HRS-1893, a cardiac myosin inhibitor, in patients with obstructive hypertrophic cardiomyopathy

A randomized, double-blind, placebo-controlled phase 1 trial

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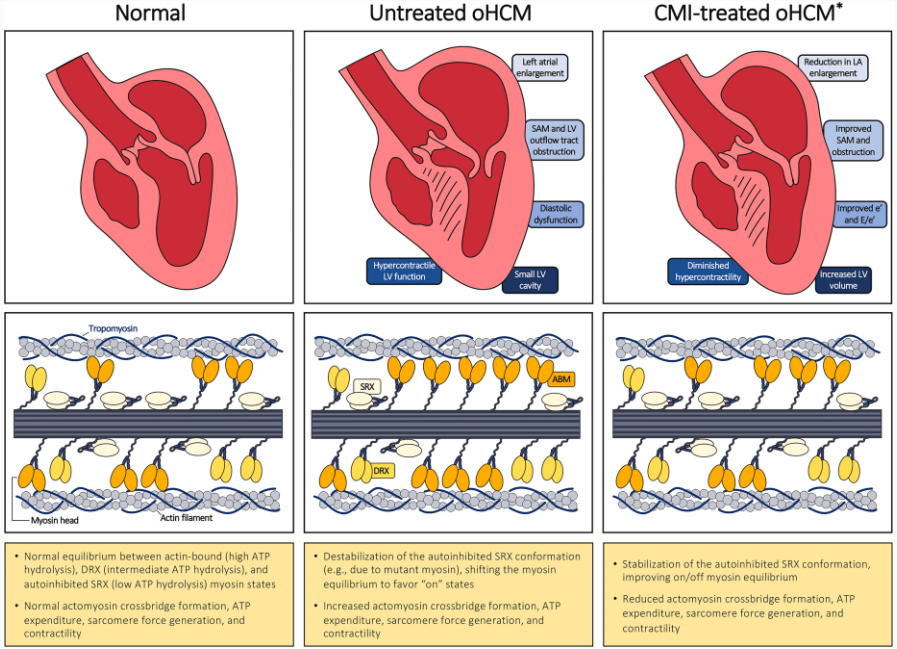
Background and objectives

- Hypertrophic cardiomyopathy (HCM) is a common heritable cardiac disease characterized by left ventricular hypertrophy and dynamic obstruction of the left ventricular outflow tract (LVOT).[1]
- Cardiac myosin inhibitors can reduce excessive cardiac contractility in HCM by inhibiting myosin ATPase enzyme and actin-myosin crossbridge formation.[2]
- **HRS-1893** is a selective reversible cardiac myosin inhibitor designed to reduce hypercontractility in HCM.
- This study aimed to evaluate the **safety, tolerability, pharmacokinetics, and pharmacodynamics** of HRS-1893 in healthy volunteers and patients with obstructive HCM. This presentation will focus on the results from the obstructive HCM patient cohort.



Mechanism of action of cardiac myosin inhibitors. J Am Coll Cardiol HF. 2023 Jul, 11 (7) 735–748.

1 J Am Coll Cardiol HF. 2018 May, 6 (5) 364–375. 2 J Am Coll Cardiol HF. 2023 Jul, 11 (7) 735–748.

Study Design (ClinicalTrials.gov: NCT05879523)

- This randomized, double-blind, placebo-controlled, phase 1 study consisted of 4 parts.
- Parts 1-3 were single ascending dose, food effect, and multiple ascending dose studies in healthy subjects.
- **Part 4 was a multiple ascending dose study in patients with obstructive HCM.**

Key Eligibility Criteria (Part 4)

- 18 to 85 years old
- Body mass index <35 kg/m^2
- Diagnosed hypertrophic cardiomyopathy
- Resting LVOT gradient (LVOT-G) ≥50 mmHg, or resting LVOT-G ≥30 mmHg with Valsalva LVOT-G ≥50 mmHg
- Left ventricular ejection fraction (LVEF) ≥60%

N = 8 for each dose cohort

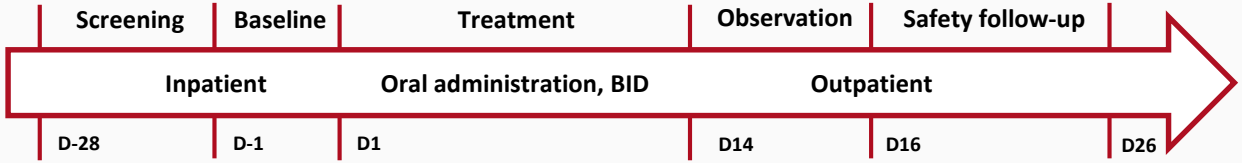
HRS-1893 : Placebo = 6 : 2

Dose escalation was decided by the Safety Monitoring Committee based on safety data 48 h following the last dose in the preceding dose cohort.

