HRS/BHB-1893, A NEXT-GENERATION CARDIAC MYOSIN INHIBITOR, IMPROVES INDICES OF DIASTOLIC FUNCTION IN NON-OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY: EVIDENCE FROM IN VITRO STUDIES AND PATIENTS

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DISCLOSURE SLIDE

del Rio CL: Employee and equity of **Braveheart Bio, SF (USA);** equity at Kardigan Bio, San Francisco, CA (USA)

(fan of the cardiac sarcomere as a therapeutic target)

…9 YEARS AGO: MYOSIN'S ROLE IN DIASTOLIC PROPERTIES

American Heart Association. life is why™ | SCIENTIFIC SESSIONS 2017

In vivo Cardiac Effects of Mavacamten (MYK-461): Evidence for Negative Inotropy and Improved Compliance

del Rio CL[1,2], Ueyama Y[2], Baker DC[1], Dalton SR[3], Janiak P[4], Lucats L[4], Olivier N[5], Lambing J[1], Evanchik MJ[1], Green EM[1]

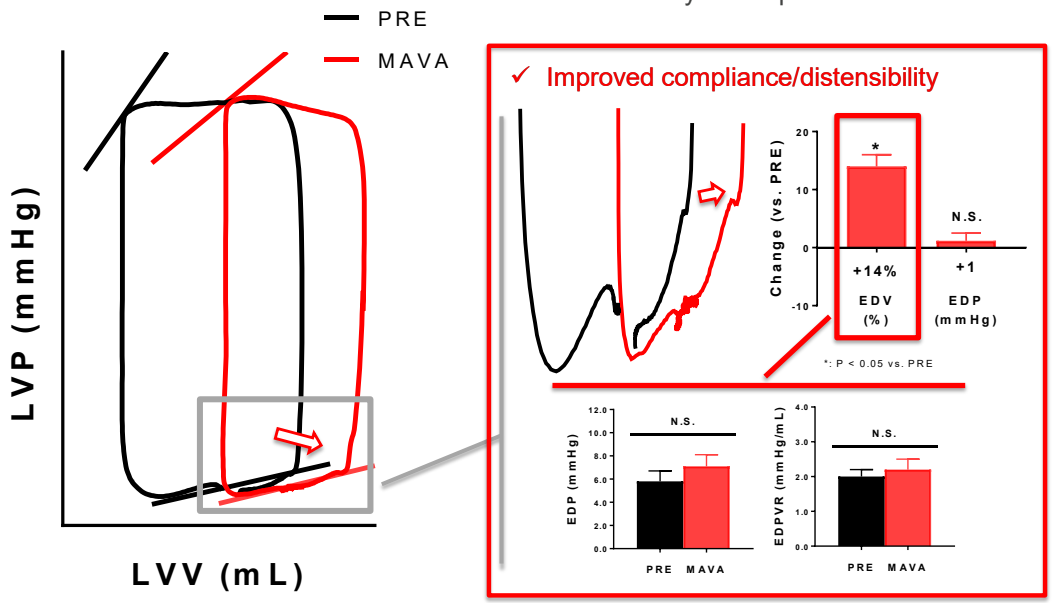
1: MyoKardia (CA, USA); 2: QTest Labs (OH, USA); 3: Covance Labs Inc. (WI, USA); 4: Sanofi R&D (Paris, France); and 5: Michigan State University (MI, USA)

- I **HAVE** the following relationship(s) to disclose:
  - MyoKardia and QTest Labs (employment/consultant)

✓ CMI Improved LV distensibility
(down-rightward shift of pressure-volume)

ACUTE, mavacamten:

- ✓ Depressed systolic function
- ✓ Preserved systemic pressures



CMI, cardiac myosin inhibitor; EDP, end-diastolic pressure; EDPVR, end-diastolic pressure-volume relationship; EDV, end-diastolic volume; LV, left ventricular; LVP, LV pressure; LVV, LV volume; MAVA, mavacamten; MYK-461, mavacamten; N.S., not significant; PRE, pre-treatment.

del Rio et al. AHA 2017 (Circulation 2018; 136 (Suppl 1): A20593
https://www.ahajournals.org/doi/10.1161/circ.136.suppl_1.20593

