Phase 2 randomized, double-blind, placebo-controlled study to evaluate BHB/HRS-1893 in adults with symptomatic non-obstructive hypertrophic cardiomyopathy

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Disclosures

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Background

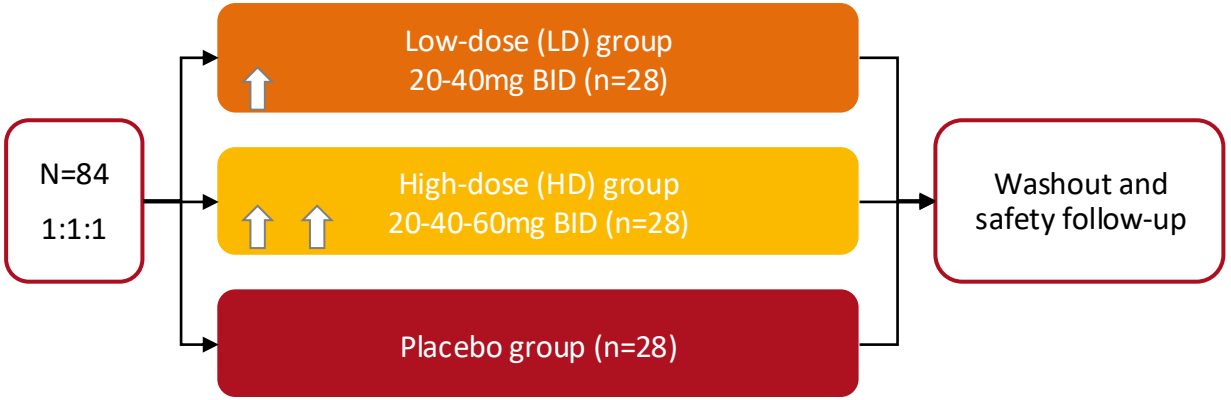
- **BHB/HRS-1893** is an investigational selective, reversible, small-molecule cardiac myosin inhibitor (CMI) engineered for rapid onset of action, minimal impact on LVEF, and ease of use.
- CMIs have improved the management of obstructive HCM and may hold promise as an effective and disease-modifying therapeutic option for nHCM, an area of significant need where options are limited.
- CMIs have been shown to be disease-modifying in the setting of obstructive HCM, but the impact on underlying disease biology in nHCM remains in question due to the mechanical relief of ventricular pressure associated with gradient obliteration.
- This placebo-controlled Phase 2 study evaluated the efficacy and safety of **multiple BHB/HRS-1893 dosing regimens** in adults with symptomatic nHCM.

LVEF = left ventricular ejection fraction; HCM = hypertrophic cardiomyopathy

Study Design

- This study enrolled adult nHCM patients with: LVEF ≥60%, NYHA class II-III, resting and Valsalva LVOT-G <30 mmHg at screening, maximal wall thickness ≥15 mm or ≥13 mm with family history of HCM, and KCCQ-CSS ≥30 to ≤85.

Design



Key Endpoints

- Primary endpoint: Safety; LVEF < 50%
- Biomarkers: NT-proBNP, cardiac troponin I
- Feel and function: KCCQ-CSS, pVO2
- Echo: Diastolic, structural

Dose Titration Criteria

LVEF (%)	Adjustment
≥55%	Increase Dose
<55% and ≥50%	Maintain Dose
<50% and ≥45%	Decrease Dose
<45%	Drug Interrupted

