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Efficacy and Safety of BHB/HRS-1893 In Symptomatic Obstructive Hypertrophic Cardiomyopathy: Results From a 12-Week Phase 2 Study

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Disclosures

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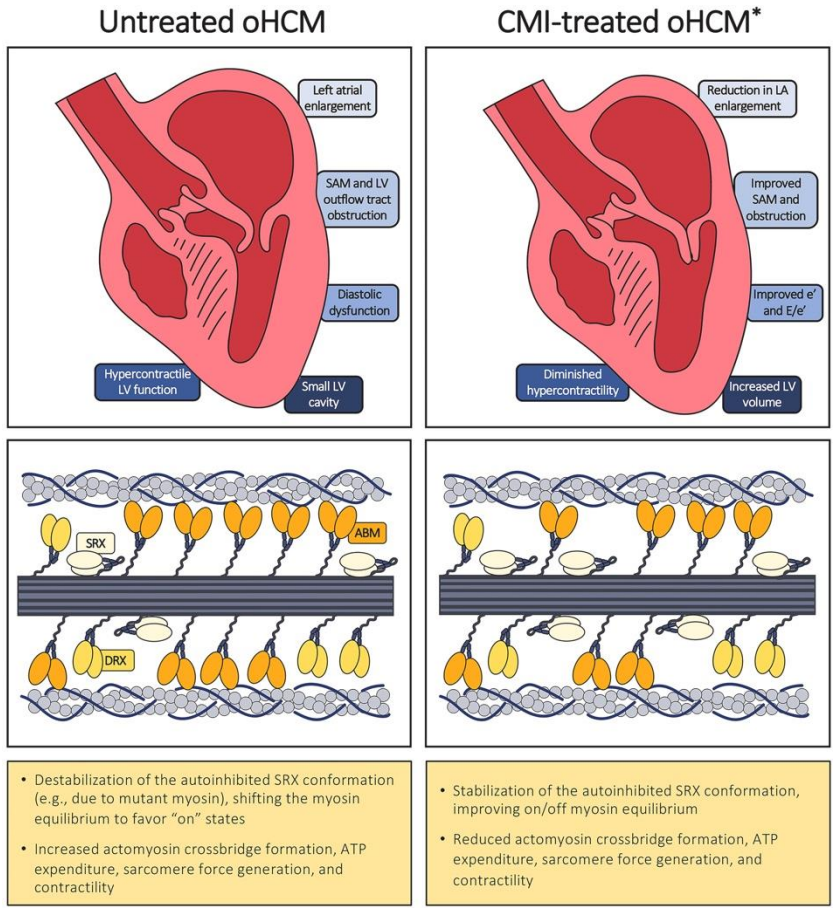
This study and presentation was funded by Jiangsu Hengrui Pharmaceuticals Co., Ltd. and Braveheart Bio, Inc.

Background

- **BHB/HRS-1893** is a selective, reversible, small-molecule cardiac myosin inhibitor (CMI) engineered for rapid onset of action, shallow LVEF, and ease of use.
  - By inhibiting cardiac myosin ATPase activity, BHB/HRS-1893 reduces actin-myosin crossbridge formation and normalizes cardiac contractibility.
- **CMIs** have improved management of symptomatic obstructive hypertrophic cardiomyopathy (oHCM), with demonstrated improvements in exercise capacity and patient symptoms.
  - Current CMIs require multi-step titration and ongoing monitoring which may limit uptake broadly and create strain on health care systems.
- This Phase 2 study evaluated the efficacy and safety of **multiple BHB/HRS-1893 dosing regimens** in adults with symptomatic oHCM.

