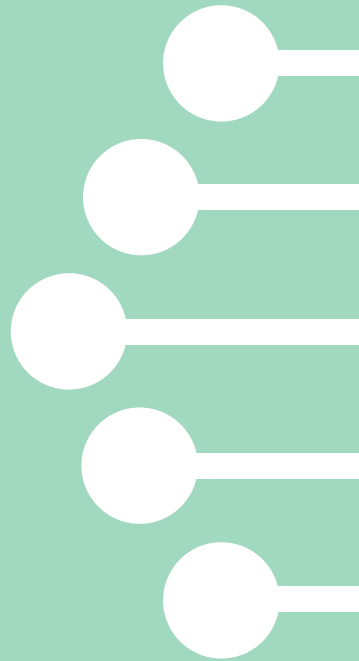


EDG-7500 in Hypertrophic Cardiomyopathy

Robert Blaustein, MD, PhD
Chief Development Officer



Disclosures

Dr. Blaustein is a full-time employee of Edgewise Therapeutics

This presentation contains forward-looking statements that involve substantial risks and uncertainties of Edgewise Therapeutics, Inc. (“Edgewise” or the “Company”). All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, are forward-looking statements. Such forward-looking statements include, among other things, statements regarding the potential of, and expectations regarding, Edgewise’s drug discovery platform, Edgewise’s product candidates and programs, including EDG-7500; Edgewise’s ability to advance additional programs; the expected milestones and timing of such milestones including for EDG-7500 and the Company’s cardiac HCM program; and statements regarding Edgewise’s financial position including its liquidity and the sufficiency of its cash resources. In some cases, you can identify forward-looking statements by terminology such as “estimate,” “intend,” “may,” “plan,” “potentially” “will” or the negative of these terms or other similar expressions.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early clinical stage company; Edgewise’s ability to develop, initiate or complete preclinical studies and clinical trials for, obtain approvals for and commercialize any of its product candidates or research programs; changes in Edgewise’s plans to develop and commercialize EDG-7500 or any other product candidates or research programs; the potential for clinical trials of EDG-7500 or any other product candidates to differ from preclinical, interim, preliminary, topline or expected results; Edgewise’s ability to enroll patients in its ongoing and future clinical trials; Edgewise’s ability to raise funding it will need to continue to pursue its business and product development plans; regulatory developments in the United States and foreign countries; Edgewise’s reliance on third parties, including contract manufacturers and contract research organizations; Edgewise’s ability to obtain and maintain intellectual property protection for its product candidates; risks associated with access to capital and credit markets; the loss of key scientific or management personnel; competition in the industry in which Edgewise operates; Edgewise’s ability to develop a proprietary drug discovery platform to build a pipeline of product candidates; 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 Securities and Exchange Commission. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such 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.

EDG-7500 has demonstrated improvement in a variety of HCM clinical manifestations in translatable models of both oHCM and nHCM

Preclinical model	Key result
 <i>In vitro</i> : Myofibril systems ¹	✓ Preserves myosin head motor function ✓ More potent at low calcium concentrations
 <i>In vivo</i> : Systolic and diastolic function assessed in healthy dogs ²	✓ Increases ventricular diastolic compliance with limited effect on end diastolic pressure
 <i>In vivo</i> : Dogs with pacing-induced left ventricular systolic dysfunction ³ HF	✓ Improves diastolic performance in model of reduced systolic function ✓ No changes in systolic performance in a model of reduced LVEF
 <i>In vivo</i> : MYBPC3 A31P feline validated oHCM model ⁴ oHCM	✓ Potent LVOT-G reduction ✓ Well tolerated at supratherapeutic exposures
 <i>In vivo</i> : MYH7 R403Q porcine validated nHCM model ^{5,6} nHCM	✓ Prevents diastolic impairment^{5,6} ✓ Restores cardiac reserve⁵ ✓ Prevents pathologic cardiac remodeling without significant effect on systolic performance⁶ ✓ Prevents increases in biomarkers associated with disease progression⁶

EDG-7500 demonstrates potent LVOT-G reduction and improvement in diastolic function in conjunction with limited reduction in systolic performance, even at highest exposures

HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVOT-G, LVOT gradient; nHCM, nonobstructive HCM; oHCM, obstructive HCM.