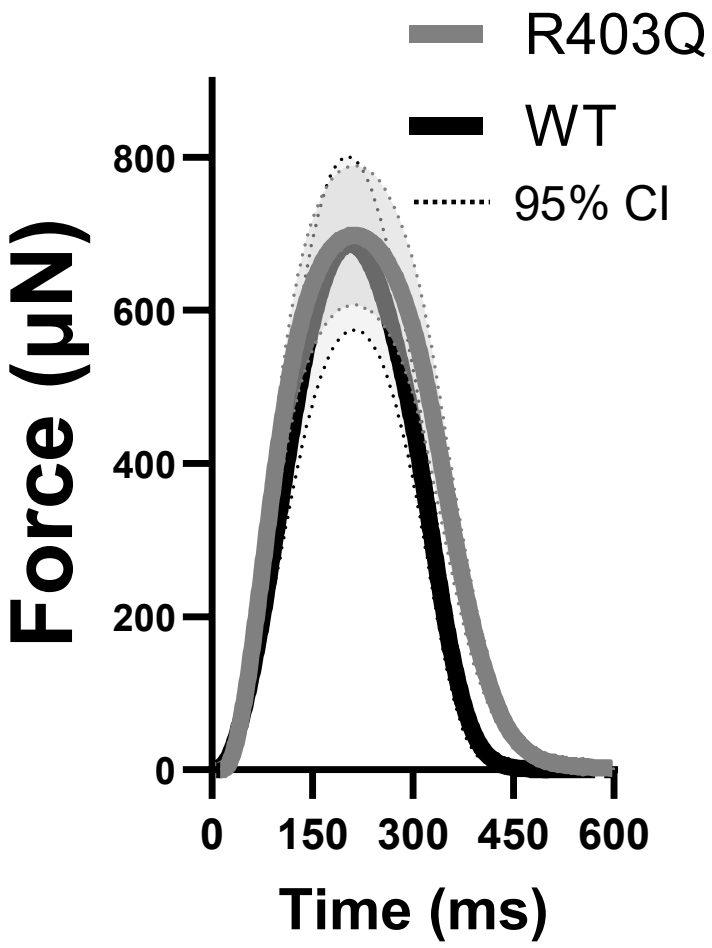
BACKGROUND

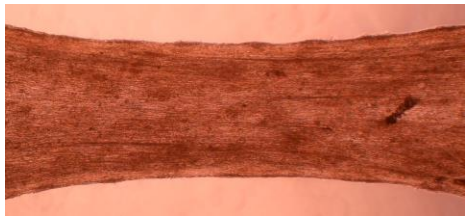
- Diastolic dysfunction resulting from **excess myosin motor activity, and non-productive actomyosin cross-bridges**, is characteristic of the HCM heart regardless of phenotype.
  - *Historically, cardiac myosin inhibition (CMI) has been associated with systolic costs that can hinder its expected diastolic benefits.*
- HRS/BHB-1893 is a clinical-stage next-generation, selective, reversible, PK-optimized cardiac myosin ATPase inhibitor that aims to lessen this limitation.

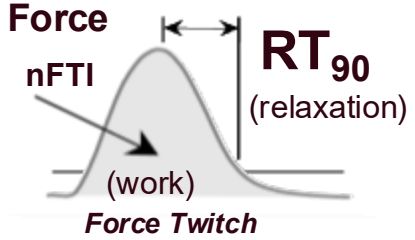
HRS/BHB-1893 was studied both in HCM engineered heart tissues (EHT) and in patients with non-obstructive HCM (nHCM) to assess its diastolic effects independently of any obstruction-relief.

ATPase, adenosine triphosphatase; HCM, hypertrophic cardiomyopathy; PK, pharmacokinetic.

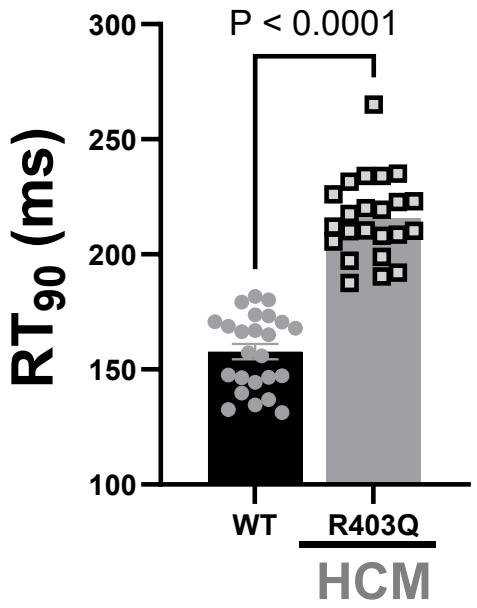
IN VITRO: EHT HCM MODEL WITH IMPAIRED RELAXATION

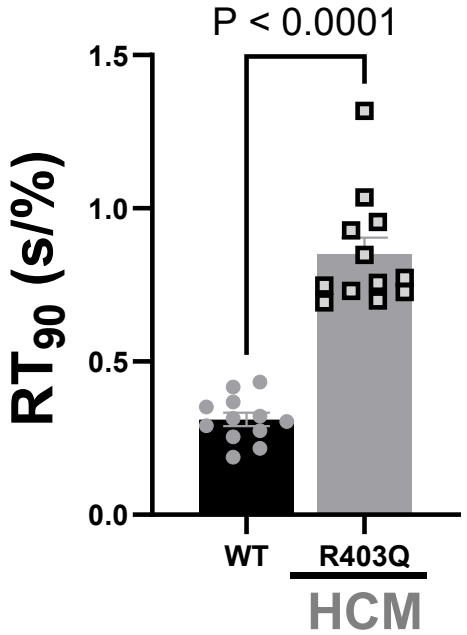


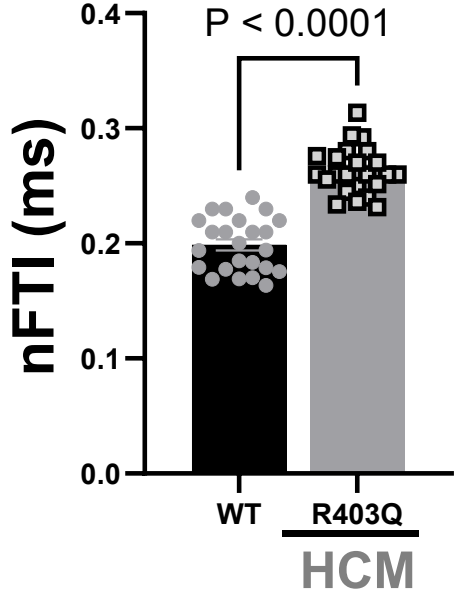




WT and **HCM** (MYH R403Q) hIPSC-derived EHTs, studied at rest and stress (+STRETCH: ±5% stretch)