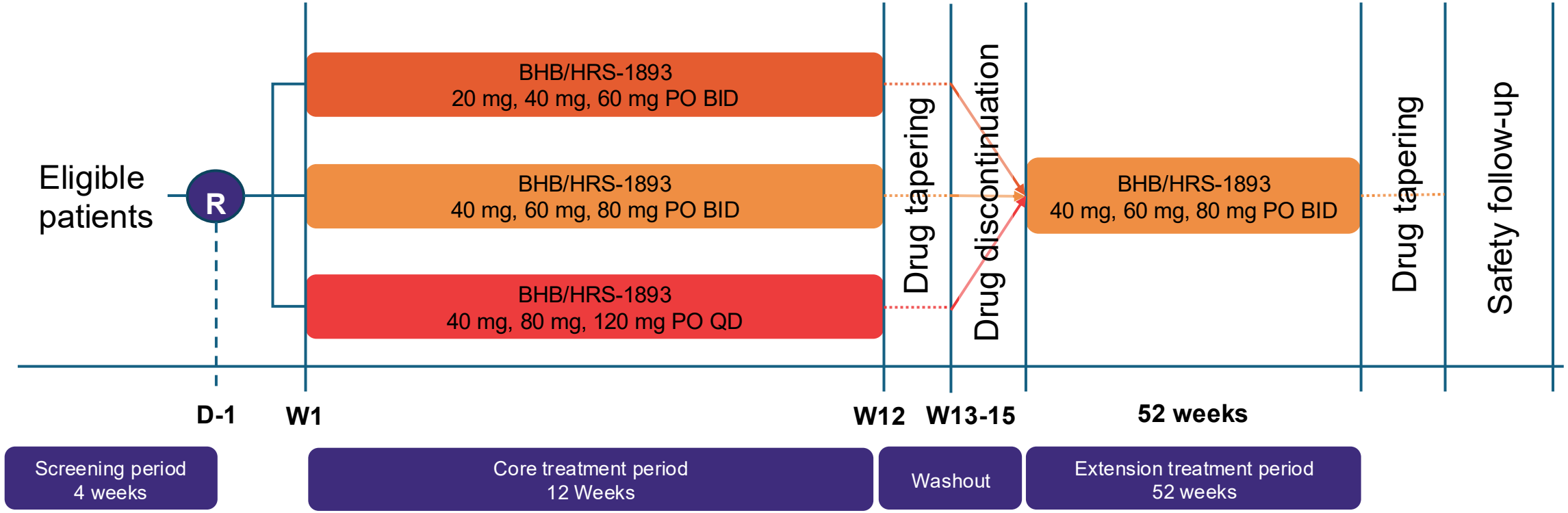


CMI mechanism of action. JACC Heart Failure. 2023 Jul, 11 (7) 735–748.

Study design

Adult patients with symptomatic oHCM who had resting LVOT-G ≥50 mmHg (or resting LVOT-G ≥30 mmHg and Valsalva LVOT-G ≥50 mmHg), LVEF ≥60%, and NYHA Class II-III were enrolled.

Option for dose titration to occur weekly ***if Valsalva LVOT-G > 30 mmHg*** and LVEF > 55%



(ClinicalTrials.gov, NCT06516068)

oHCM, obstructive hypertrophic cardiomyopathy; LVOT-G, left ventricular outflow tract gradient; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PO, oral administration; BID, twice daily; QD, once daily.

Study endpoints

Primary endpoint

- Change in Valsalva LVOT-G from baseline to Week 12

Key secondary endpoints

- Change from baseline in:
  - Peak oxygen uptake (pVO_2)
  - KCCQ-CSS
  - Resting LVOT-G
  - NT-proBNP
- Proportion with NYHA class improvement of ≥1

