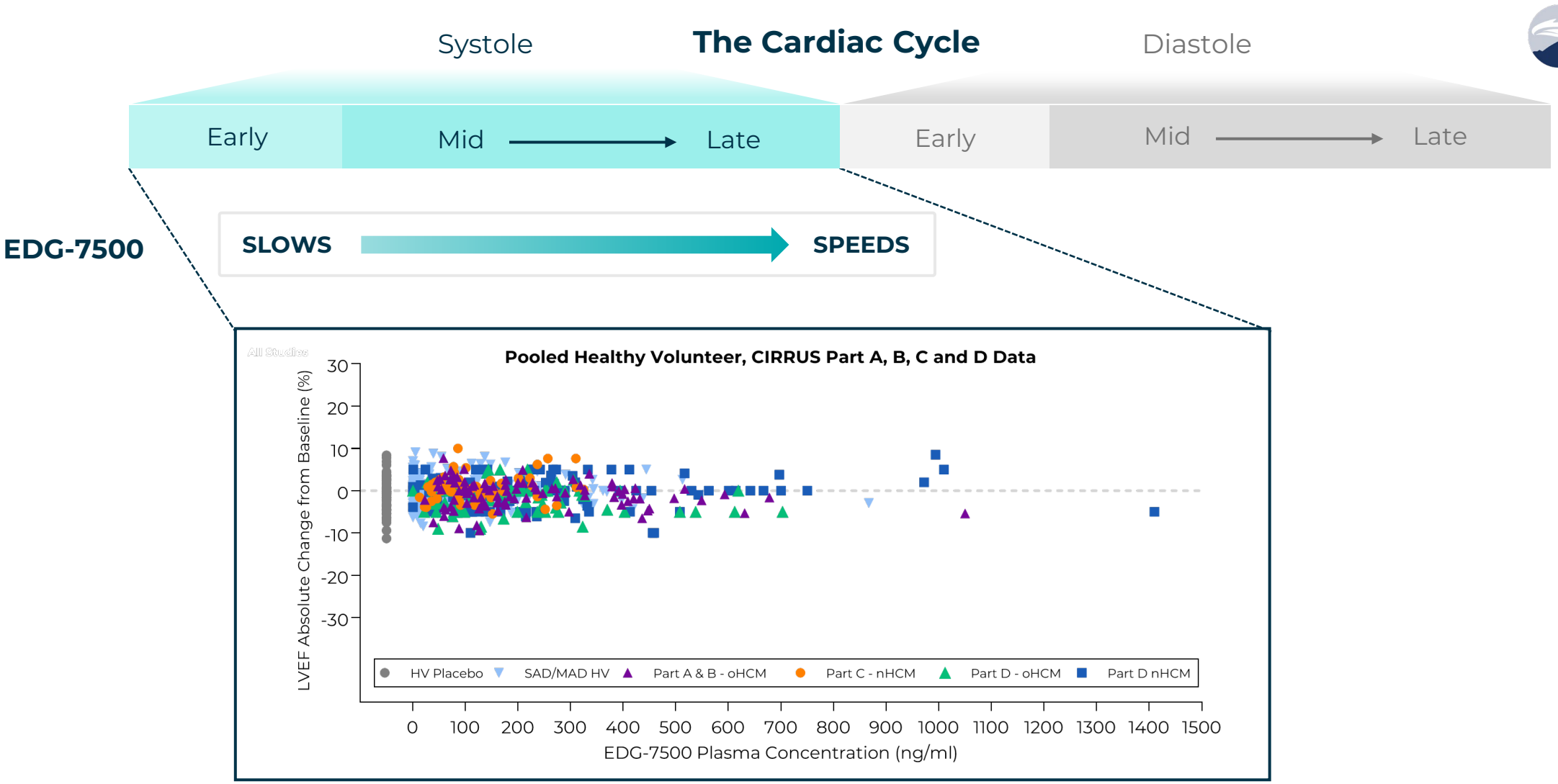


Rapidly lengthen ***myosin heads re-engage***





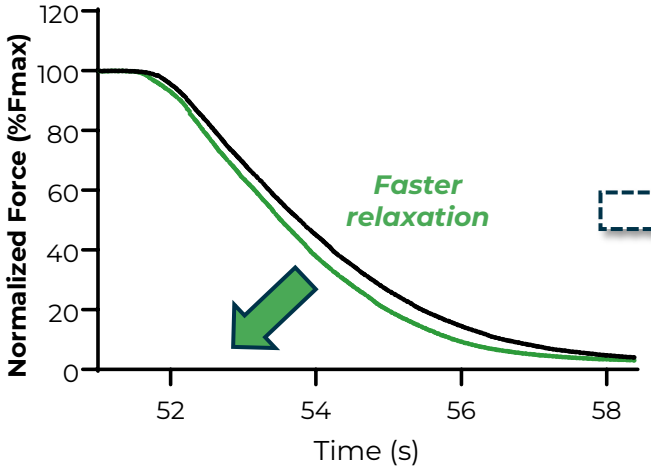
Clinically, EDG-7500 Has Not Affected LVEF