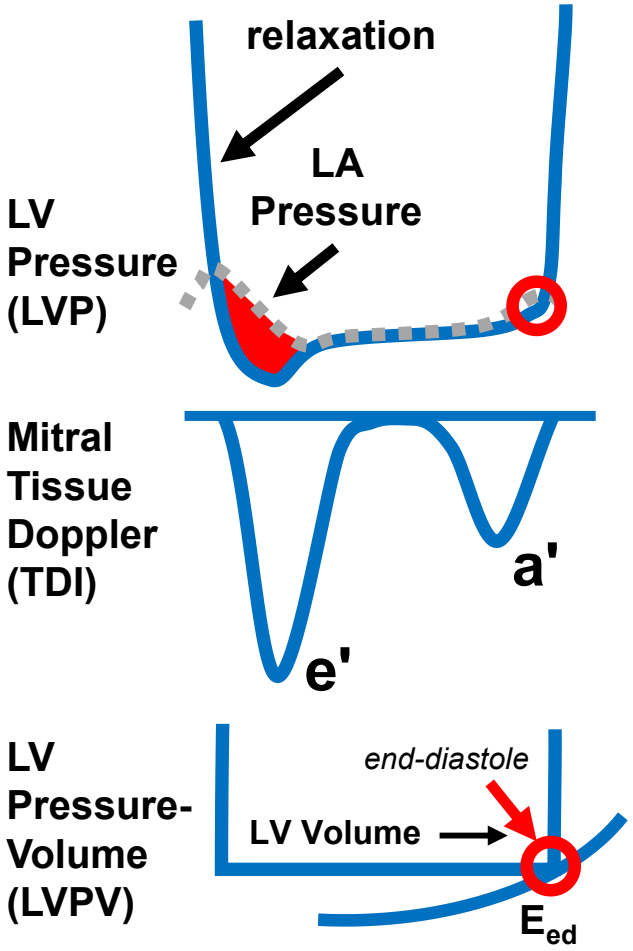




Prolonged Relaxation | **…worsens w/ stress** | **↑ non-productive work**

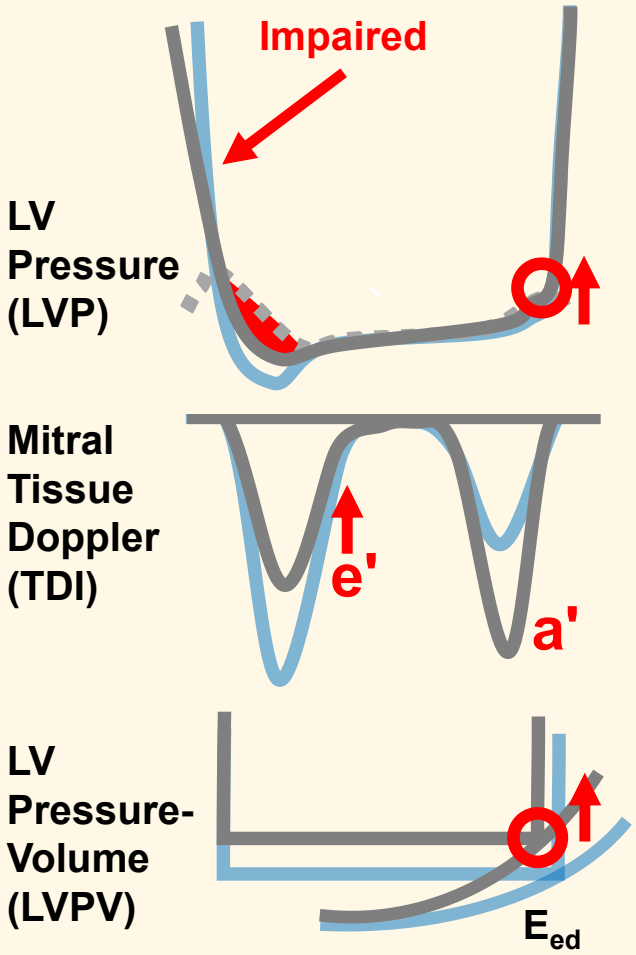
Twitch traces are mean (solid) ± 95% CI (dotted); bar data are mean ± SEM. CI, confidence interval; EHT, engineered heart tissue; HCM, hypertrophic cardiomyopathy; hiPSC, human induced pluripotent stem cell; MYH, myosin heavy chain; nFTI, normalized force-time integral; RT_{90}, time to 90% relaxation; SEM, standard error of the mean; WT, wild type.

WHY DO WE CARE? LV RELAXATION DETERMINES LV FILLING



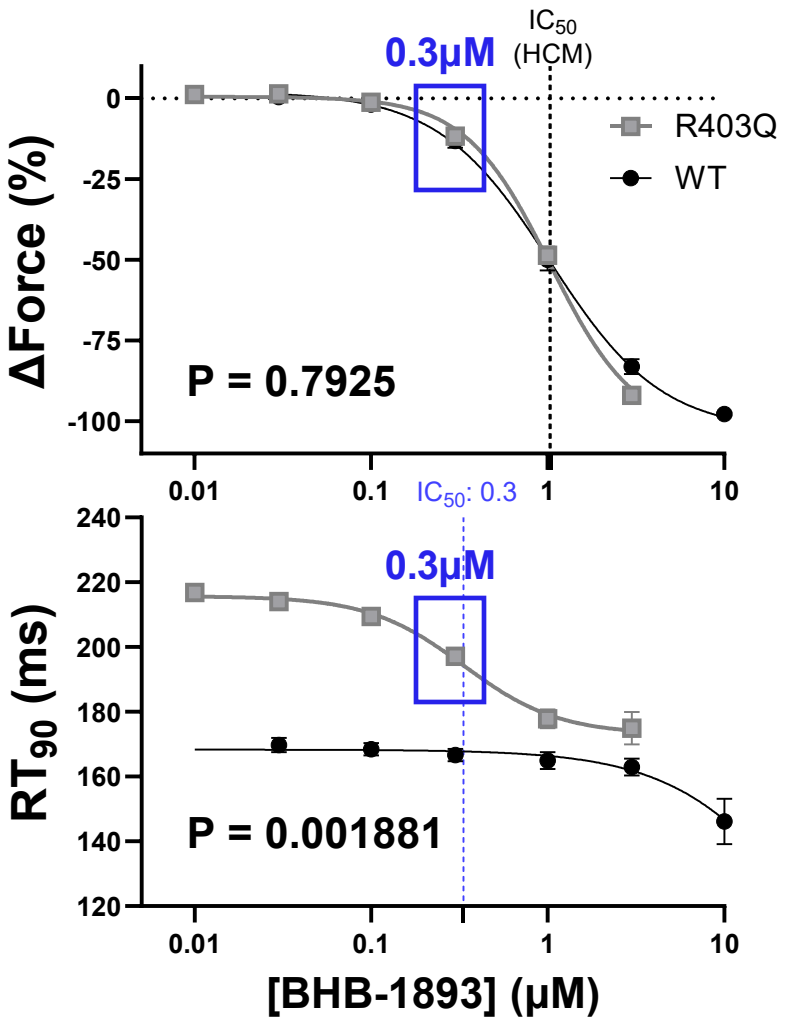
DISEASE

- **RESIDUAL CROSS-BRIDGES**
- **SLOWED RELAXATION** (↑*tau*, ↑*IVRT*, or ↑*RT90 in vitro*)
- **IMPAIRED FILLING** (↓***e'***, ↑*E/e'*, or ↑*DT*)
- **REDUCED COMPLIANCE** (↑***EDP***, ↓*EDV*, ↑*LAP*)
- **REMODELING** (↑***LAVI***, ↑*fibrosis*, ↑*cTn*)