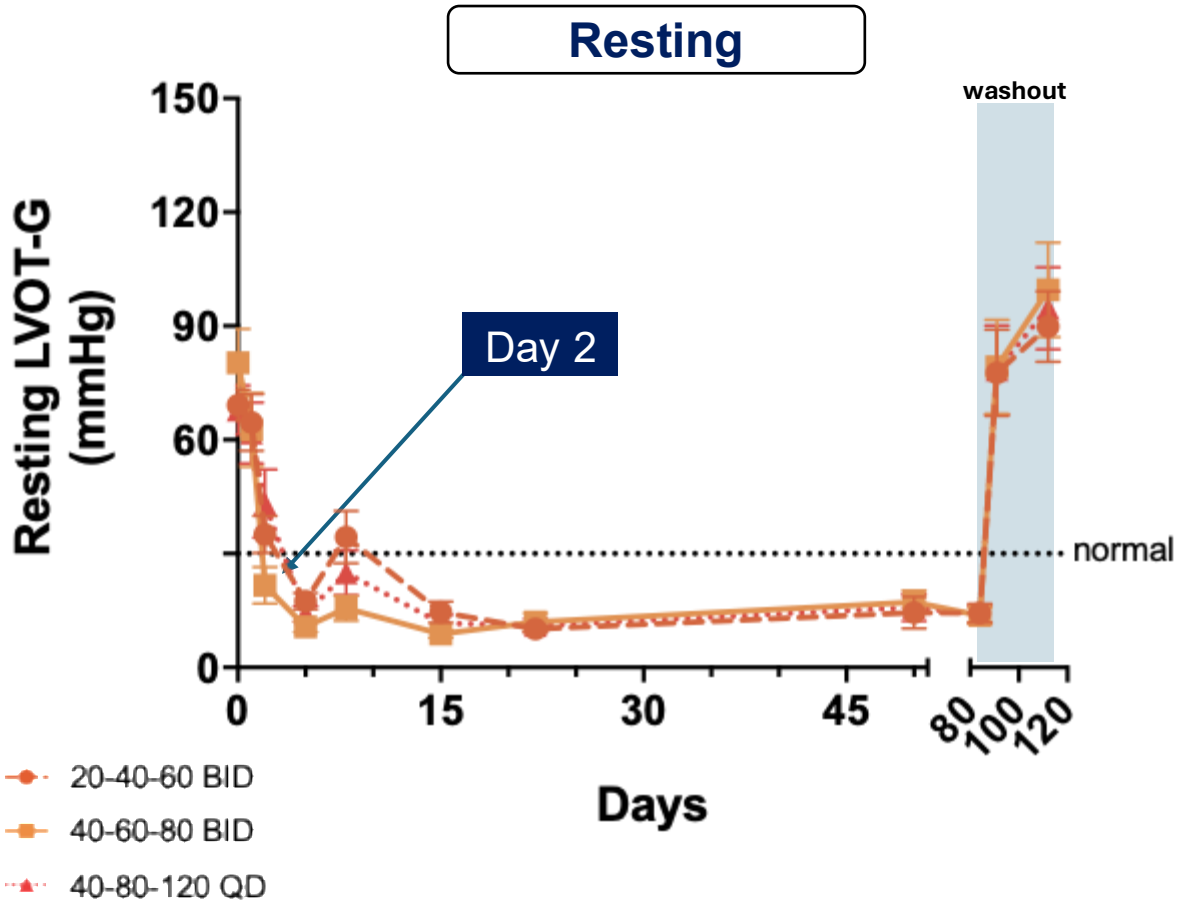
LVOT-G, left ventricular outflow tract gradient; LVEF, left ventricular ejection fraction; pVO_2, peak oxygen uptake; NT-proBNP, N-terminal pro-B-type natriuretic peptide; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NYHA, New York Heart Association.