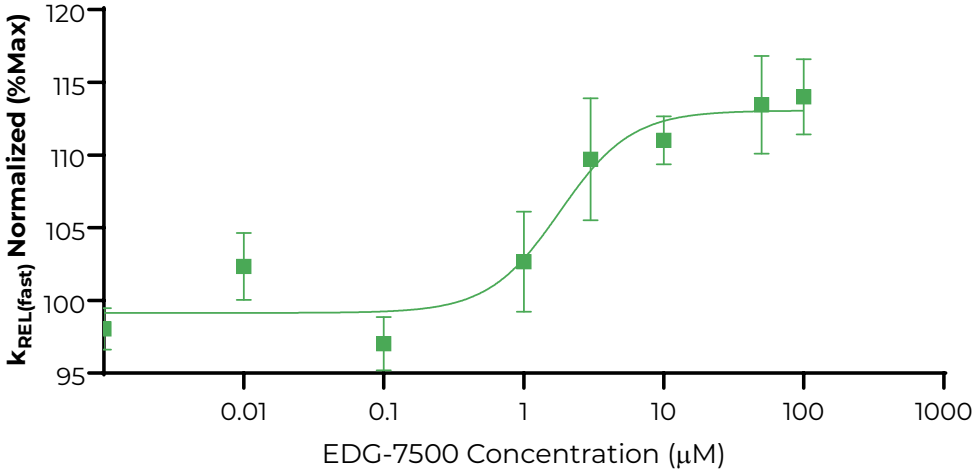


Healthy volunteers received doses of placebo or 5-300 mg in the SAD and placebo or 25-100 mg in the MAD CIRRUS Part A participants received single doses of 50 mg, 100 mg and 200 mg; CIRRUS Part B and C participants received fixed dose of either 25 mg, 50 mg or 100 mg; CIRRUS Part D participants received 25-200 mg Based on core lab read echoes
Abbreviations: HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; MAD, multiple ascending dose; nHCM, nonobstructive HCM; oHCM, obstructive HCM; SAD, single ascending dose.

How might EDG-7500 improve relaxation?

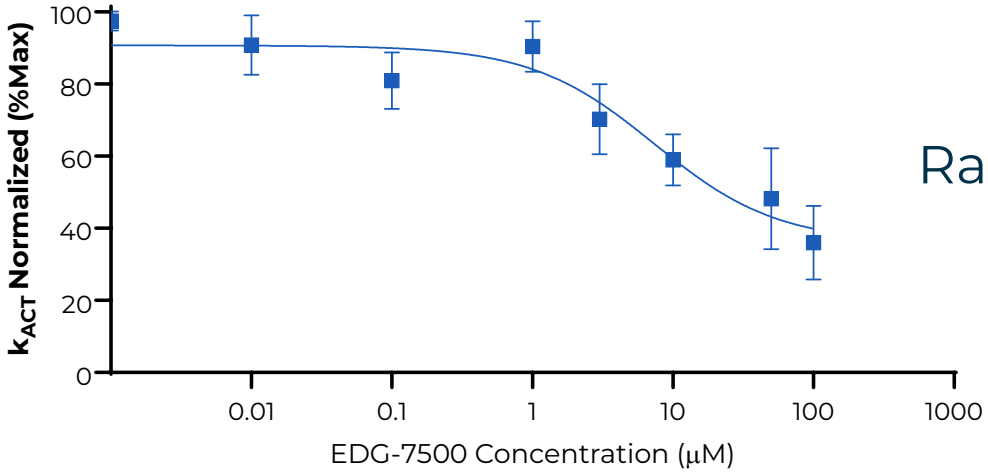
EDG-7500 Preferentially Speeds Relaxation in Cardiac Fibers





Rate of Relaxation
(**Diastolic**)

EDG-7500 4X more potent at enhancing relaxation



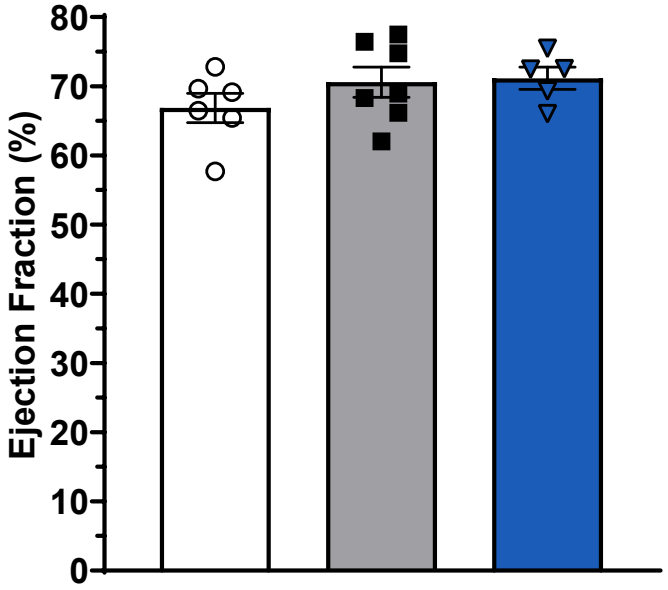
Rate of Force Development
(**Systolic**)

Abbreviations: k_{ACT}, normalized rate of activation; k_{REL}, normalized rate of relaxation

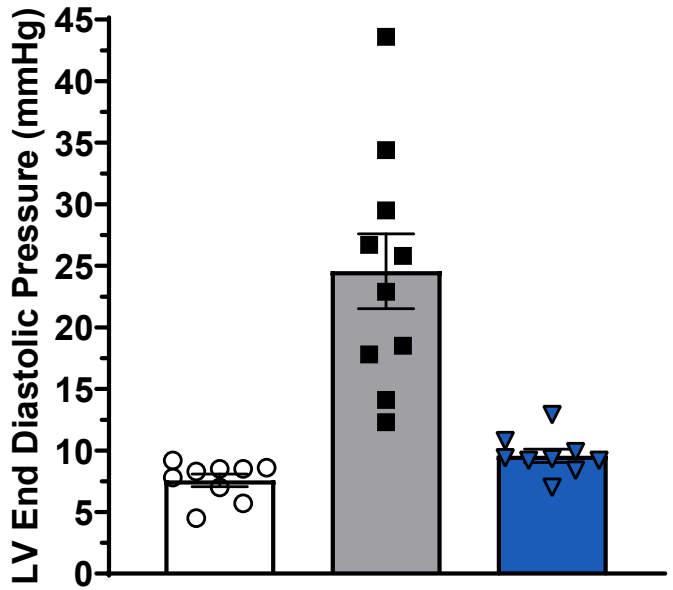
EDG-7500 Improves Left Ventricular Relaxation Without Systolic Cost in Pig Model of nHCM