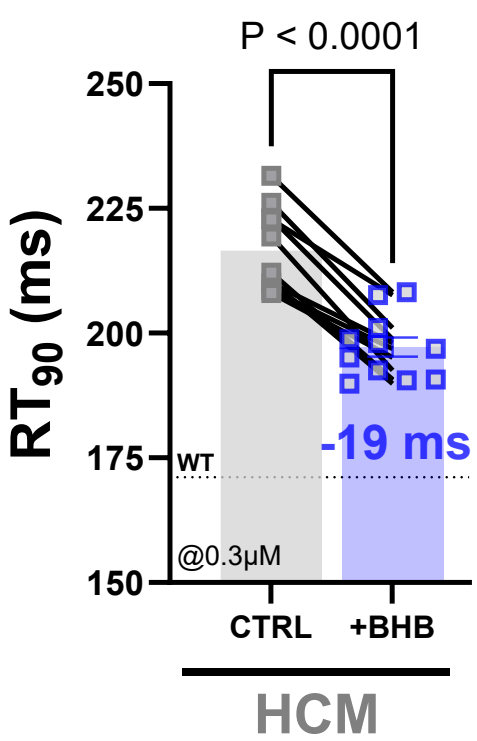
a', late diastolic mitral annular velocity; cTn, cardiac troponin; DT, deceleration time; e', early diastolic mitral annular velocity; E/e', ratio of early mitral inflow velocity to e'; EDP, end-diastolic pressure; EDV, end-diastolic volume; E_{ed}, end-diastolic elastance; IVRT, isovolumic relaxation time; LA, left atrial; LAP, LA pressure; LAVI, LA volume index; LV, left ventricular; LVP, LV pressure; LVPV, LV pressure-volume; RT90, time to 90% relaxation; tau, time constant of LV relaxation; TDI, tissue Doppler imaging.

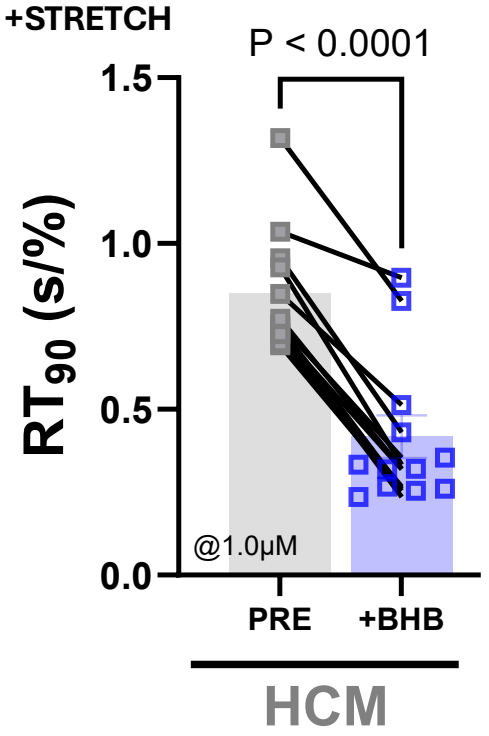
IN VITRO: BHB-1893 RESCUED RELAXATION IN HCM

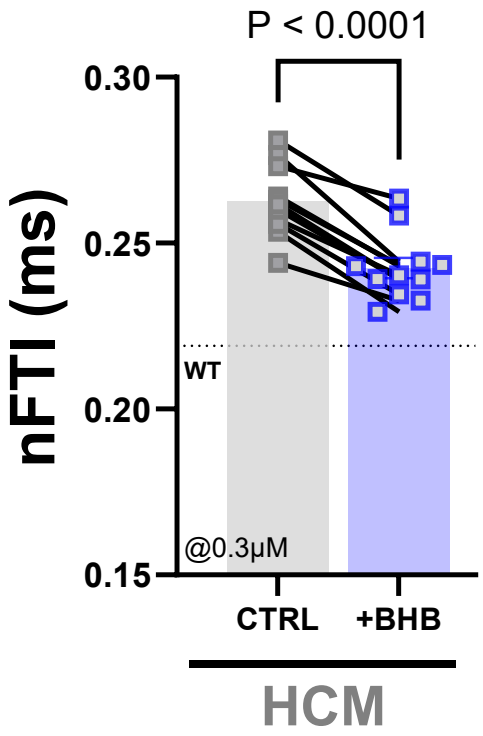


Preserved Twitch Force

Negligible (~10%) peak force reduction at 0.3 μM in both WT and HCM, suggesting predictable LVEF changes







Shortened Relaxation in HCM

Rescued stress response (+STRETCH)