80 mg BID

60 mg BID

40 mg BID (optional)



Demographics and baseline characteristics

- In healthy volunteers, HRS-1893 at 40 mg BID showed a favourable safety profile, but a dose-dependent reduction in LVEF was observed. Given that obstructive HCM patients tolerate myosin inhibition better due to their hypertrophic myocardium, the initial therapeutic dose for obstructive HCM patients in the multiple ascending dose part was set at 60 mg.
- Dose escalation was discontinued following successful proof-of-concept demonstration in the 60 mg cohort.

	HRS-1893 60 mg (N = 6)	Placebo (N = 2)
Age, years, median (IQR)	50.0 (37.0, 60.0)	53.0 (51.0, 55.0)
Sex, n (%)		
Male	4 (66.7)	1 (50.0)
Female	2 (33.3)	1 (50.0)
BMI, kg/m^2	28.7 (3.2)	30.4 (3.8)
LVEF, %	69.5 (3.1)	73.5 (3.5)
Resting LVOT-G, mmHg	71.2 (24.9)	62.6 (0.0)
Valsalva LVOT-G, mmHg	66.7 (26.8)	68.1 (6.2)

Data are shown as mean (standard deviation) unless otherwise specified. BMI, body mass index; IQR, interquartile range; LVEF, left ventricle ejection fraction; LVOT-G, left ventricle outflow tract gradient.

Safety and pharmacokinetics

Safety

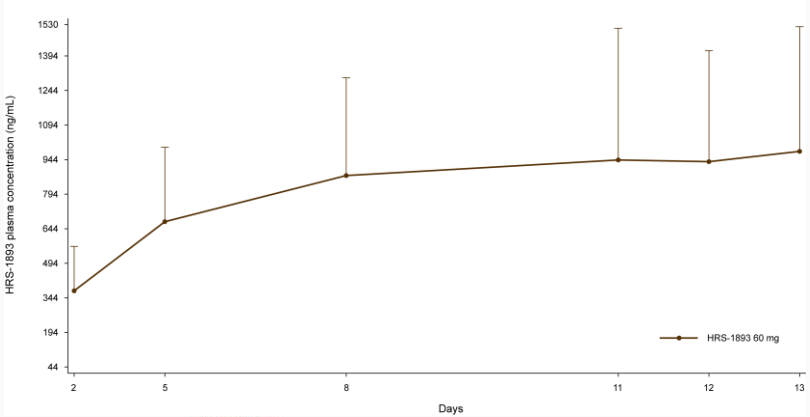
- HRS-1893 was well-tolerated, with all adverse events being mild in severity.
- The mean LVEF reduced slightly (9.1%) after HRS-1893 treatment. None of the HRS-1893-treated patients had an LVEF of <50% during the study.

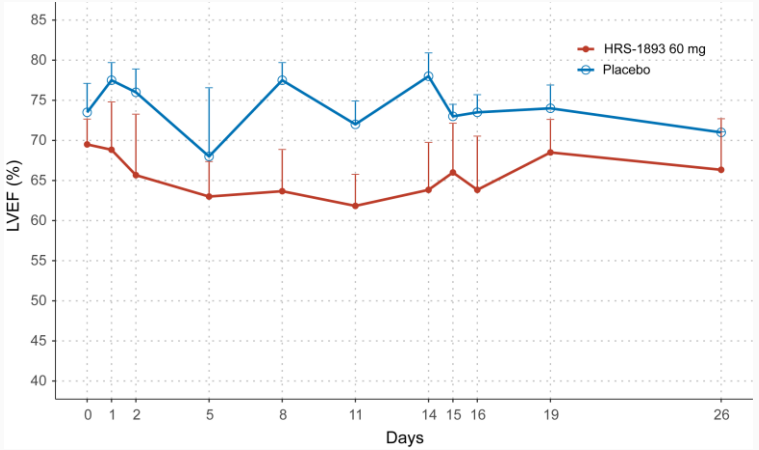
Pharmacokinetics

- HRS-1893 plasma concentration reached a steady state on Day 8. The ratio of accumulation at steady state was 1.30 for C_{max} and 2.04 for AUC_{tau}.