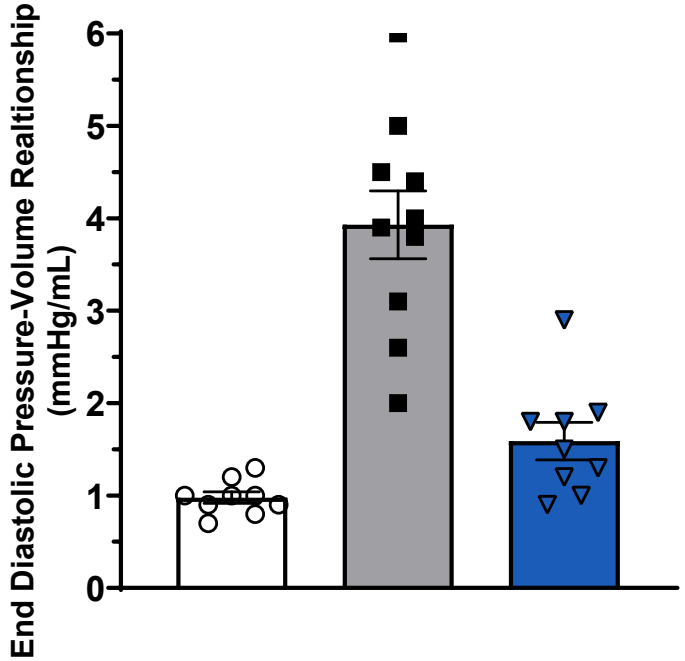
LVEF



LVEDP



EDPVR



WT Control ■ R403Q + Placebo ▼ R403Q + EDG-7500

KEY TAKEAWAY: In the R403Q pig, 6 months of EDG-7500 treatment decreases LV filling pressure and improves compliance (pressure-volume) without altering LVEF% (cMRI)

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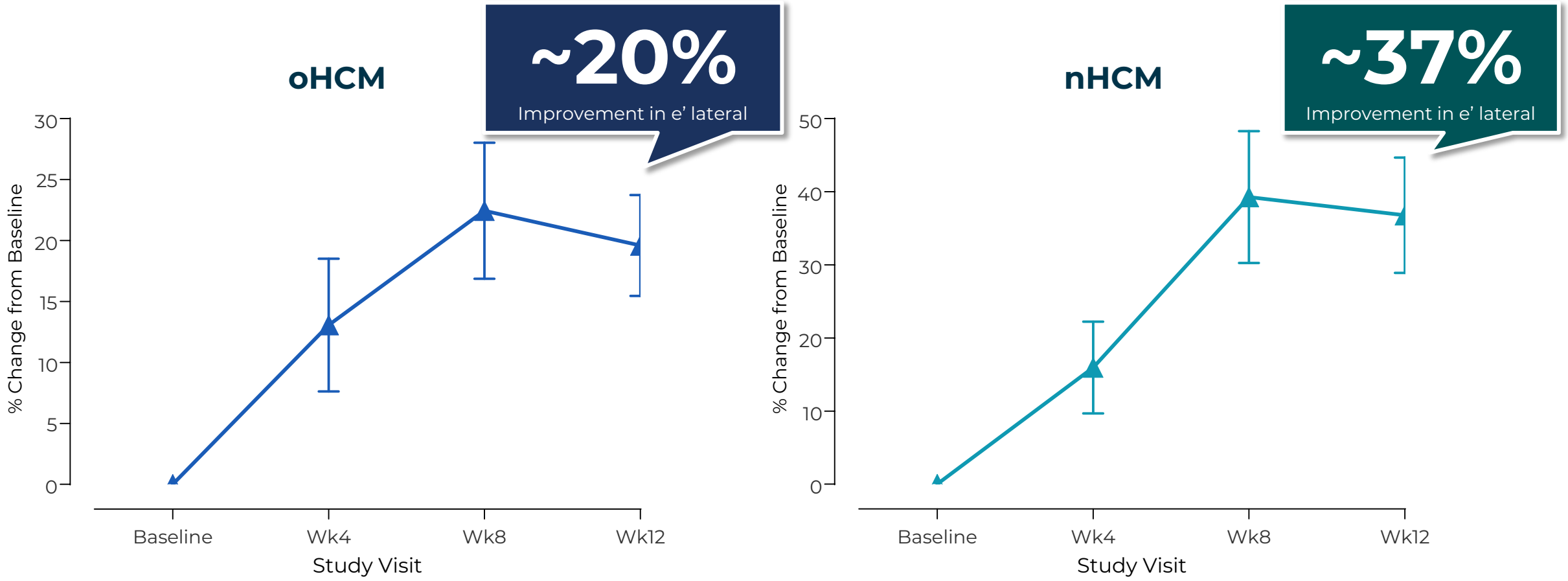
Abbreviations: LVEF, left ventricular ejection fraction; LVEDP, left ventricular end diastolic pressure; EDPVR, end diastolic pressure volume relationship; nHCM, nonobstructive hypertrophic cardiomyopathy; cMRI, cardiac magnetic resonance imaging

Administration of EDG-7500 Led to Increases in e' Lateral Suggesting Positive Lusitropic Effects