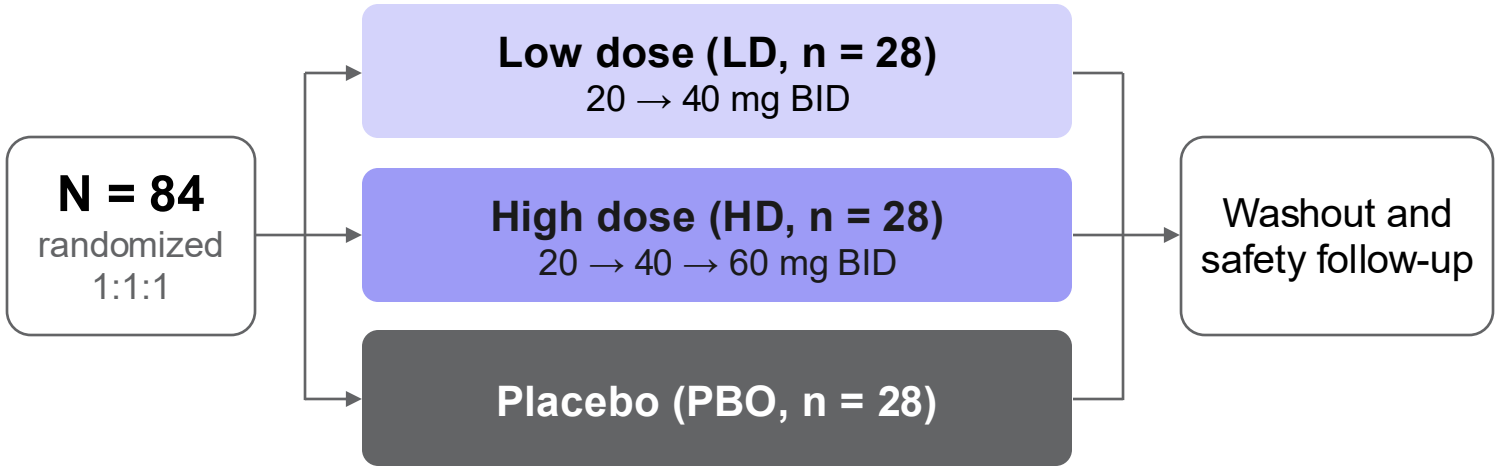
…reduced non-productive work

Data are mean ± SEM. BHB, HRS/BHB-1893; HCM, hypertrophic cardiomyopathy; IC_{50}, half-maximal inhibitory concentration; LVEF, left ventricular ejection fraction; RT_{90}, time to 90% relaxation; SEM, standard error of the mean; WT, wild type.

nHCM: HRS-1893-202 STUDY DESIGN (NCT06816251)

Adults with nHCM: LVEF ≥60%, NYHA class II–III, resting and Valsalva LVOT-G <30 mmHg, maximal wall thickness ≥15 mm (≥13 mm with family history of HCM), KCCQ-CSS 30–85, and NT-proBNP > 300 pg/mL

Design



Dose checks at W2 (both doses) and W3 (high dose); increases only if LVEF criteria are met

Key endpoints

- **Primary:** safety (LVEF <50%)
- **Biomarkers:** NT-proBNP, cardiac troponin I
- **Feel and function:** KCCQ-CSS, pVO_2
- **Echo:** diastolic and structural

Dose titration criteria

LVEF	Adjustment
≥55%	Increase dose
<55% and ≥50%	Maintain dose
<50% and ≥45%	Decrease dose
<45%	Interrupt drug

BID, twice daily; HCM, hypertrophic cardiomyopathy; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LVEF, left ventricular ejection fraction; LVOT-G, LV outflow tract gradient; nHCM, non-obstructive HCM; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen uptake; W, week.

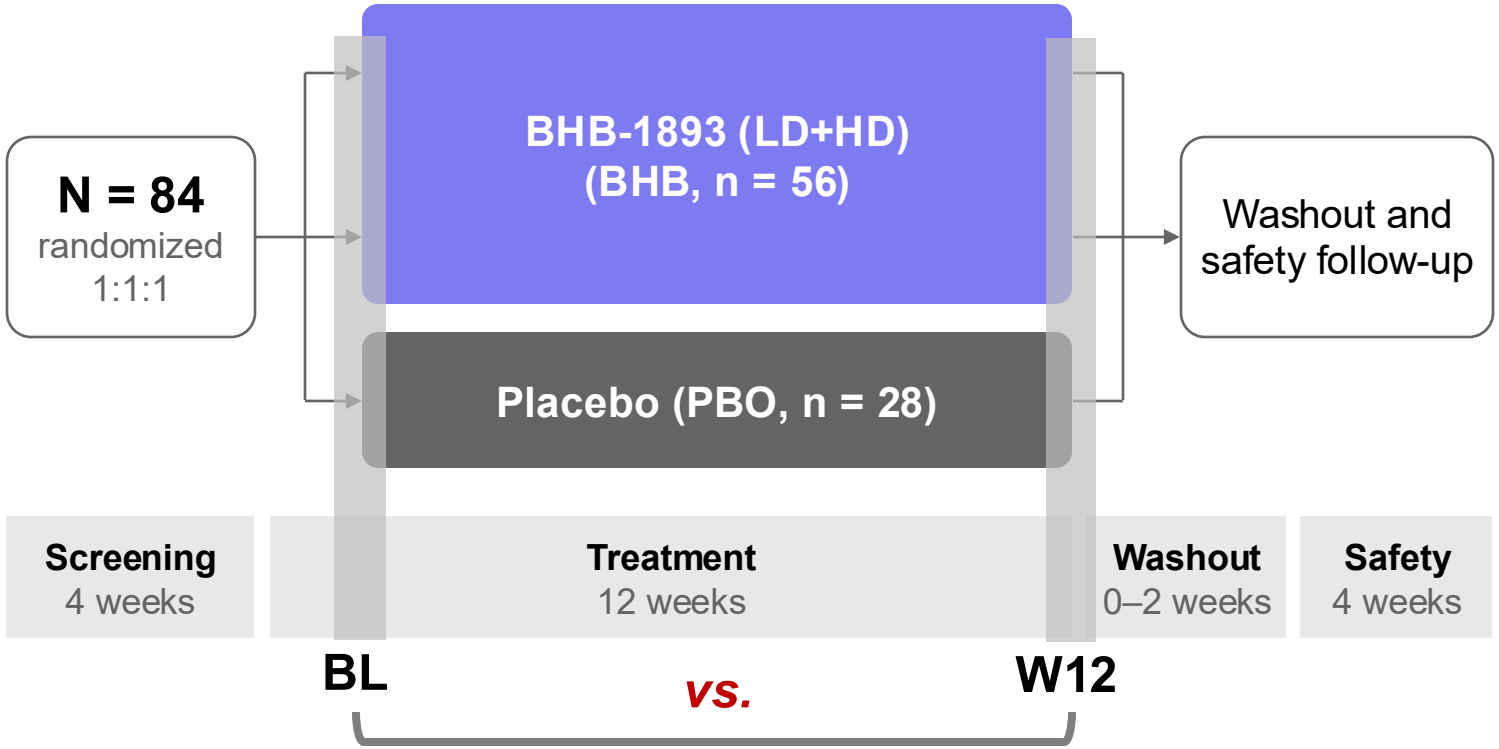
Wang et al. ESC-HF 2026
https://esc365.escardio.org/presentation/324648

Heart Failure 2026 World Congress on Acute Heart Failure

nHCM: HRS-1893-202 (AD-HOC POOLED ANALYSIS)

Adults with nHCM: LVEF ≥60%, NYHA class II–III, resting and Valsalva LVOT-G <30 mmHg, maximal wall thickness ≥15 mm (≥13 mm with family history of HCM), KCCQ-CSS 30–85, and NT-proBNP > 300 pg/mL