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. Evanchik M et al. American Heart Association's Basic Cardiovascular Sciences Scientific Sessions. Chicago, IL. July 22–25, 2024. Abstract #We094; 4. Kaplan JL et al. 2023 American College of Cardiology 72nd Annual Scientific Sessions. New Orleans, LA. March 4–6, 2023. Poster #1066-13; 5. Evanchik M et al. 2024 American College of Cardiology 73rd Annual Scientific Sessions. Atlanta, GA. April 6–8, 2024. Poster #1087-05; 6. Emter C et al. 2024 American Heart Association Scientific Sessions. Chicago, IL. November 16–18, 2024. Abstract #4142919.

EDG-7500: Key drug attributes observed to date¹

EDG-7500 parameters



Targeted effect on diastole



No meaningful changes in LVEF

Human T _{1/2}	30 hours
LVEF impact	Minimal
CYP inhibition (IC ₅₀)	>30 µM (all isoforms)
Dosing	Oral, once daily
Time to steady state	3-4 days
Substrate for transporters?	No

EDG-7500 is specifically designed to **slow early contraction velocity** and **address impaired cardiac relaxation** associated with HCM

CIRRUS-HCM: Clinical trial design^{1,2}

Primary objective

Safety and tolerability
in adults with HCM

Key inclusion criteria

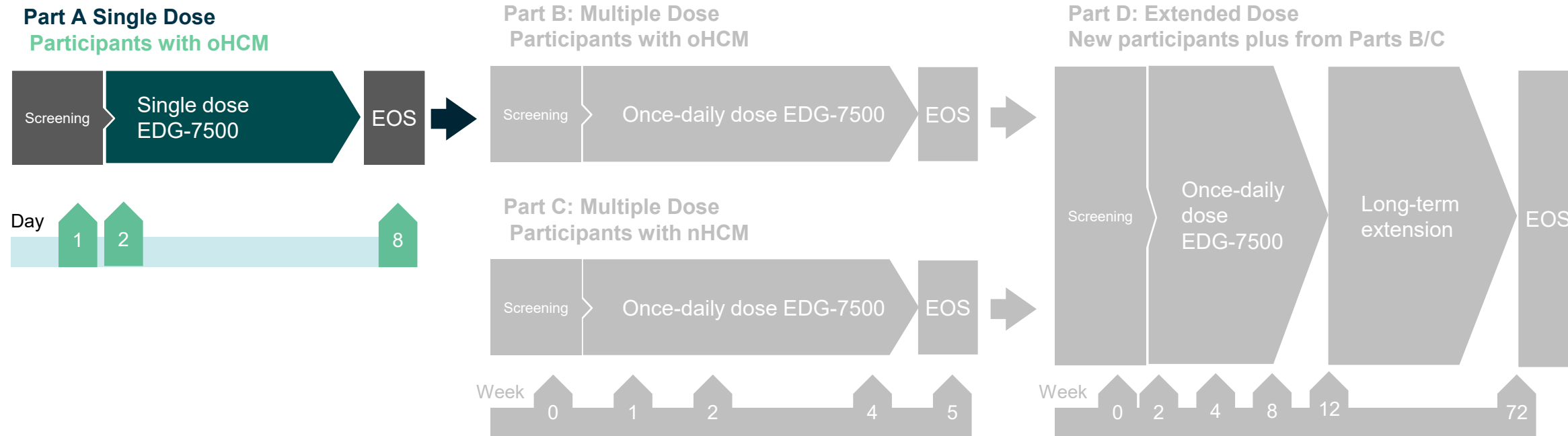
Male and female participants
≥18 years of age with HCM
LVEF ≥60%