	HRS-1893 60 mg (N = 6)	Placebo (N = 2)
TEAE	2 (33.3)	2 (100)
TRAE	1 (16.7)	1 (50.0)
SAE	0	0
TEAE leading to treatment discontinuation	0	0
TEAE leading to death	0	0
Common TEAEs		
Nasal obstruction	2 (33.3)	0
Asthenia	1 (16.7)	0
Insomnia	1 (16.7)	0
Nausea	0	1 (50.0)
Vomiting	0	1 (50.0)
Alanine aminotransferase increased	0	1 (50.0)
Aspartate aminotransferase increased	0	1 (50.0)
Bilirubin conjugated increased	0	1 (50.0)
Blood bilirubin increased	0	1 (50.0)
Dizziness	0	1 (50.0)
Productive cough	0	1 (50.0)

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

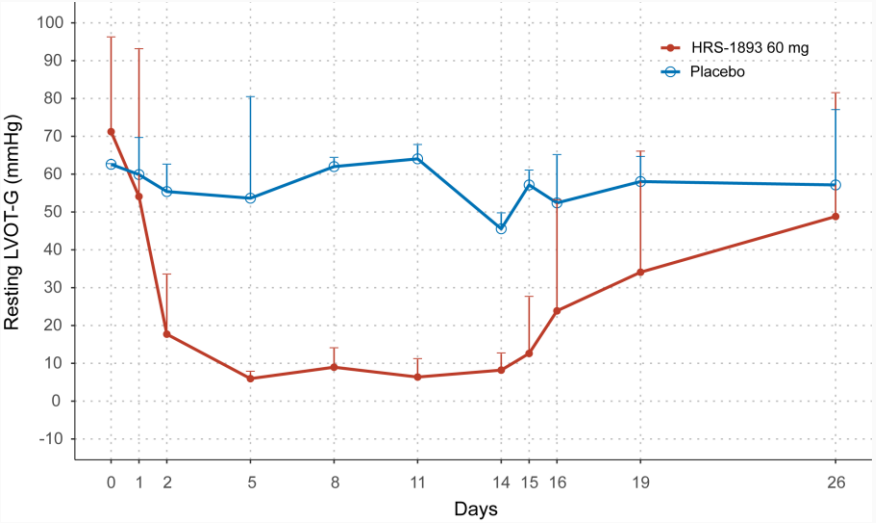


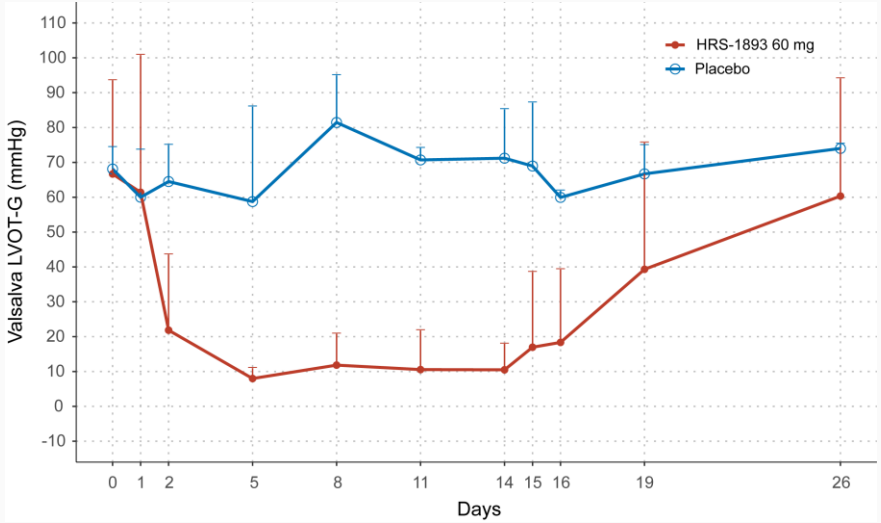


Data are shown as mean (standard deviation).

Left ventricular outflow tract gradient

- HRS-1893 induced significant hemodynamic improvements.
- By Day 5, the mean **resting LVOT-G decreased by 91% (from 71.2 mmHg to 6.0 mmHg)**, and the mean **Valsalva LVOT-G decreased by 87.4% (from 66.6 mmHg to 8.0 mmHg)**.
- On Day 14, all patients in the HRS-1893 group had Valsalva LVOT-G of ≤30 mmHg.