Design



Key endpoints

Echo parameters

DIASTOLE

- **e′ septal/lateral**: early filling velocity
- **E/e′**: LV filling pressure (surrogate)
- **LAVI**: left atrial size
- **LV EDV**: end-diastolic volume

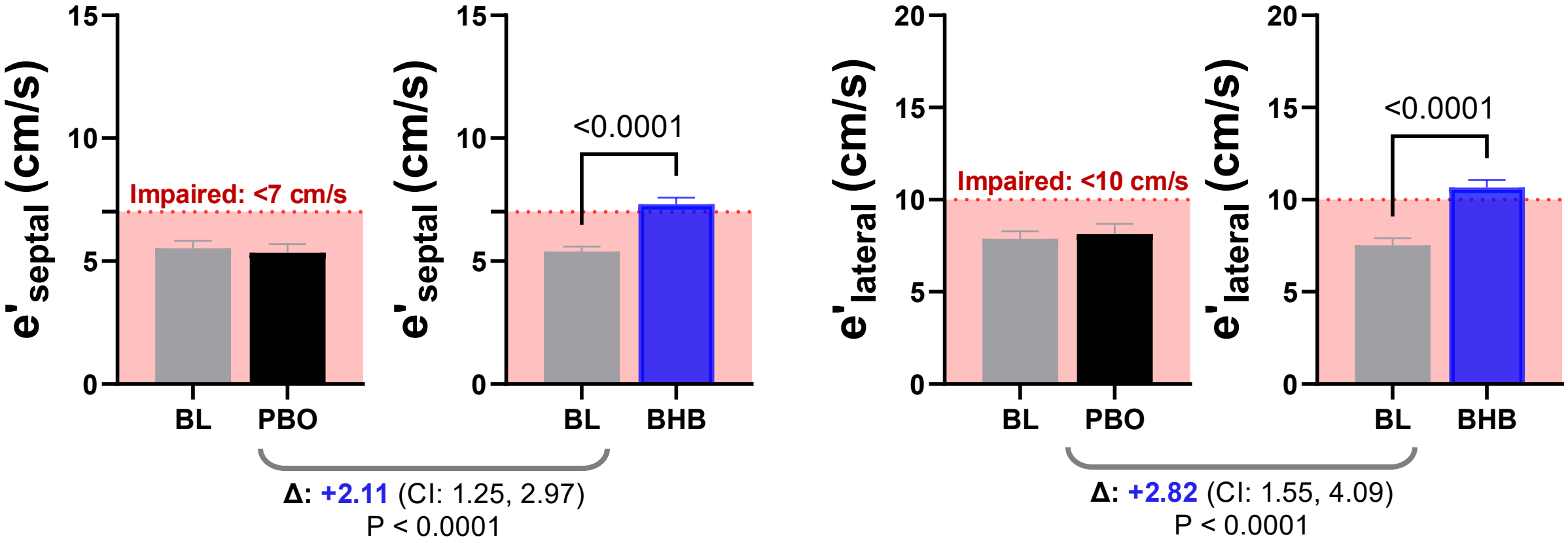
- **LVEF**: LV ejection fraction
- **LV GLS**: LV longitudinal strain

ANALYSIS

Change from baseline (BL) to week 12 (W12) within group (paired t-test), **pooled BHB-1893 (BHB)** vs. **placebo (PBO)**

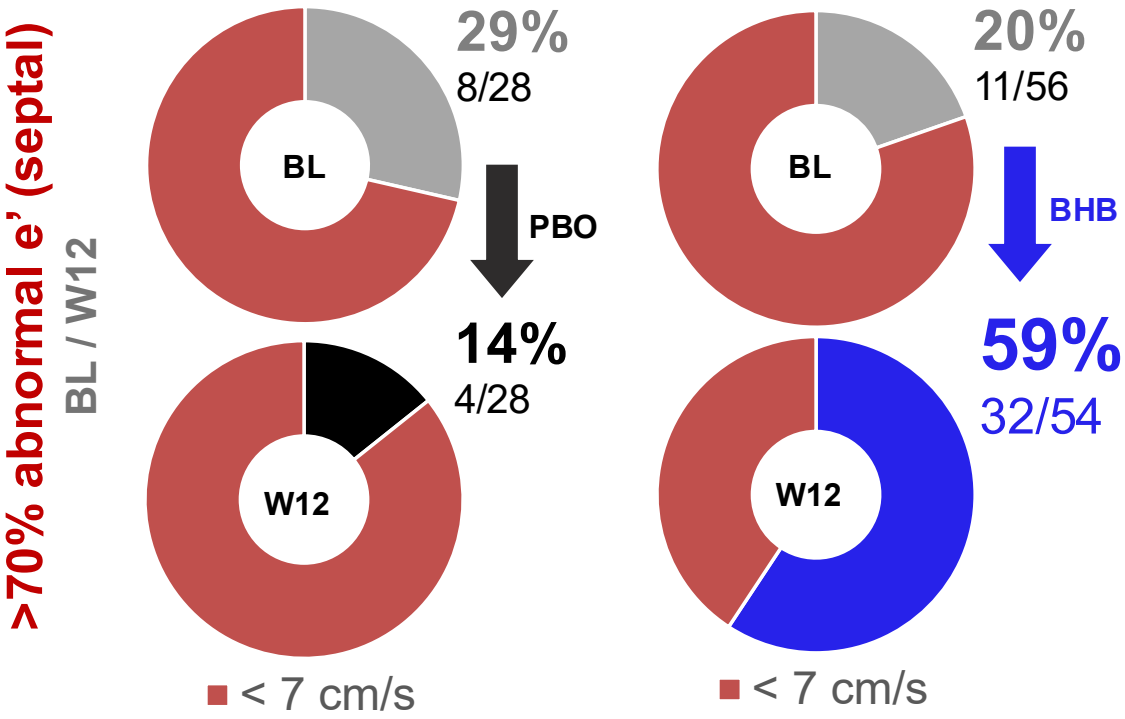
BID, twice daily; e', early diastolic mitral annular velocity; E/e', ratio of early mitral inflow velocity to e'; GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; HD, high dose; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LAVI, left atrial volume index; LD, low dose; LV, left ventricular; LVOT-G, LV outflow tract gradient; nHCM, non-obstructive HCM; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen uptake; W, week.

nHCM: BHB-1893 IMPROVED EARLY FILLING VELOCITIES (e')



Data are mean ± SEM. BHB, pooled HRS/BHB-1893 (low + high dose); BL, baseline; CI, 95% confidence interval; e', early diastolic mitral annular velocity; PBO, placebo; SEM, standard error of the mean. Thresholds: Nagueh SF, et al. J Am Soc Echocardiogr 2016;29:277–314.