Target enrollment

≈75

Key outcome measures

- Cardiovascular PD
- LVEF
- Biomarkers
- PK



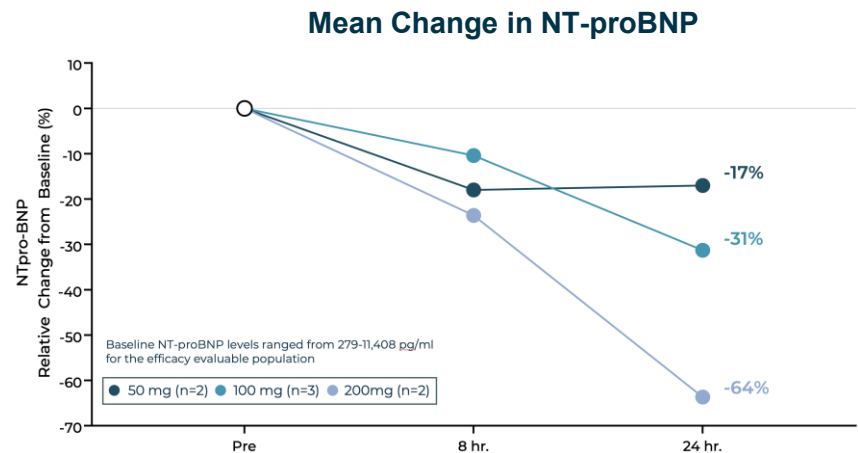
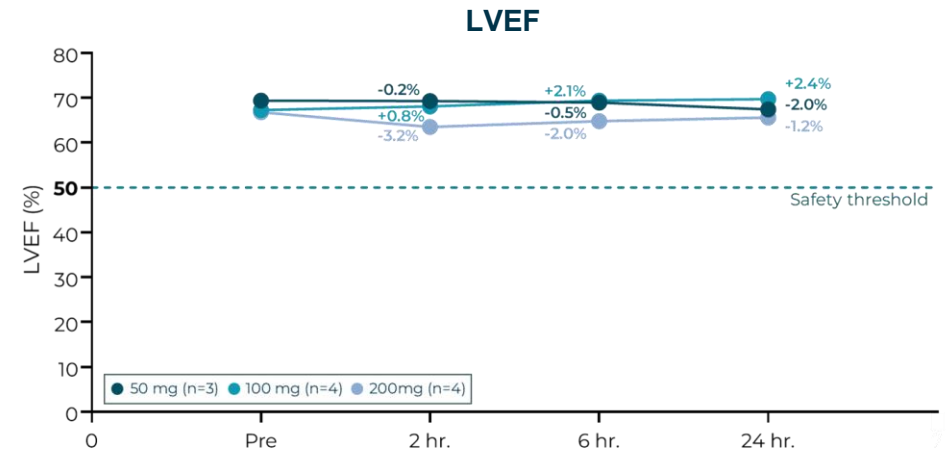
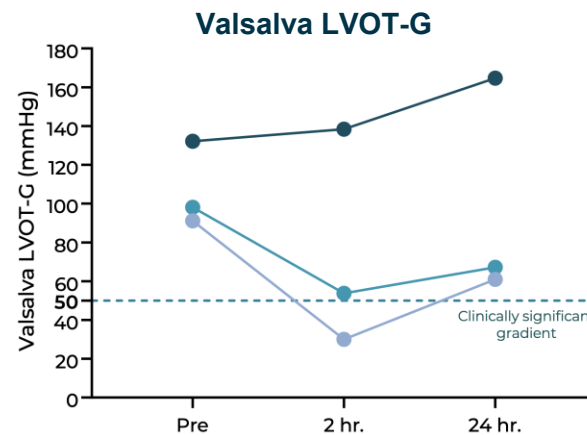
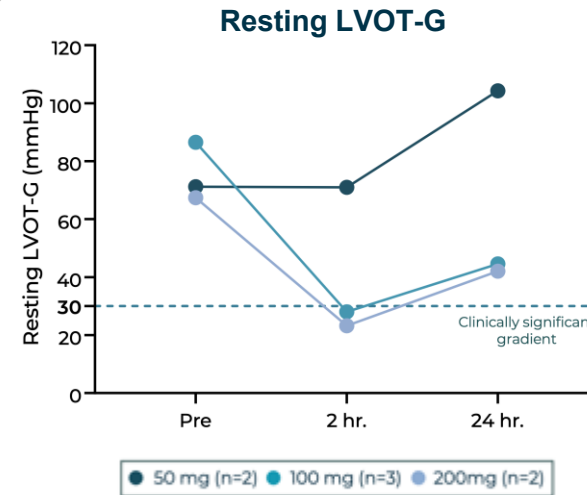
EOS, end of study; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; nHCM, nonobstructive HCM; oHCM, obstructive HCM; PD, pharmacodynamics; PK, pharmacokinetics.

1. ClinicalTrials.gov. NCT06347159. A Study of EDG-7500 in Adults with Hypertrophic Cardiomyopathy (CIRRUS-HCM). Updated October 23, 2024. Accessed December 13, 2024.

<https://clinicaltrials.gov/study/NCT06347159>; 2. Edgewise Therapeutics. Data on File.