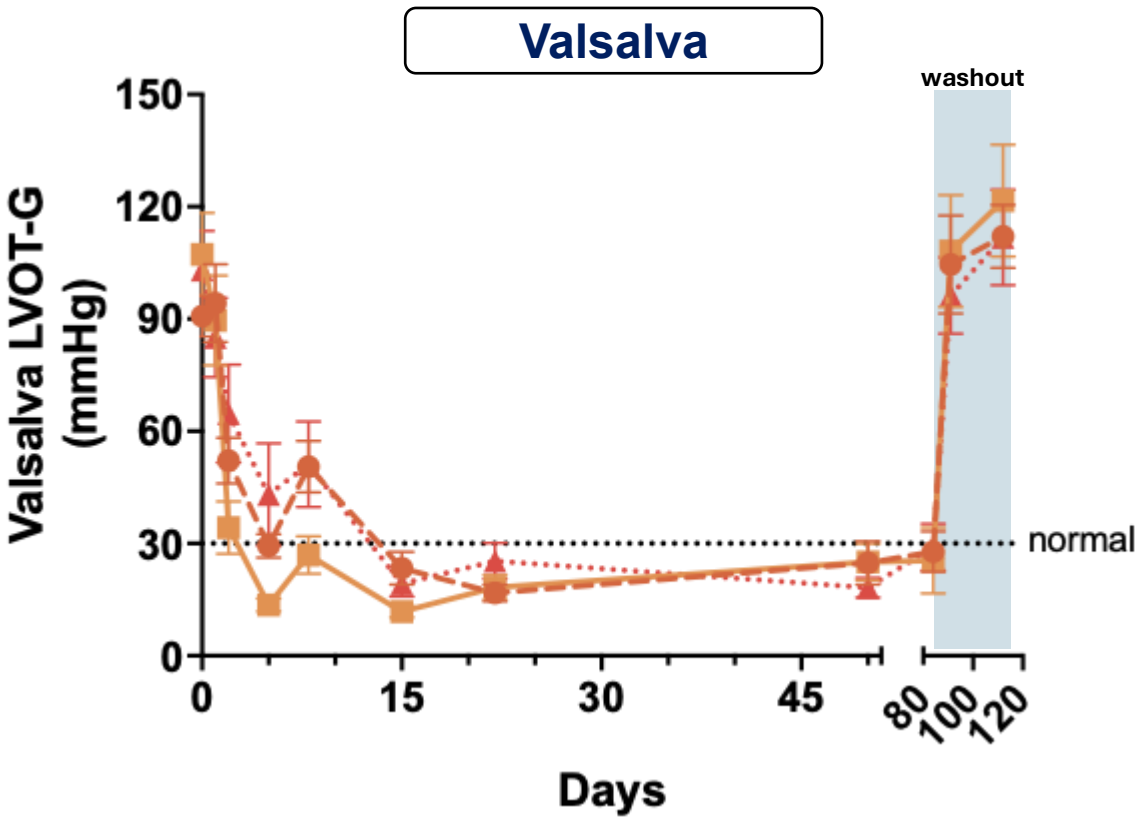
Baseline characteristics

	20-40-60 BID (N = 14)	40-60-80 BID (N = 14)	40-80-120 QD (N = 14)
Age, years, mean(SD)	48.4 (12.5)	51.5 (10.4)	54.8 (11.2)
Male, n (%)	10 (71.4)	9 (64.3)	7 (50.0)
Background therapy, n (%)			
Beta blockers	13 (92.9)	12 (85.7)	12 (85.7)
Calcium channel blockers	0	1 (7.1)	1 (7.1)
History of Atrial Fibrillation	0	2 (14.3)	0
Valsalva LVOT-G, mmHg, mean(SD)	90.8 (20.4)	107.2 (41.7)	103.1 (39.2)
Resting LVOT-G, mmHg, mean(SD)	69.2 (15.4)	80.3 (33.4)	67.9 (24.5)
LVEF, %	71.0 (2.8)	69.3 (3.5)	69.2 (3.5)
pVO_2, mL/kg/min, mean(SD)	19.3 (2.9)	17.5 (3.2)	18.4 (4.3)
NYHA class, n (%)			
Class II	12 (85.7)	14 (100.0)	14 (100.0)
Class III	2(14.3)	0 (0.0)	0 (0.0)
KCCQ-CSS, mean (SD)	82.6 (13.3)	86.0 (12.9)	76.4 (13.2)

Data are shown as mean (standard deviation) unless otherwise specified.
LVOT-G, left ventricular outflow tract gradient; LVEF, left ventricular ejection fraction; pVO_2, peak oxygen uptake.