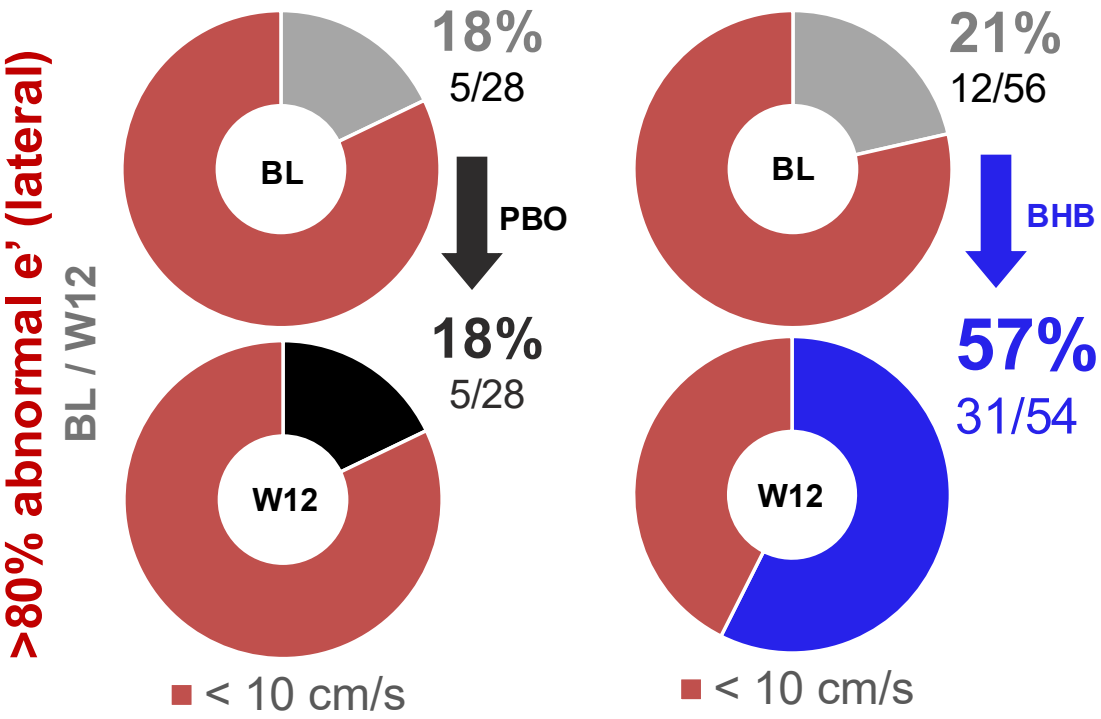
nHCM: >50% BHB-1893 GROUP REACHED NORMAL e'



Δ: +2.11 (CI: 1.25, 2.97)
P < 0.0001

59% normal

(P<0.001 vs. PBO) W12 w/ BHB



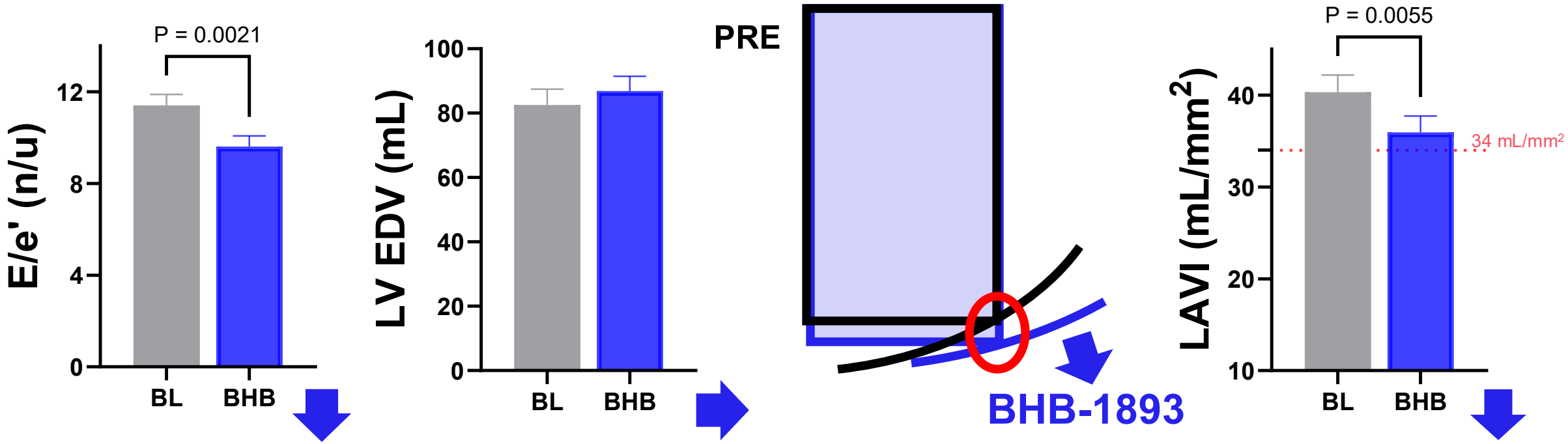
Δ: +2.82 (CI: 1.55, 4.09)
P < 0.0001

57% normal

(P<0.001 vs. PBO) W12 w/ BHB

Data are mean ± SEM. *Comparisons via Fisher's exact test (2-sided). BHB, pooled HRS/BHB-1893 (low + high dose); BL, baseline; CI, 95% confidence interval; e', early diastolic mitral annular velocity; PBO, placebo; SEM, standard error of the mean; W12, week 12. Thresholds: Nagueh SF, et al. J Am Soc Echocardiogr 2016;29:277–314.