NCT: 06816251

Baseline characteristics

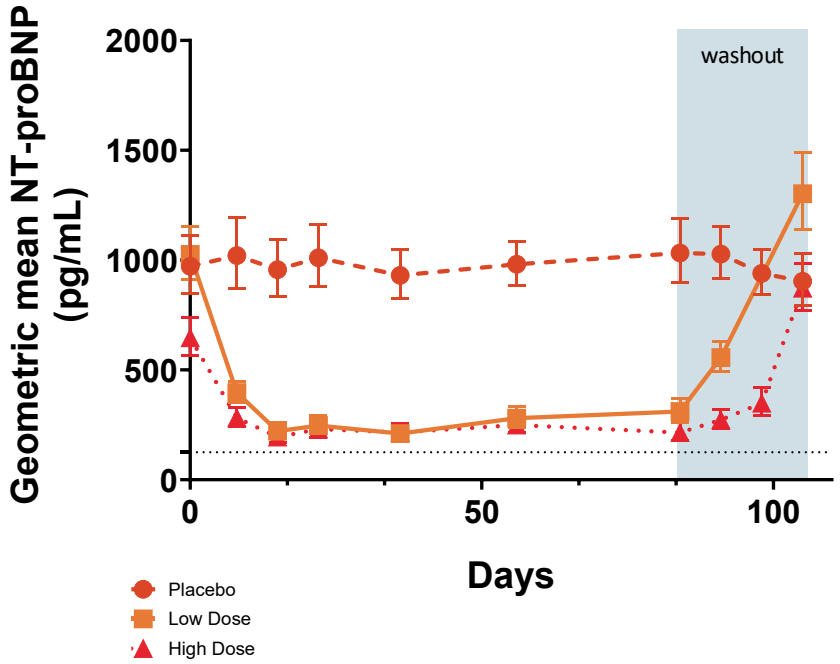
Characteristic	BHB-1893 Low-dose group (N=28)	BHB-1893 High-dose group (N=28)	Placebo (N=28)
Age (years)	44.5 (11.0)	51.0 (12.0)	47.3 (14.6)
Sex: Female	14 (50.0%)	8 (28.6%)	9 (32.1%)
BMI (kg/m2)	25.3 (3.87)	25.0 (3.39)	24.6 (3.54)
LVEF (%)	68.2 (3.97)	68.2 (4.14)	68.0 (4.21)
KCCQ-CSS	72.5 (8.23)	68.7 (8.85)	69.9 (7.96)
NYHA Class II	100%	100%	100%
pVO2 (mL/min/kg)	19.7 (1.81)	18.3 (3.27)	18.5 (4.93)
NT-proBNP (pg/mL)	1026 (1.8)	646 (2.0)	972 (2.0)
hs-cTnI (pg/mL)	108 (7.2)	63.8 (6.4)	69.2 (4.4)

Data are shown as mean (SD) unless otherwise specified. NT-proBNP and Hs-cTnI geometric mean (geo SD). NYHA, New York Heart Association; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; pVO_2, peak oxygen uptake; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide. pV02 data presented for the prespecified analysis on adequate CPET

Distribution of dose levels indicated most patients titrated to highest dose available

Last Dose (mg)	BHB-1893 Low-dose (N=28)	BHB-1893 High-dose (N=28)	BHB-1893 Total (N=56)	Placebo (N=28)
20 mg BID	1 (3.6%)	1 (3.6%)	2 (3.6%)	0 (0.0%)
40 mg BID	27 (96.4%)	7 (25.0%)	34 (60.7%)	15 (53.6%)
60 mg BID	NA	20 (71.4%)	20 (35.7%)	13 (46.4%)

NT-proBNP, a key biomarker of heart failure, fell rapidly, deeply, and durably



68%

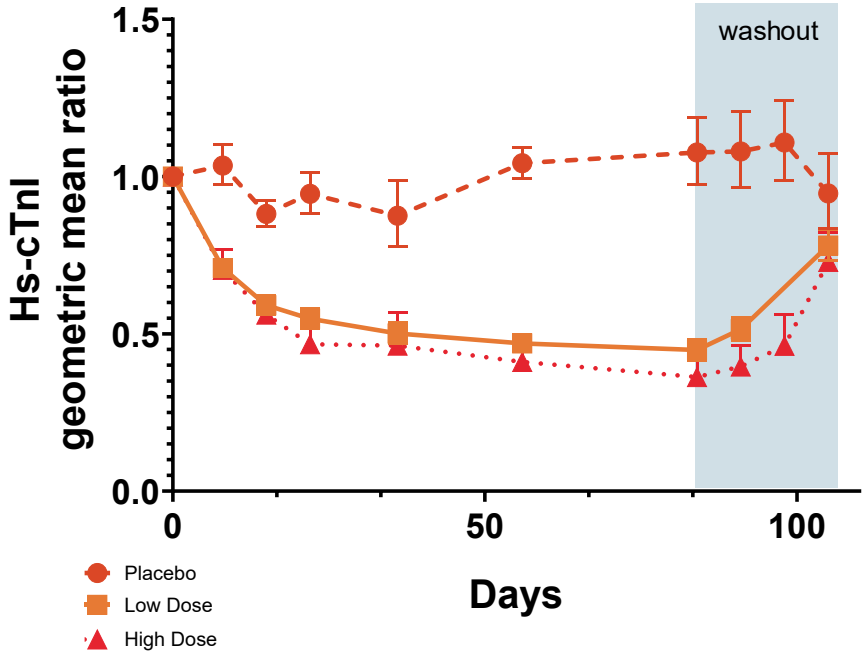
Drop from baseline in high dose group

42%

of patients at 60 mg below 125 pg/mL*

Geometric mean and SE; n≥27 (D0 to D84); * 125 pg/mL upper limit of normal for individuals < 75 years old and cutoff for ruling out heart failure: 2022 AHA/ACC/HFSA guidelines. LD = low dose; HD = high dose

cTnI levels fell rapidly and low levels were sustained, indicating reduction in heart tissue injury