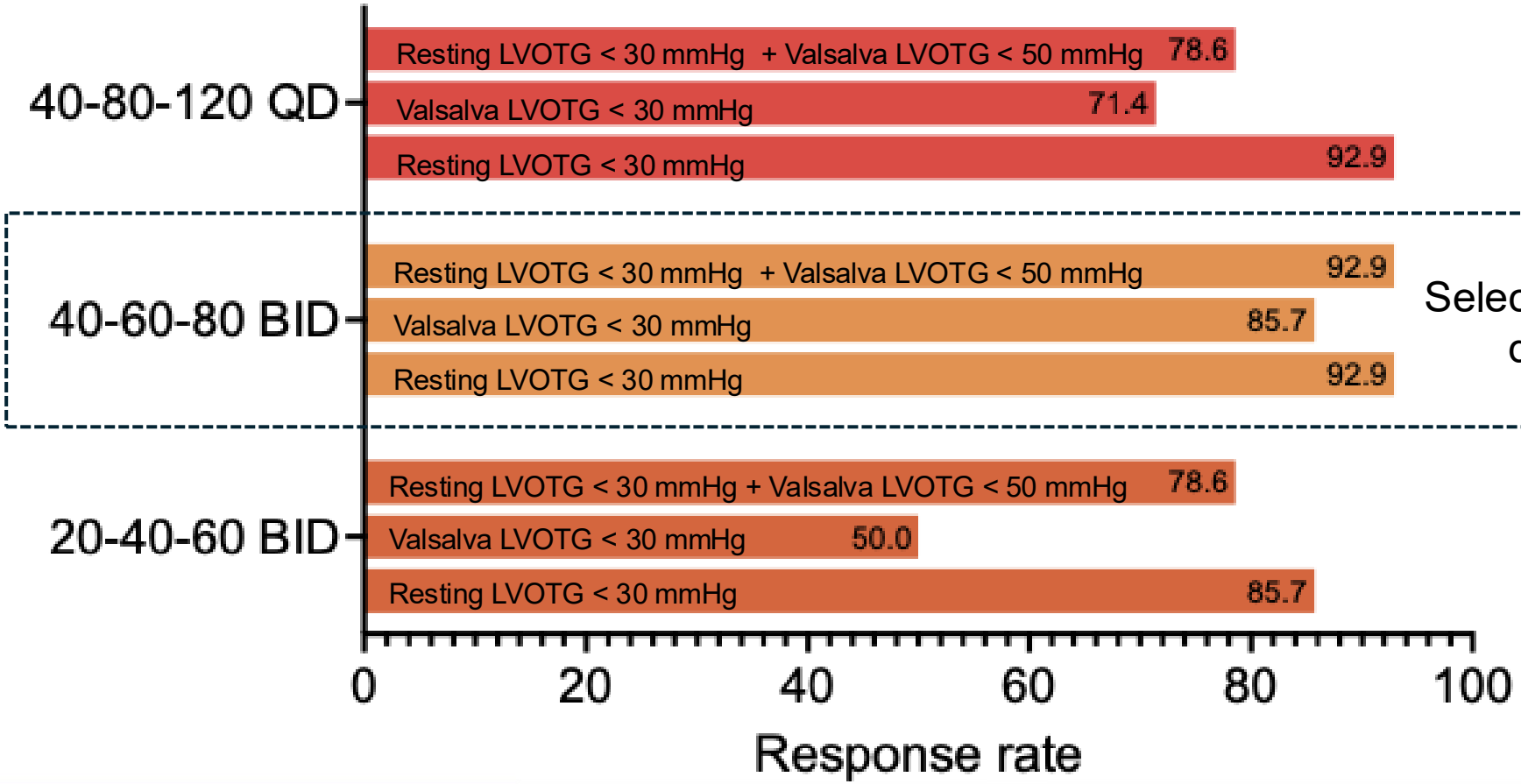
Rapid, deep, and reversible gradient reduction





Data are shown as mean, SEM.
LVOT-G, left ventricular outflow tract gradient.

86% of patients in 40-60-80 BID cohort achieved Valsalva <30 mmHg gradient response