CIRRUS-HCM Part A summary: single-dose study in oHCM

- EDG-7500 was well tolerated across all doses studied in participants with oHCM
- 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



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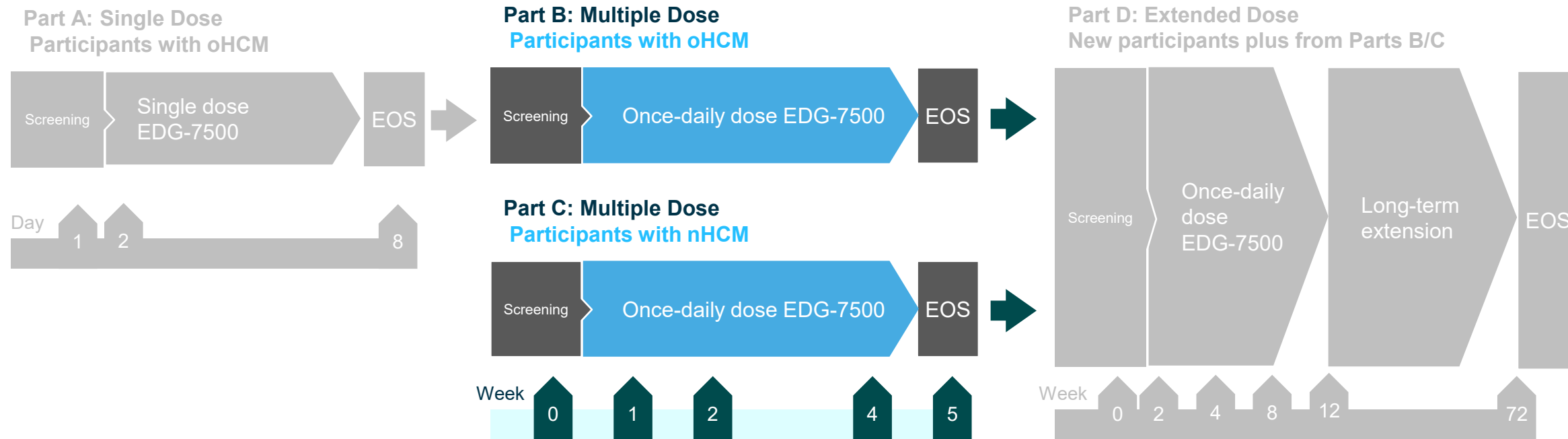
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- **Substantial improvements** in resting and Valsalva LVOT, NT-proBNP, and KCCQ in Part B oHCM
- **Rapid and robust reductions** in NT-proBNP and improvements in KCCQ in Part C nHCM