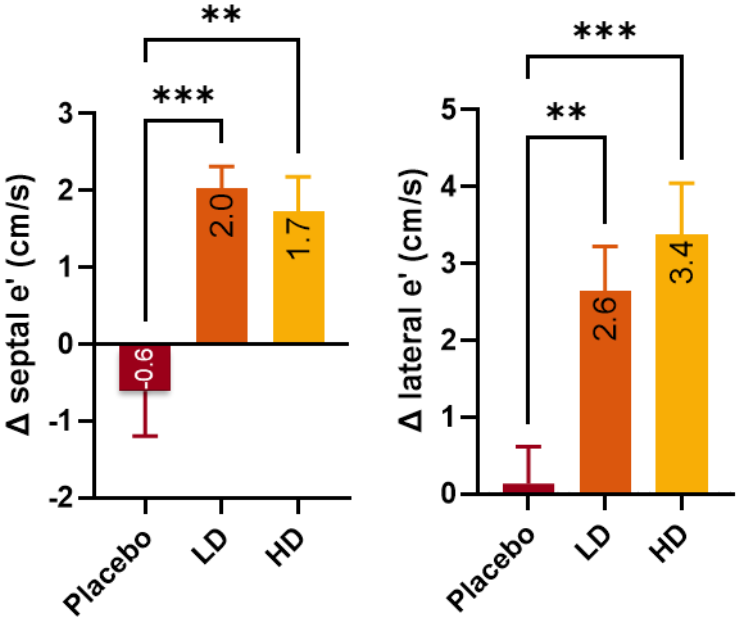
60%

decrease from baseline in high dose group

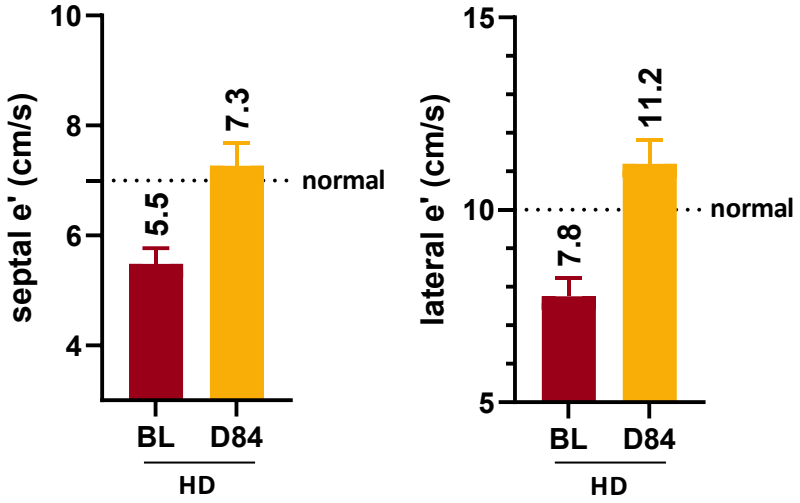
Geometric mean and SE; n ≥27 (D0 to D84); Hs-cTnI: high sensitivity cardiac troponin I, a marker of heart muscle injury, often associated with microvascular ischemia or wall stress