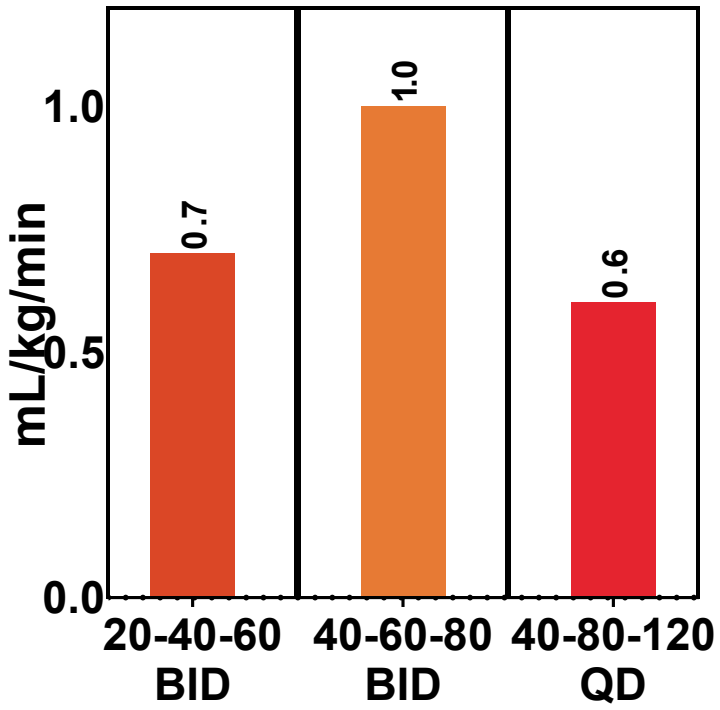
Selected OLE dose

42 of 42 patients in the 12 week core treatment rolled into the OLE

At week 39 of OLE treatment period, **88%** had Valsalva LVOTG < 30 mmHg

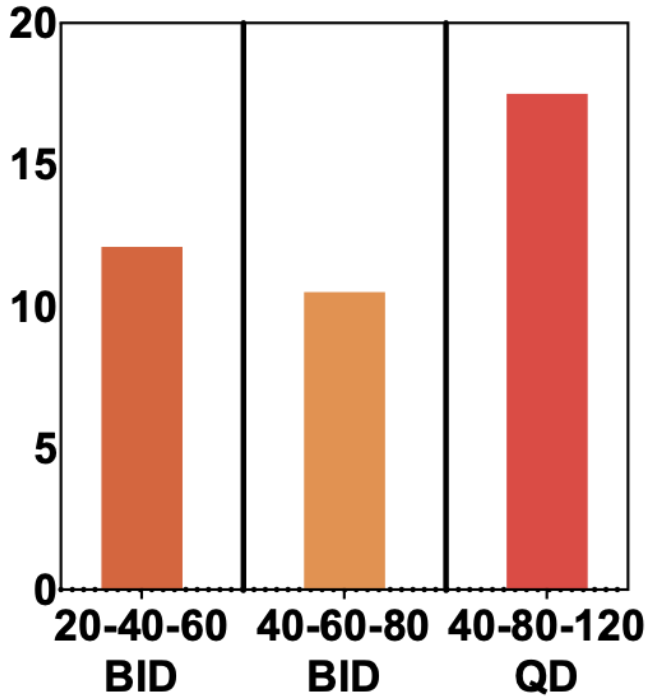
Functional capacity and symptom improvement displayed across clinical endpoints