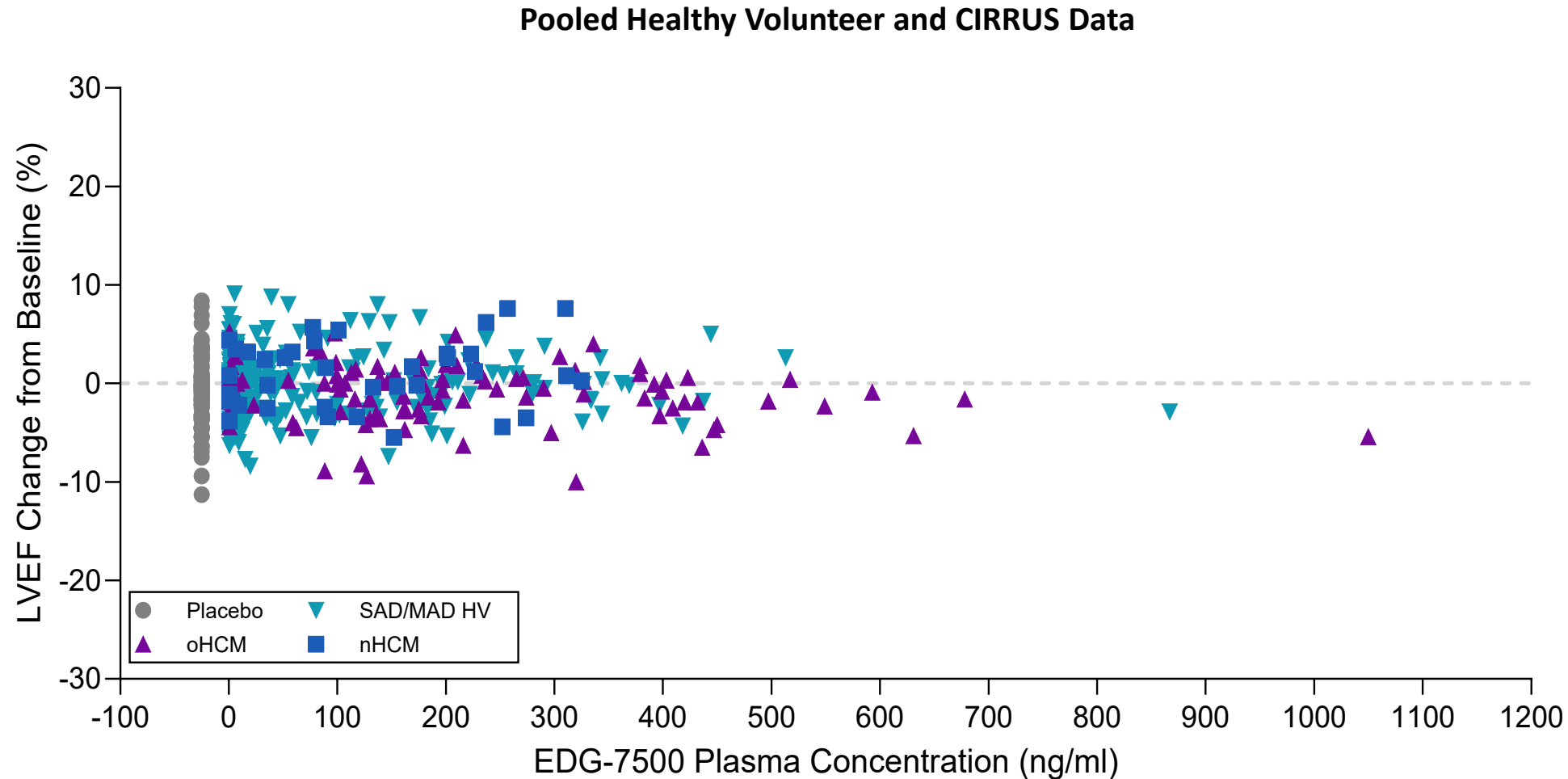
CIRRUS-HCM: A Multiple-Dose Phase 2 Study of Safety, Tolerability, and Effects on Hemodynamics and Functional Capacity of the Novel Cardiac Sarcomere Modulator EDG-7500 in Hypertrophic Cardiomyopathy

Presented by Dr. Anjali Owens

Plenary Session 16:30



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



HV, healthy volunteer; LVEF, left ventricular ejection fraction; MAD, multiple ascending dose; nHCM, nonobstructive hypertrophic cardiomyopathy; oHCM, obstructive cardiomyopathy; SAD, single ascending dose.

Owens A et al. 2025 Heart Failure Association Congress, May 18-20, 2025.