CIRRUS HCM

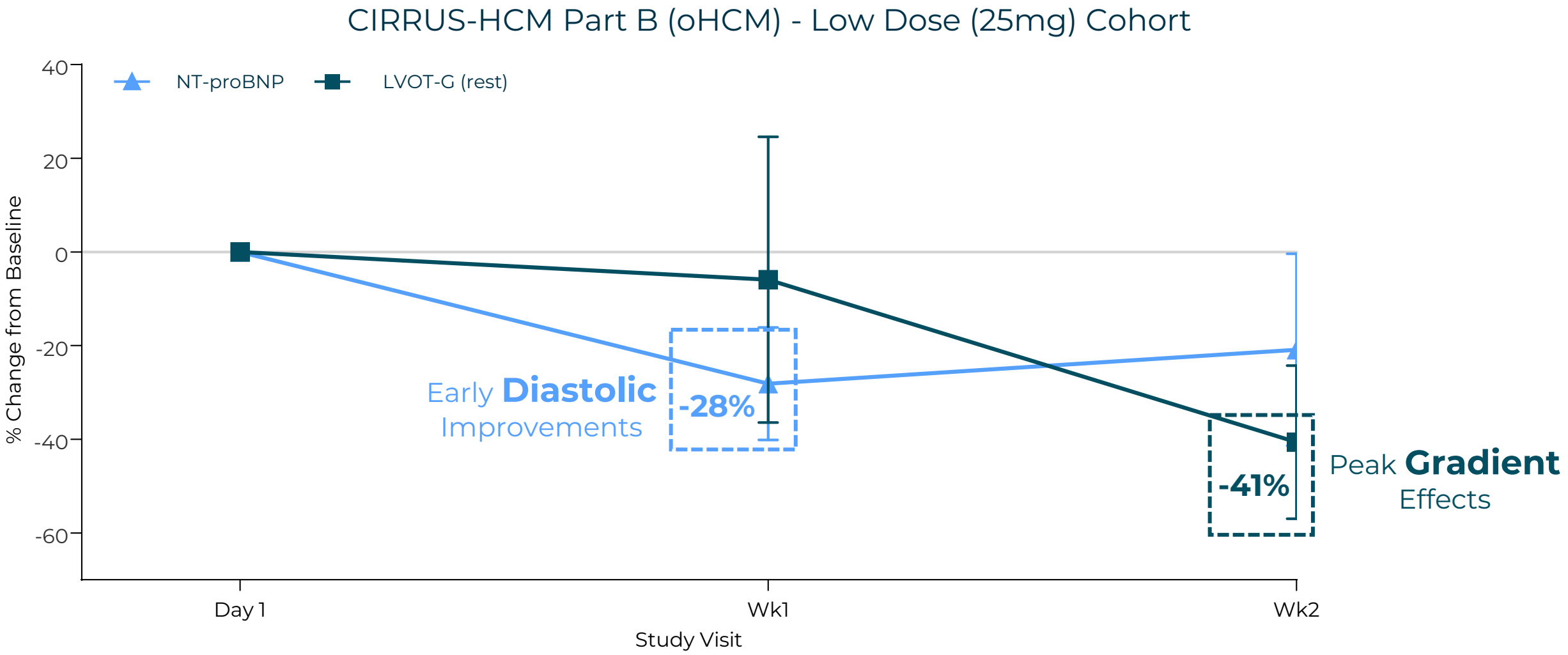
oHCM / nHCM: Rapid Improvements in Mean e' Lateral Observed (means ±SE)



CIRRUS-HCM Part D 12-Week Data: Owens AT, et al., European Society of Cardiology (ESC), Munich, Germany, August 2026.
Abbreviations: e' lateral, early diastolic tissue velocity of the lateral mitral annulus

Lusitropic Benefits Observed Even at Lower Exposures

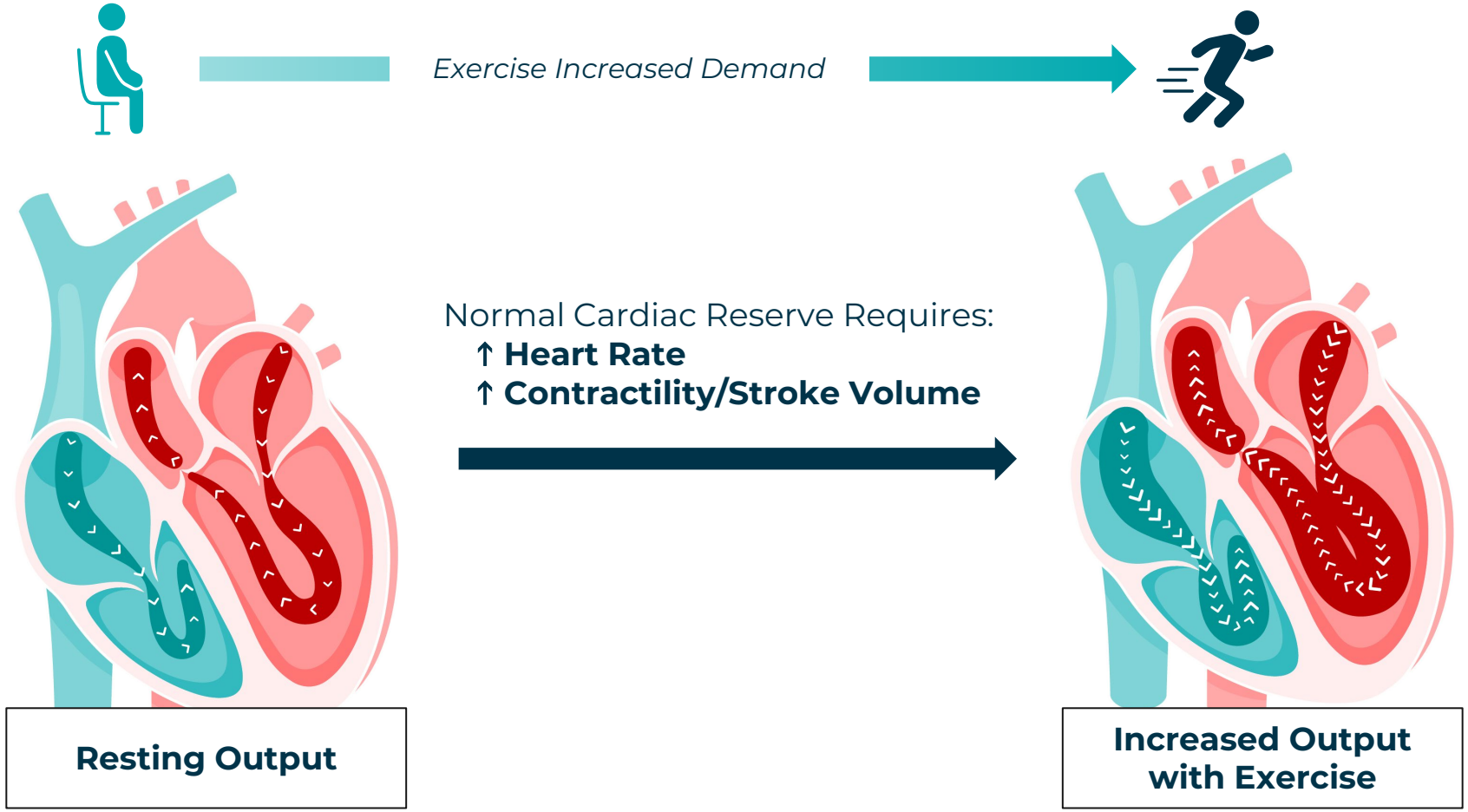
CIRRUS HCM



Abbreviations: oHCM, obstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro b-type natriuretic peptide; LVOT-G, left ventricular outflow tract gradient