Peak VO2

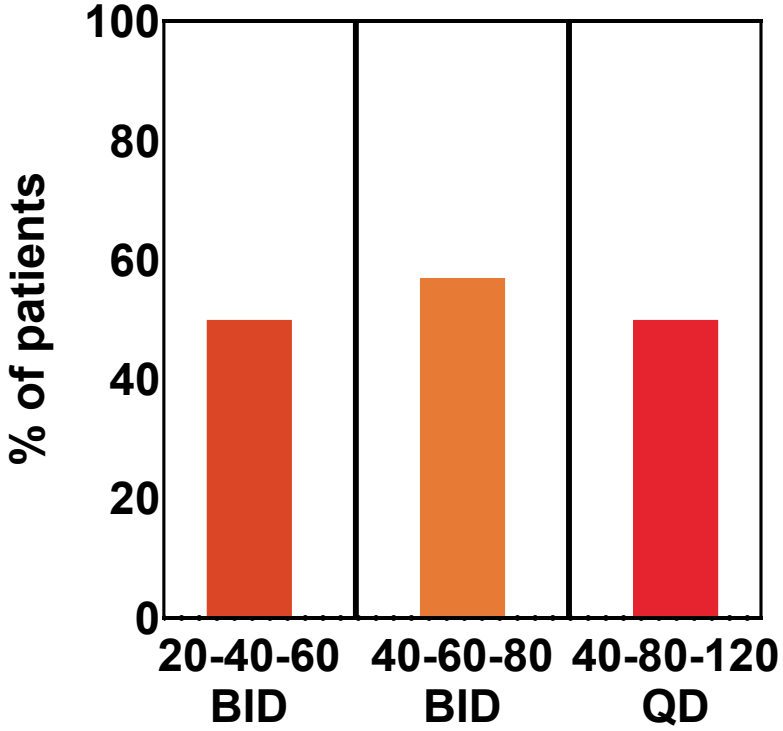


100% cycle based CPET

KCCQ-CSS



NYHA Class Improvement ≥1



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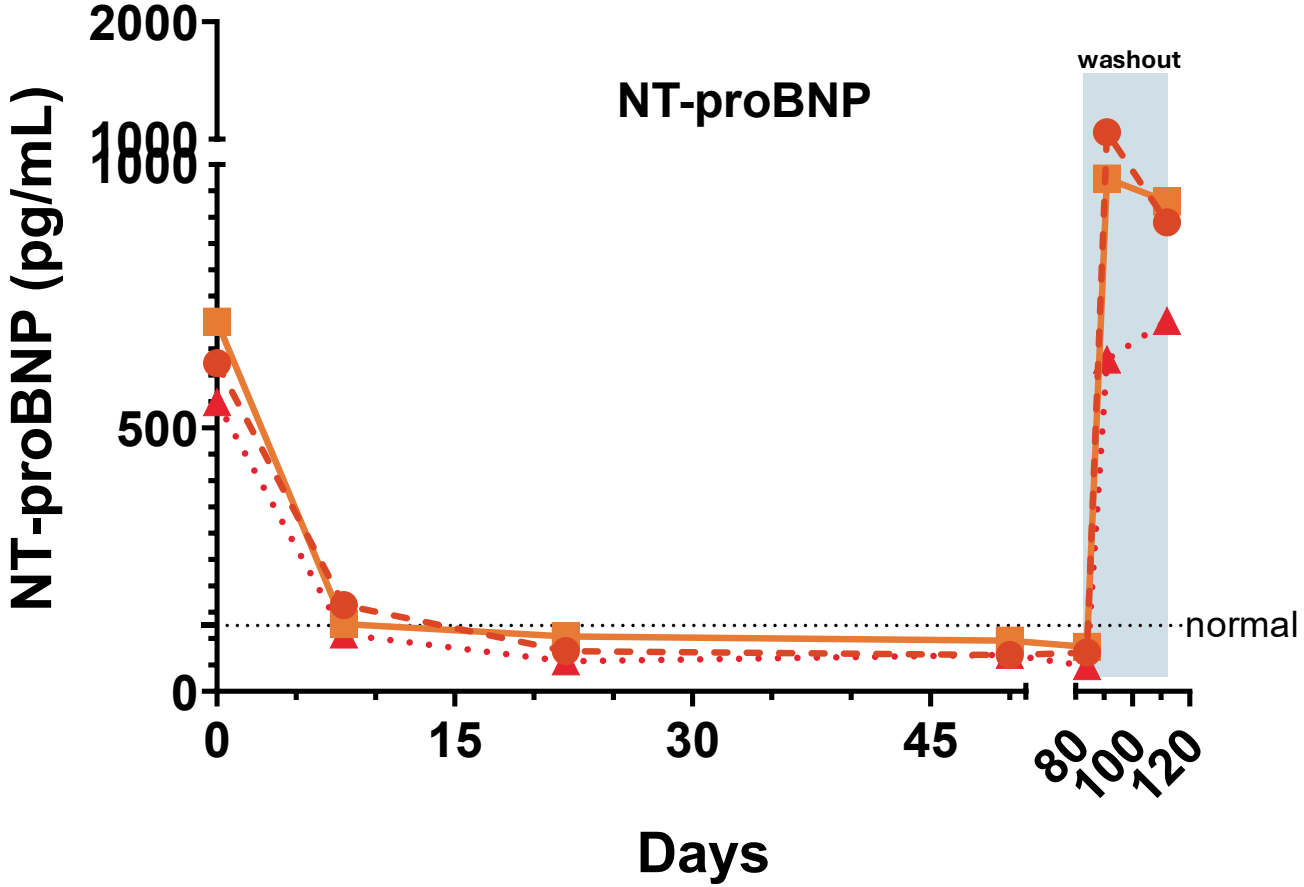
Peak VO_2, peak oxygen uptake; CPET, cardiopulmonary exercise test; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

NT-proBNP, key biomarker of heart failure, rapidly normalized in >80% of patients



NT-proBNP (pg/mL)	20-40-60 mg BID	40-60-80 mg BID	40-80-120 mg QD
Baseline (Geometric Mean)	622.8	701.9	549.2
Post - Treatment (Geometric Mean)	73.9	84.1	48.0
Post - Treatment to Baseline Ratio (Geometric Mean)	0.12	0.12	0.09