Myocardial relaxation improved with BHB/HRS-1893

Early diastolic relaxation improved

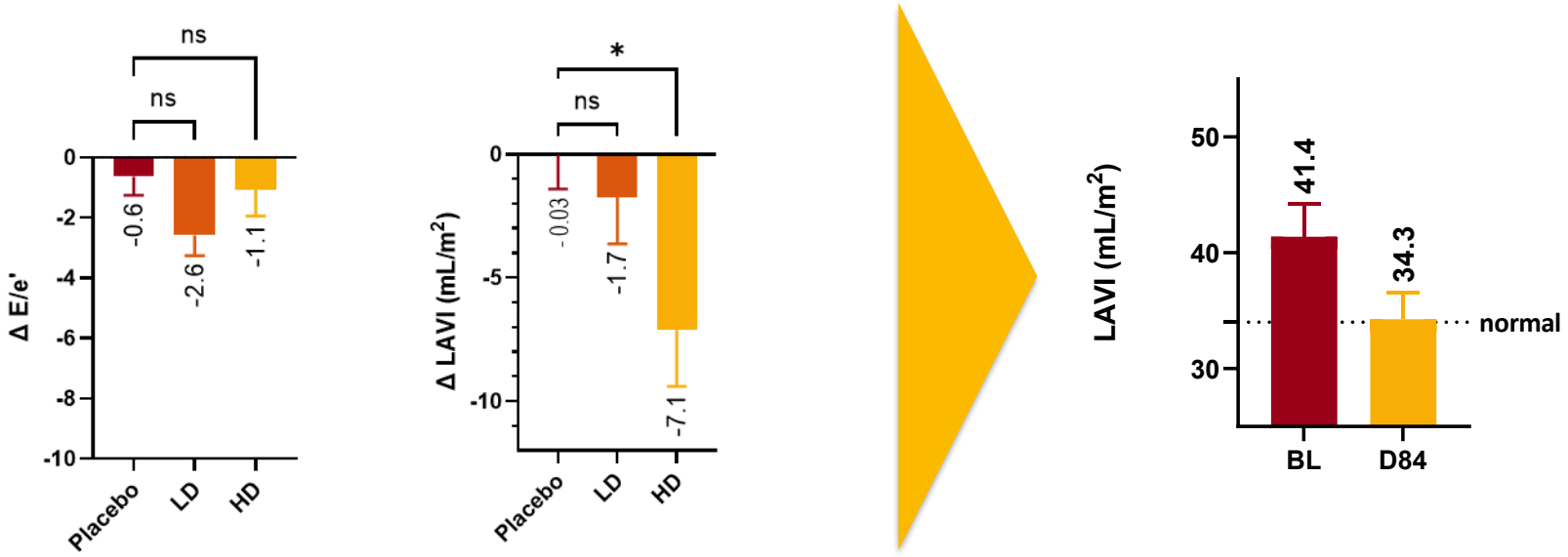


Velocities moved from abnormal toward normal



Data presented as mean (SEM); **: p<0.01, ***: p<0.001

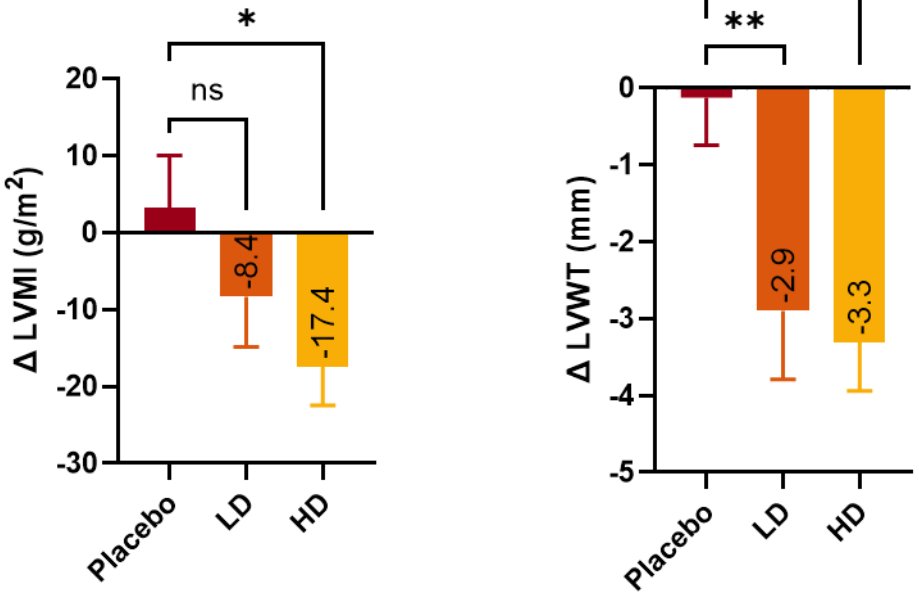
Hemodynamic benefit observed with BHB/HRS-1893, with left atrial volume normalizing



Observed normalization of left atrial volume index suggests the atrium is no longer pressure-overloaded

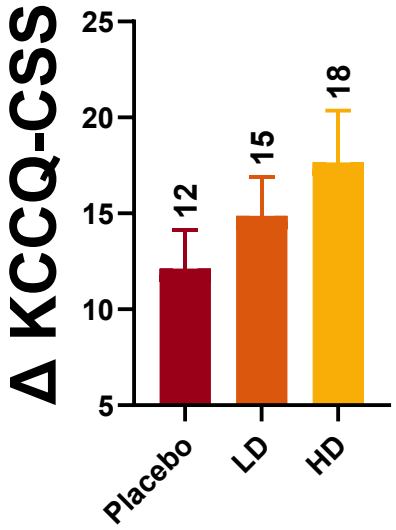
Data presented as mean (SEM); n.s.: not significant, *: p<0.05;
E/e' = Mitral inflow velocity / average (lateral and septal) mitral annular velocity: an estimate of left ventricular filling pressure; LAVI = left atrial volume index