nHCM: IMPROVED LV COMPLIANCE AND SMALLER LEFT ATRIA



…lowered filling pressure with preserved LV EDV

Data are mean ± SEM. BHB, pooled HRS/BHB-1893 (low + high dose); E/e', ratio of early mitral inflow velocity to early diastolic mitral annular velocity; EDV, end-diastolic volume; LA, left atrium; LAVI, left atrial volume index; LV, left ventricular; n/u, no units; PRE, baseline; SEM, standard error of the mean; W12, week 12.

nHCM: WELL TOLERATED (CONSISTENT WITH PRIOR STUDIES)

- There were no serious AEs or AEs leading to treatment interruption, discontinuation, or death (BHB group)
- LVEF <50%: LVEF 46% to 49%; all returned to normal with dose reduction

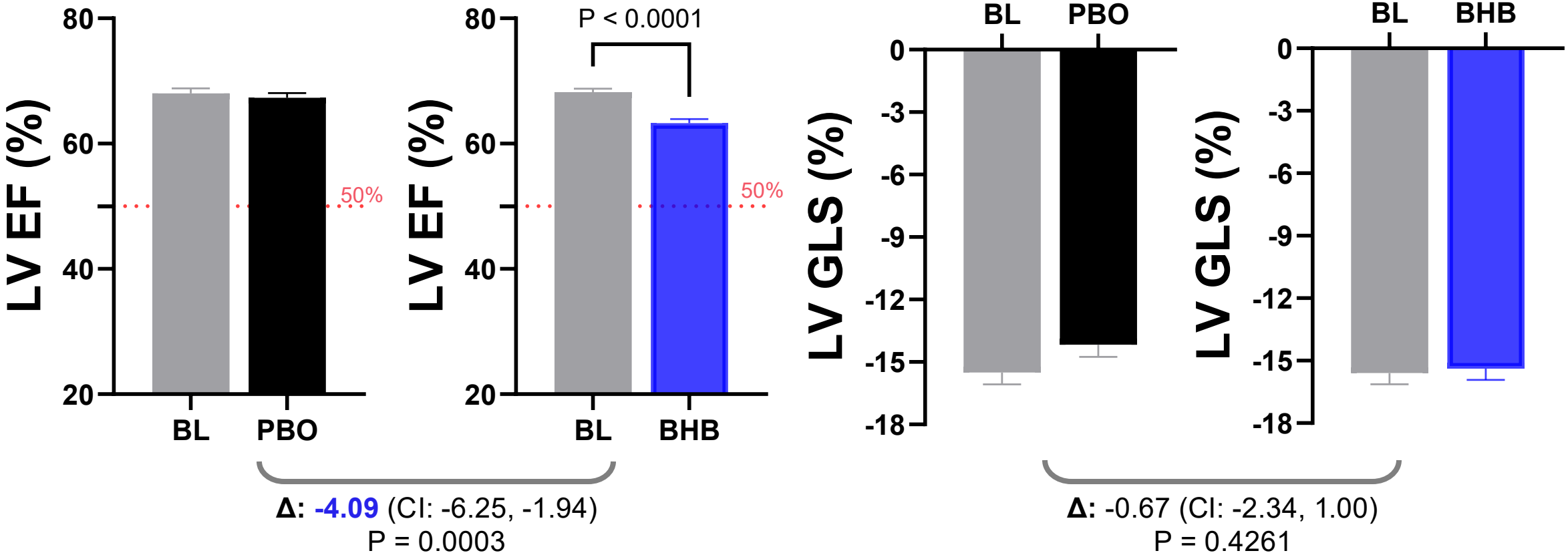
	Low dose N = 28	High dose N = 28	BHB-1893 total N = 56	Placebo N = 28
Any TEAE	23 (82.1)	24 (85.7)	47 (83.9)	19 (67.9)
Mild	18 (64.3)	18 (64.3)	36 (64.3)	17 (60.7)
Moderate	5 (17.9)	6 (21.4)	11 (19.6)	2 (7.1)
Severe	0	0	0	0
TEAE leading to discontinuation	0	0	0	0
TEAE leading to drug interruption	0	0	0	1 (3.6)
Any serious TEAE*	2 (7.1)	1 (3.6)	3 (5.4)	1 (3.6)
LVEF <50%	1 (3.6)	3 (10.7)	4 (7.1)	0

Data are n (%). *Serious TEAEs: low dose, cellulitis, otolithiasis; high dose, atrial fibrillation; placebo, atrial tachycardia (n = 1 each). AE, adverse event; BHB, HRS/BHB-1893; LVEF, left ventricular ejection fraction; nHCM, non-obstructive hypertrophic cardiomyopathy; TEAE, treatment-emergent adverse event.
Source: Wang et al., ESC-HF 2026 (NCT06816251).

Wang et al. ESC-HF 2026
https://esc365.escardio.org/presentation/324648

Heart Failure & World Congress on Acute Heart Failure 2026

nHCM: ↓ HYPERDYNAMIC LV EF WITH PRESERVED LV STRAIN



Δ: -4.09 (CI: -6.25, -1.94)
P = 0.0003

Δ: -0.67 (CI: -2.34, 1.00)
P = 0.4261

7.1% (4/56) had LVEF <50% (range: 46 to 49%)
All returned to > 50% with dose adjustment.

39% of BHB group improved GLS by ≥10%#
vs 15% on PBO (P < 0.05*)

Data are mean ± SEM. *Comparison via Fisher's exact test (2-sided). BHB, pooled HRS/BHB-1893 (low + high dose); BL, baseline; CI, 95% confidence interval, global longitudinal strain; LV, left ventricular; LVEF, LV ejection fraction; PBO, placebo; SEM, standard error of the mean; W12, week 12. #: -1.6% is 10% of the mean LVGLS at baseline for all participants.

CONCLUSIONS

- **HRS/BHB-1893 improved indices of diastolic function with predictable effects in systolic performance**, both in vitro and in patients with nHCM
  - ✓ *diastolic improvements independent of gradient relief*
- These observations further support the role of CMIs to address excess cardiac actomyosin residual cross-bridges, a key driver of diastolic dysfunction in HCM
- Supports **HRS/BHB-1893 as a next-generation CMI** with **consistent diastolic activity** across models

CMI, cardiac myosin inhibitor; HCM, hypertrophic cardiomyopathy; nHCM, non-obstructive HCM.