>80%
of patients achieved normal NT-proBNP levels

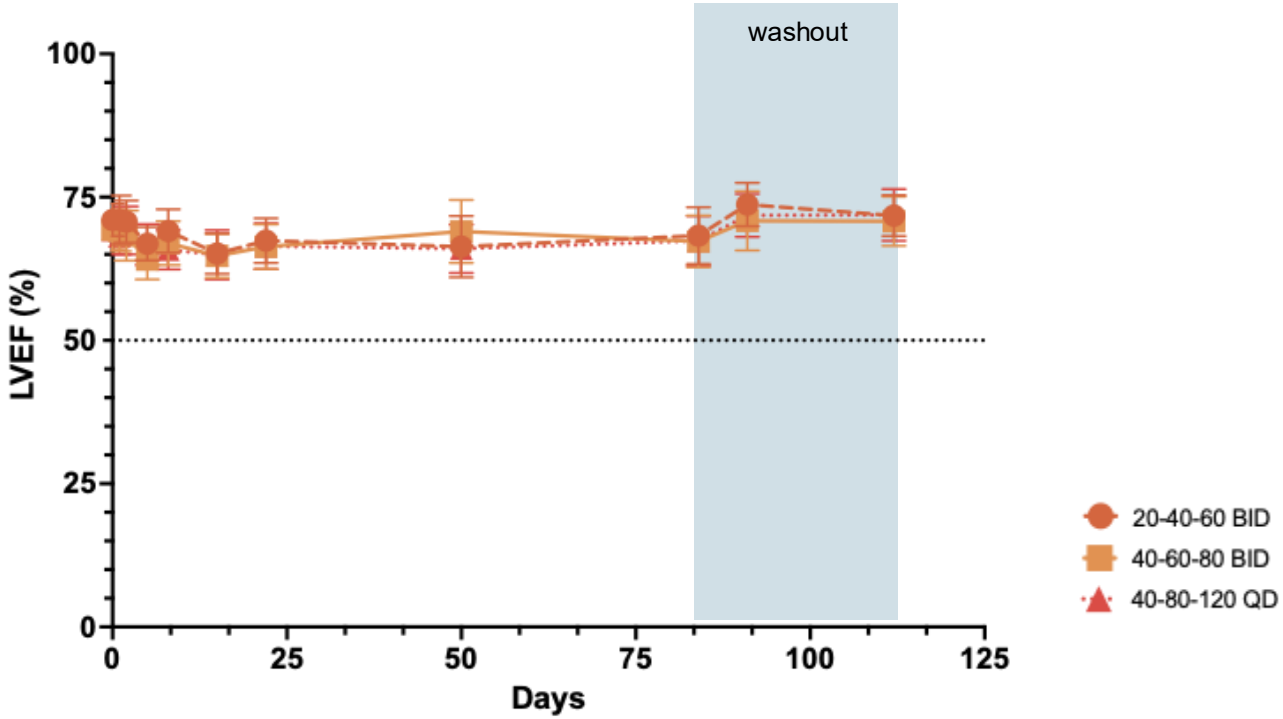
Data are shown as geometric mean, SEM.
NT-proBNP, N-terminal pro-B-type natriuretic peptide

BHB/HRS-1893 drove deep and rapid reductions in LVOT-G with low impact to LVEF

0
Dose reductions

0
LVEF events below 55%

Dose (mg) Schedule	LVEF, change (D84)
20-40-60 BID	-2.7%
40-60-80 BID	-2.1%
40-80-120 QD	-1.8%



Data are shown as mean, SD.
LVEF, left ventricular ejection fraction

Potential for highly simplified dose regimen

Dose distribution at Week 12

	20 mg BID	40 mg BID	60 mg BID	80 mg BID
20-40-60 mg BID	2	8	4	
40-60-80 mg BID		9	4	1

100%
of doses selected by LVOT-G < 30 mmHg

89% **of patients received 40 or 60 mg BID at last dose**

Adverse events

- AEs were mild or moderate in severity.
- There were no serious AEs or AEs leading to treatment interruption, discontinuation, or death.

	BHB/HRS-1893 Group 1 (N = 14)	BHB/HRS-1893 Group 2 (N = 14)	BHB/HRS-1893 Group 3 (N = 14)	Total (N = 42)
Any TEAEs	**12 (85.7)**	**10 (71.4)**	**14 (100)**	**36 (85.7)**
Mild	11 (78.6)	8 (57.1)	14 (100)	33 (78.6)
Moderate	1 (7.1)	2 (14.3)	0	3 (7.1)
Severe	0	0	0	0
Any TRAEs	**3 (21.4)**	**3 (21.4)**	**8 (57.1)**	**14 (33.3)**
Mild	3 (21.4)	2 (14.3)	8 (57.1)	13 (31.0)
Moderate	0	1 (7.1)	0	1 (2.4)
Severe	0	0	0	0

Data are shown as n (%).
AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

- Best-in-class potential across efficacy, safety, and ease-of-use
- BHB/HRS-1893 treatment resulted in **rapid, deep, and durable reductions in LVOT obstruction** at rest and after Valsalva
  - In the twice-daily setting, most patients start and end at the same dose, 40 mg BID; **89% served by 40 or 60 mg BID**
- BHB/HRS-1893 displayed low LVEF cost
  - Zero patients experienced an LVEF less than 55%
  - **Zero patients required dose reduction**
- Global Phase 3 development of BHB/HRS-1893 underway

(ClinicalTrials.gov, NCT06516068)

Acknowledgement

- All patients and their families
- All investigators and research personnel who conducted this trial
- Study sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd., China
- Braveheart Bio, Inc.