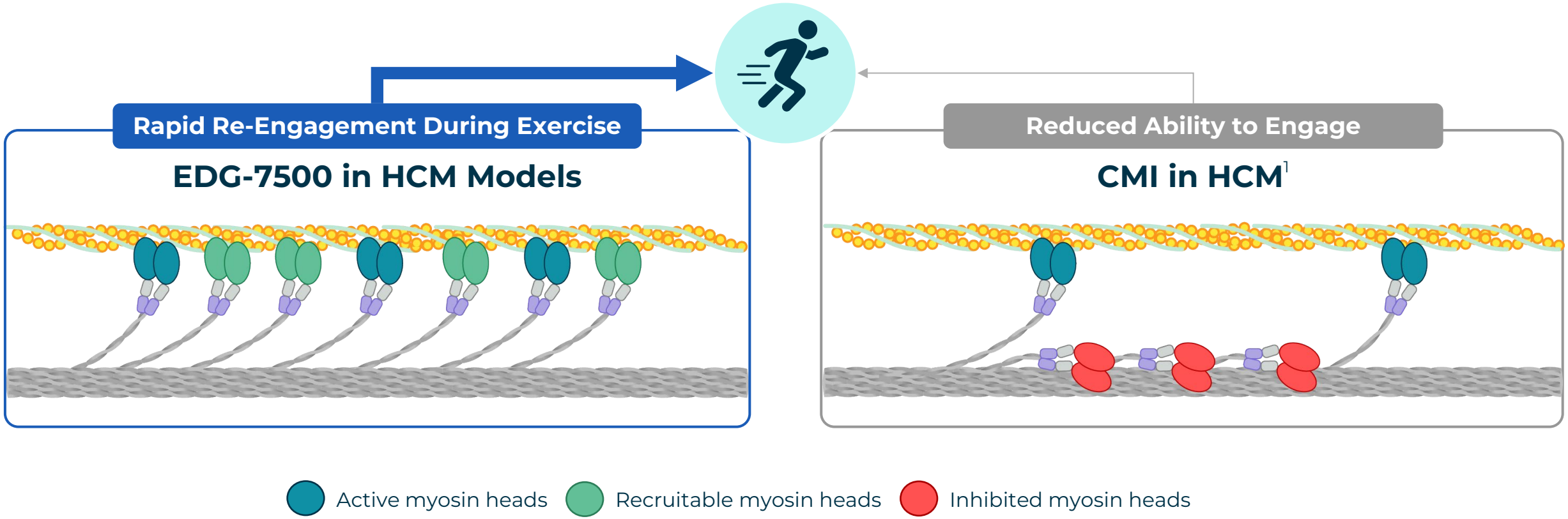
Why might EDG-7500 translate into meaningful improvements in symptoms and functional capacity?

With Exercise, Cardiac Output Increases



KEY TAKEAWAY: Preservation of recruitable myosin pool is central to maintaining a normal cardiac reserve

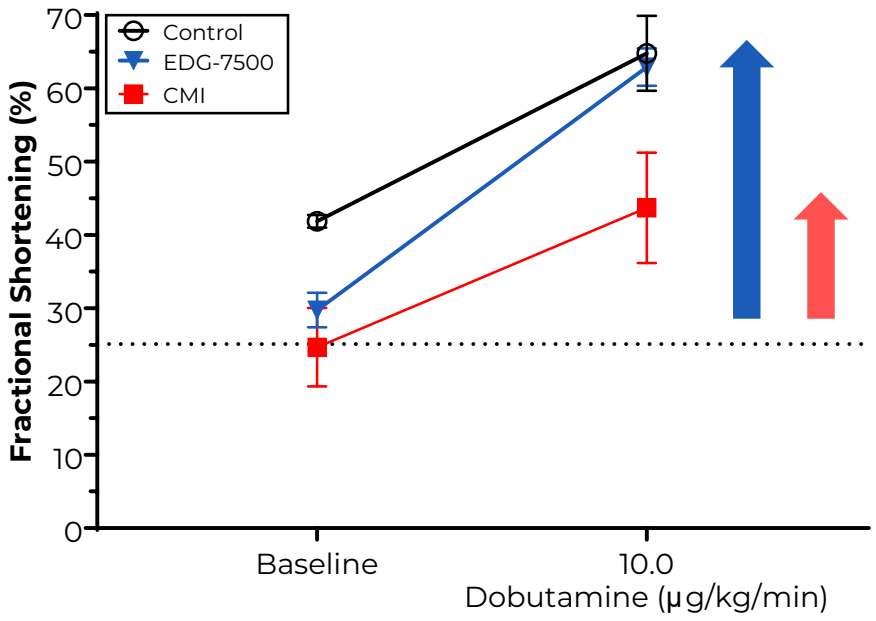
Increasing Cardiac Output Relies Heavily on Myosin Availability