Left ventricular mass and wall thickness decreased showing structural reverse remodeling in the absence of outflow tract obstruction



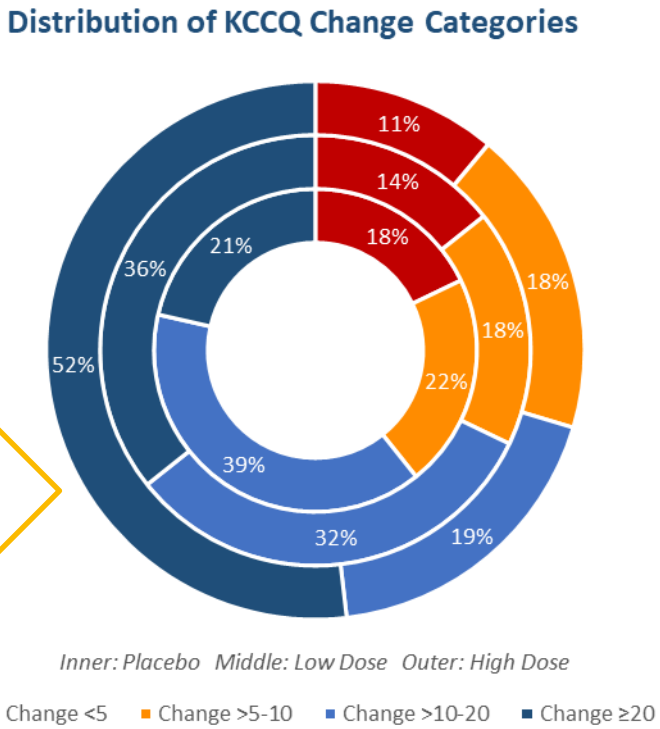
Data presented as mean (SEM); n.s.: not significant, *: p<0.05, **: p<0.01; LVMI = left ventricular mass index; LVWT = left ventricular wall thickness

BHB/HRS-1893 demonstrated a dose-dependent, placebo-adjusted, mean improvement in KCCQ-CSS



Placebo-adjusted increase of +5.5 pts

52% of high dose group reported symptom improvement in the ≥ 20 pt category



KCCQ-CSS = Kansas City Clinical Questionnaire clinical summary score. Data is mean (SEM), distribution based on D84 assessment

BHB/HRS-1893 demonstrated a placebo-adjusted improvement in pVO2 after 12 weeks of treatment

Placebo-adjusted

+0.5 mL/min/kg

mean improvement in pVO2 in high dose group,

+1.7 mL/min/kg

absolute change

55%

of patients in high dose group achieved

≥1.5 mL/min/kg

mean increase from baseline pVO2

Placebo-adjusted

+0.9 mL/min/kg

mean improvement in patients receiving **60 mg BID,**

+2.1 mL/min/kg

absolute change

100% cycle-based CPET; prespecified analysis on adequate CPET

Safety and tolerability were generally consistent with prior studies of BHB/HRS-1893

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

	BHB/HRS-1893 Low-Dose (N = 28)	BHB/HRS-1893 High-Dose (N = 28)	BHB/HRS-1893 Total (N = 56)	Placebo (N = 28)
Any TEAEs	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
Any TEAE leading to permanent discontinuation	0	0	0	0
Any TEAE leading to study 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

*LD: cellulitis (n=1), otolithiasis (n=1); HD: atrial fibrillation (n=1); placebo: atrial tachycardia (n=1)

Conclusions

- Rapid and sustained improvement in clinically relevant biomarkers of diastolic wall stress and microvascular ischemia, NT-proBNP and cTnI, respectively, was observed.
- Dose-dependent cardiac functional and structural data suggest **disease-modifying** profile:
  - Improvements in diastolic function as measured by early diastolic relaxation
  - Hemodynamic benefit highlighted by reduced chronic filling pressures
  - Reduction in LVMI and LVWT in the setting of nHCM, which lacks the mechanical relief of wall stress seen when gradients drop in oHCM, suggests direct suppression of the hypertrophic signaling cascade.
- Placebo-adjusted, dose-dependent improvement in KCCQ-CSS and pVO2 reflects meaningful gains in patients' feel and function.
- No severe AEs or any AEs leading to permanent discontinuation.
  - Four subjects (7% of treated population) dose reduced due to LVEF less than 50%.
  - All subjects LVEF returned to greater than 50% with dose reduction.

Acknowledgements

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