CIRRUS-HCM: Clinical trial design^{1,2}

Primary objective

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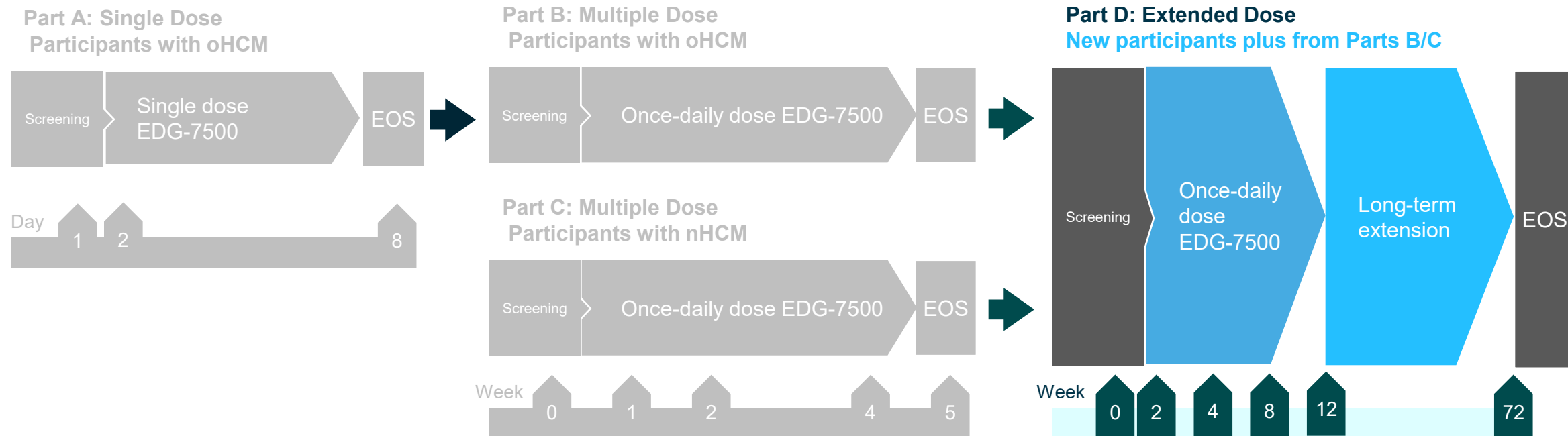
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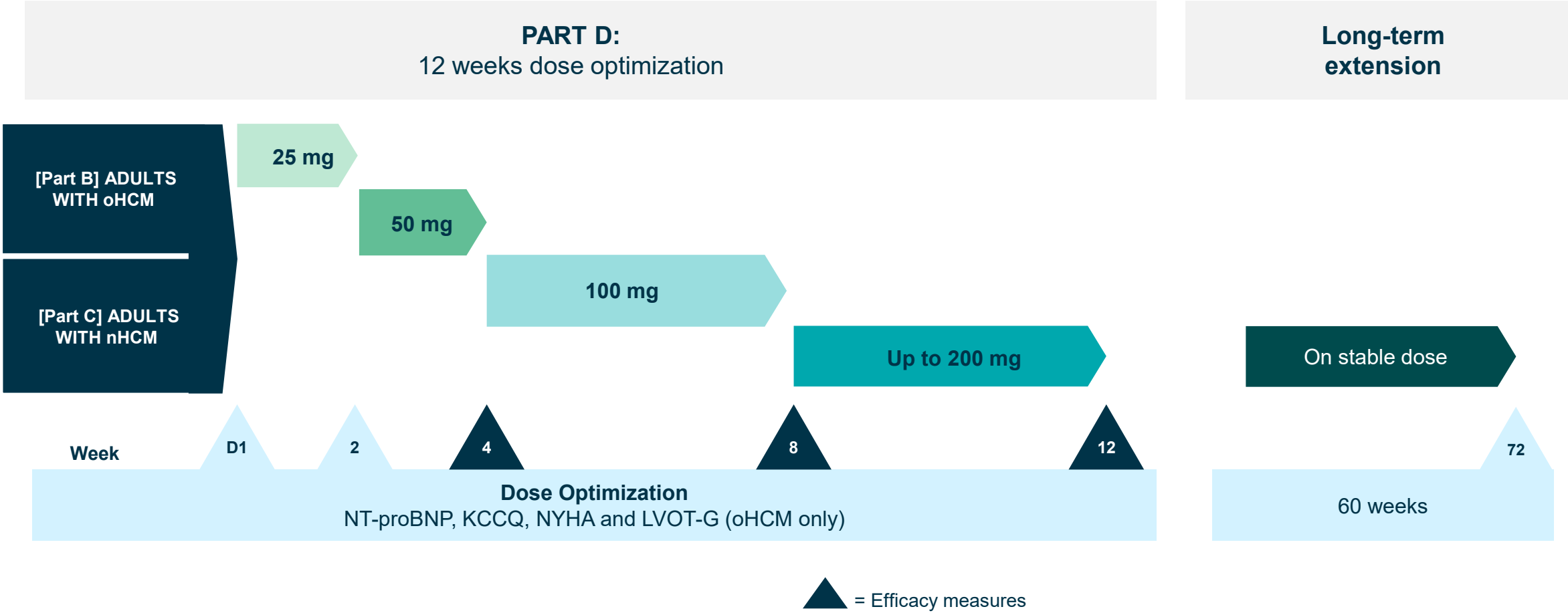
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Intra-Patient Dose Optimization in Part D



Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT-G, left ventricle outflow tract gradient; oHCM, obstructive hypertrophic cardiomyopathy; nHCM, nonobstructive hypertrophic cardiomyopathy.



Conclusions

- **EDG-7500** has the potential to emerge as an exciting new therapeutic option for both **oHCM** and **nHCM**
- EDG-7500 treatment appears to be generally well tolerated across a broad exposure range **without meaningful impact on LVEF**
- Treatment with EDG-7500 was shown to **improve LVOT-G, NT-proBNP, e', KCCQ, and NYHA**
- In the 12-week Part D portion of CIRRUS-HCM, intra-patient dose optimization is being explored