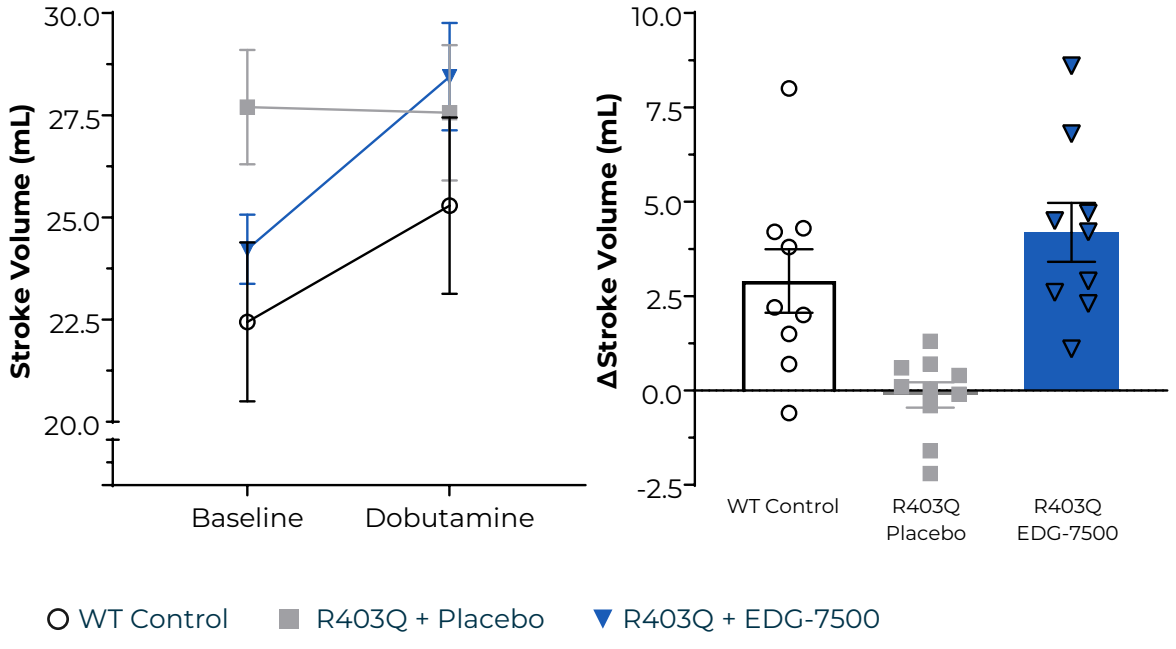
[1]Anderson RL, *et. al., PNAS*, 2018
Abbreviations: HCM, hypertrophic cardiomyopathy; CMI, cardiac myosin inhibitor

EDG-7500 Restores Cardiac Reserve in Two Animal Models

Normal Rat



nHCM Pig (MYH7R403Q)



KEY TAKEAWAY: Normal responses to cardiac demand are intact with EDG-7500, clinical KCCQ correlate

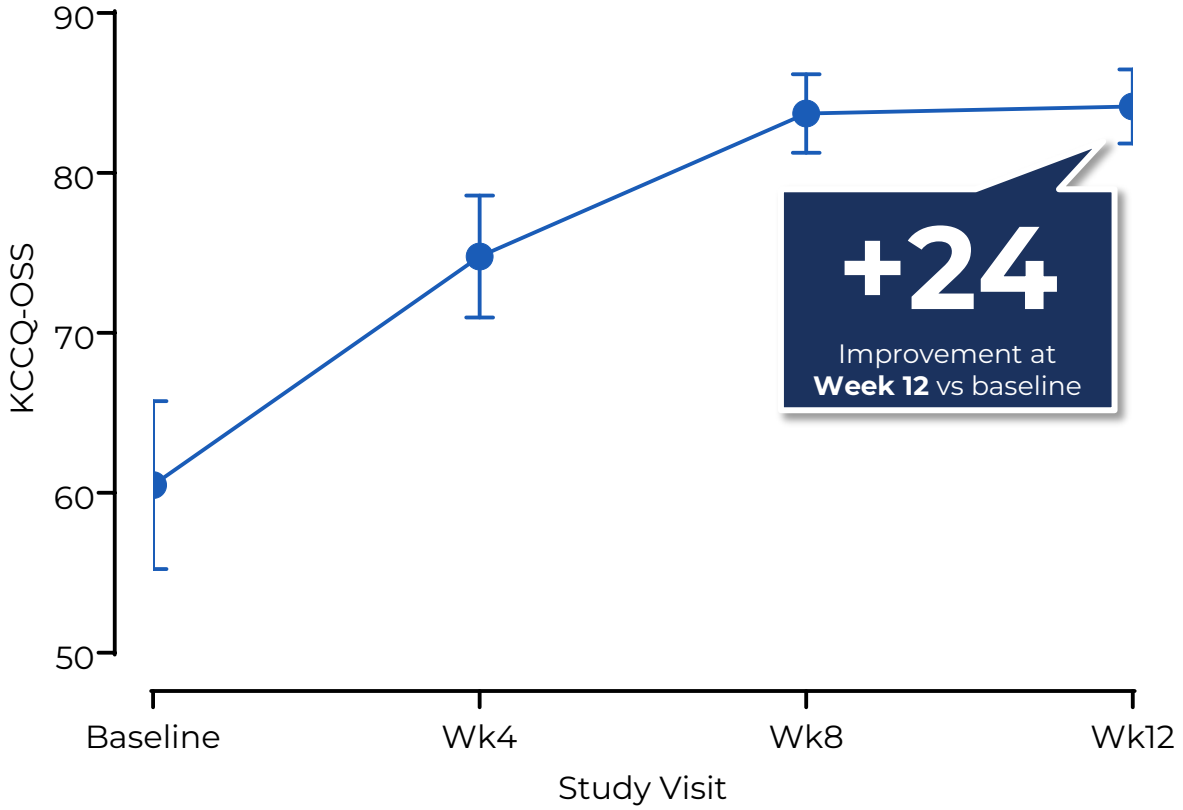
Edgewise THERAPEUTICS

Dobutamine administration mimics exercise challenge
Abbreviations: nHCM, nonobstructive hypertrophic cardiomyopathy; CMI, cardiac myosin inhibitor; WT, wild-type; MYH7, myosin heavy chain 7