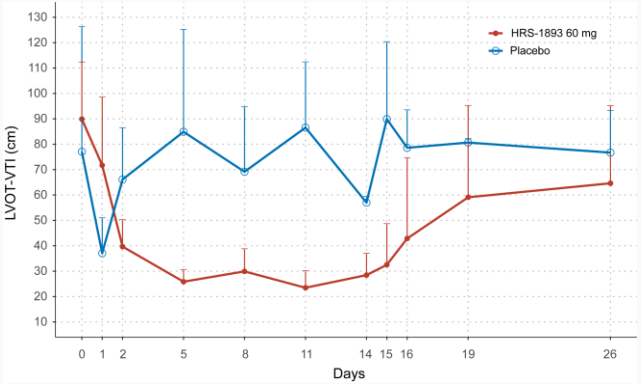


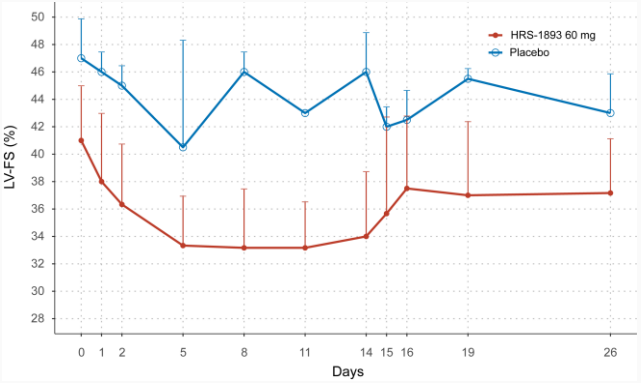


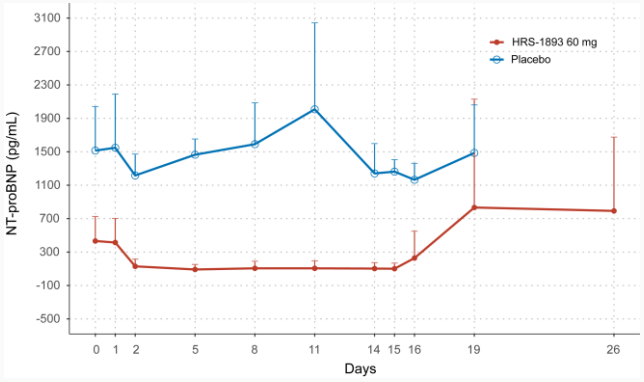
Data are shown as mean (standard deviation).

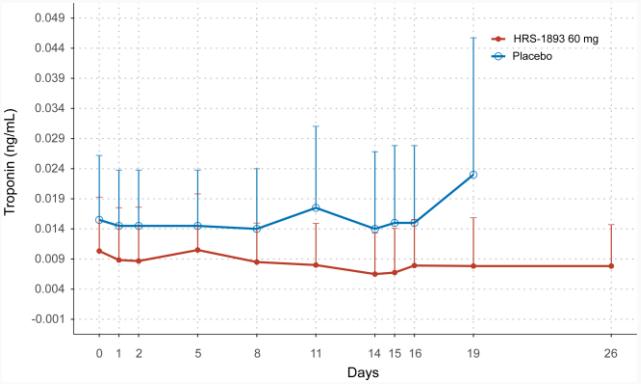
Other cardiac indicators

- Decreasing trends were observed in **left ventricular outflow tract velocity time integral** and **left ventricular fractional shortening** in the HRS-1893 group, while no significant changes were observed in the placebo group.
- On Day 14, **N-terminal pro-B-type natriuretic peptide** showed 64.9% reduction from baseline, and **cardiac troponin** showed 42.5% reduction from baseline in the HRS-1893 group.









Data are shown as mean (standard deviation).

Conclusion

- **HRS-1893 at 60 mg BID was well-tolerated in patients with obstructive HCM.**
  - All adverse events were mild in severity, and there were no serious adverse events or adverse events leading to treatment discontinuation or death.
  - LVEF reduced slightly following HRS-1893 treatment and returned to the baseline level after treatment discontinuation.
  - Individual LVEF were above 50% at all study visits.
- **HRS-1893 showed favourable pharmacokinetic characteristics.**
  - A steady state plasma concentration was reached in 8 days.
  - HRS-1893 allows for a much shorter dose titration period compared to other cardiac myosin inhibitors.
- **HRS-1893 rapidly and effectively reduced resting and Valsalva LVOT-G.**
  - LVOT-G reduction was achieved in 5 days and maintained throughout the treatment period.
  - Resting LVOT-G decreased by 91% and Valsalva LVOT-G decreased by 87.4%.
  - On Day 14, all patients achieved a Valsalva LVOT-G of ≤30 mmHg.
- **This study provided basis for the further development of HRS-1893, suggesting its potential as a novel treatment option for patients with obstructive HCM.**