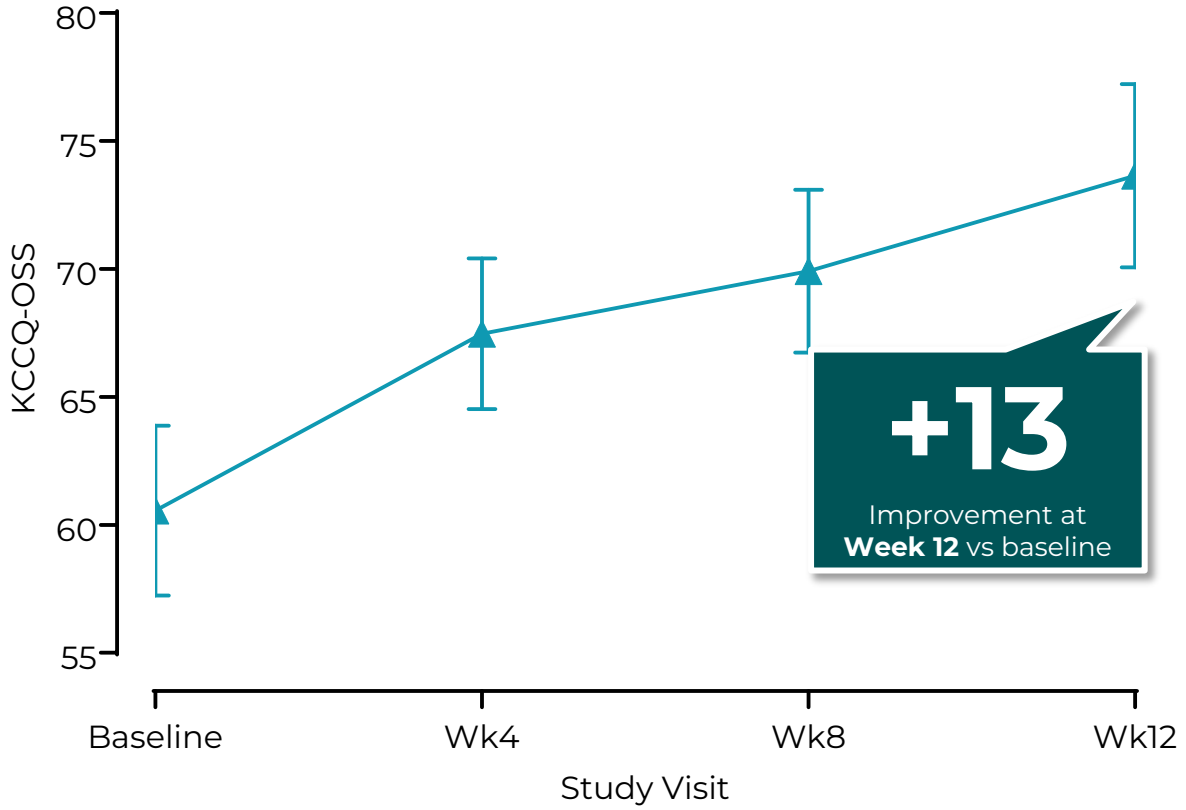
With Administration of EDG-7500, KCCQ Improvements are Consistent with Increased Cardiac Reserve

CIRRUS HCM

oHCM: Mean KCCQ-OSS (N=20)



nHCM: Mean KCCQ-OSS (N=33)



Edgewise THERAPEUTICS

Means ± Std Err presented
Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; oHCM, obstructive hypertrophic cardiomyopathy; nHCM, nonobstructive hypertrophic cardiomyopathy

EDG-7500's Unique MoA Consistent with Observations in Clinic

EDG-7500 Mechanistic Translatability	Clinical Observations
01 | RELIEVING OBSTRUCTION • Slowed rate of contraction (fiber bundles) • Slowing rate of pressure development	⇨ **DECREASES** in LVOT-G (rest and Valsalva)
02 | PRESERVING SYSTOLIC FUNCTION • Slowed early contraction (fiber bundles) • Accelerated late contraction (fiber bundles)	⇨ **NO DECREASE** in LVEF, GLS, GCS
03 | IMPROVING DIASTOLIC FUNCTION • Enhanced relaxation potency (single fibers) • Reduced end diastolic pressure and EDPVR in nHCM pigs	⇨ **DECREASE** in NT-proBNP Even at Low Exposures
04 | IMPROVING FUNCTIONAL STATUS • No suppression of LVEF • Reduced end diastolic pressure (instrumented pigs) • Retained cardiac reserve (single fibers, rat echo, pig PV loops)	⇨ **LARGE IMPROVEMENTS** in KCCQ/NYHA

Edgewise THERAPEUTICS

Abbreviations: oHCM, obstructive hypertrophic cardiomyopathy; nHCM, nonobstructive hypertrophic cardiomyopathy; KCCQ, Kansas City Cardiomyopathy Questionnaire Overall Summary Score, NYHA, New York Heart Association Functional Class; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; GLS, Global Longitudinal Strain; GCS, Global Circumferential Strain; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PV loop, pressure-volume loop; EDPVR, end diastolic pressure volume relationship

A New Era of Direct Positive Lusitropes at Edgewise

1897

Four Tropy's

Defining cardiac properties

- Inotropy
- Chronotropy
- Dromotropy
- Bathmotropy

Theodore Wilhelm Engelmann

1982

Lusitropy

- 'Relaxation of the myocardium'
- Changed the view of the heart from a pump driven by contraction to a dynamic cycle

Dirk. L. Brutsaert

2015 - 2025

Indirect

- Selective SERCA activators showed some lusitropic action but yielded no promising candidates
- CMI lusitropic effects coupled to systolic impact and lifestyle compromise

2026 - Future

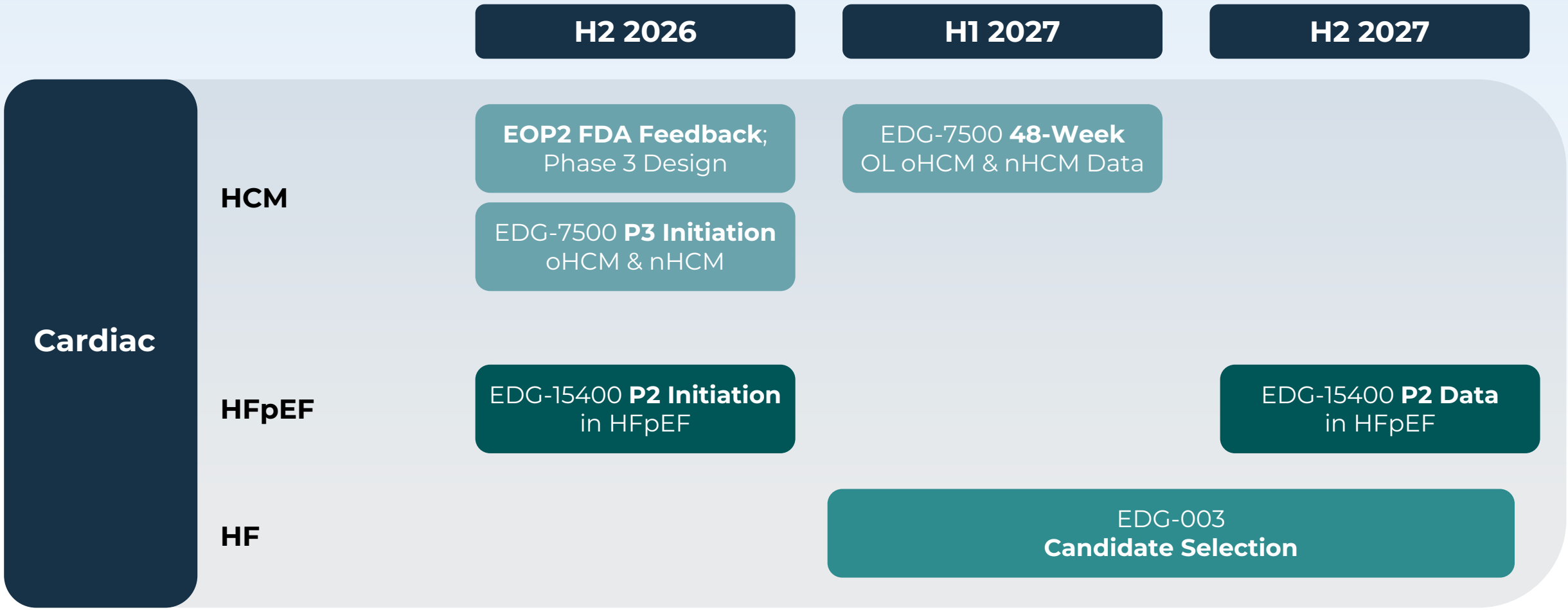
Direct Lusitropic Agents

- The world's first direct lusitropic agents
- EDG-7500, EDG-15400
- Directly improving the speed of cardiac relaxation without adverse payoffs

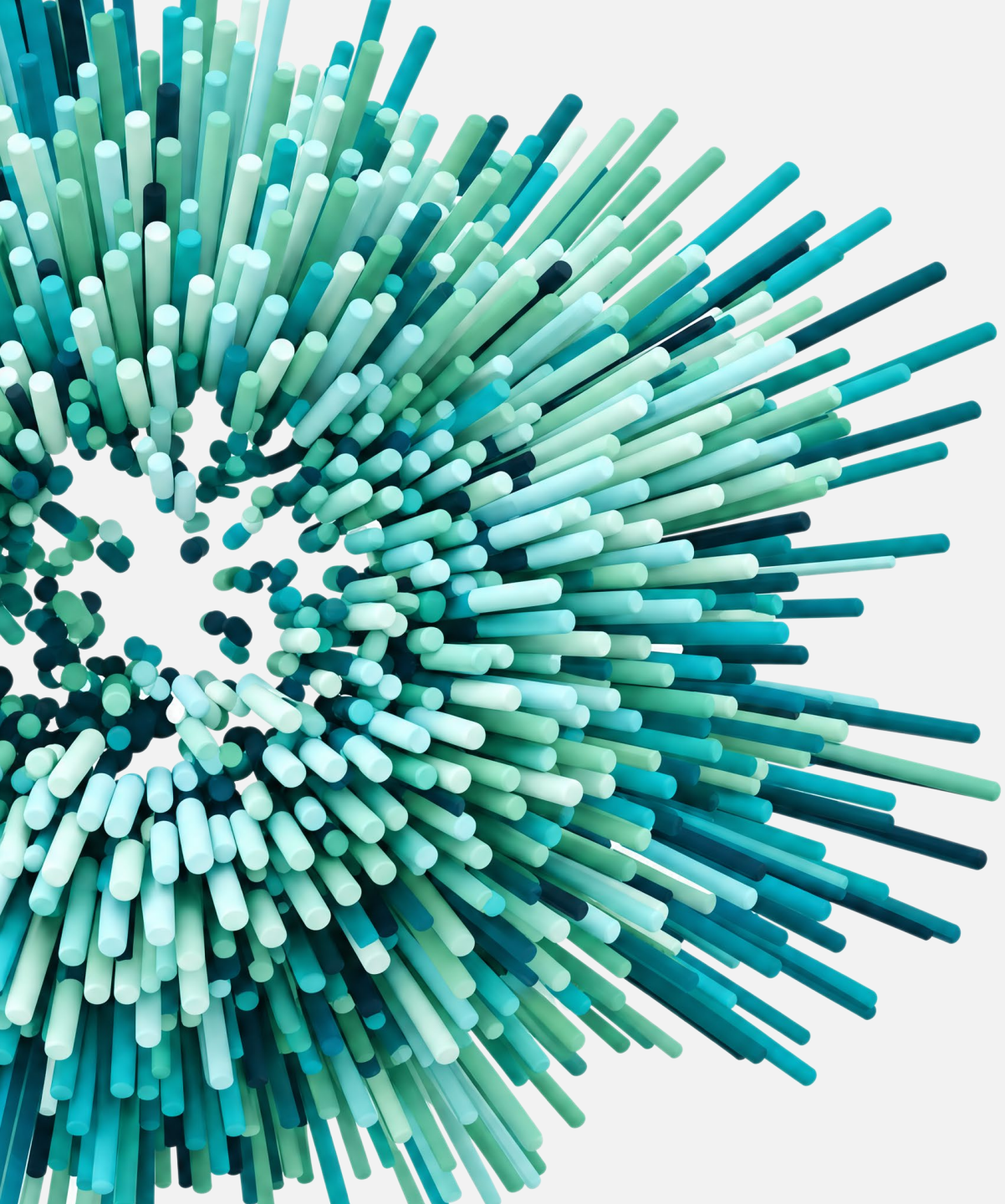
Edgewise® THERAPEUTICS

Edgewise® THERAPEUTICS

Edgewise Pipeline is Rich in Anticipated Near-Term, Value-Creating Catalysts



Abbreviations: HV, healthy volunteers; oHCM, obstructive hypertrophic cardiomyopathy; nHCM, non-obstructive hypertrophic cardiomyopathy; CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; HF, heart failure; OL, open label; EOP2, end of phase 2



Q & A

Edgewise® THERAPEUTICS