Cardioprotective Effects of HM17321, a Novel UCN2 Analog, in Rodent Heart Failure Models and a Translational Non-human Primate Model

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Poster
2872-LB

Abstract

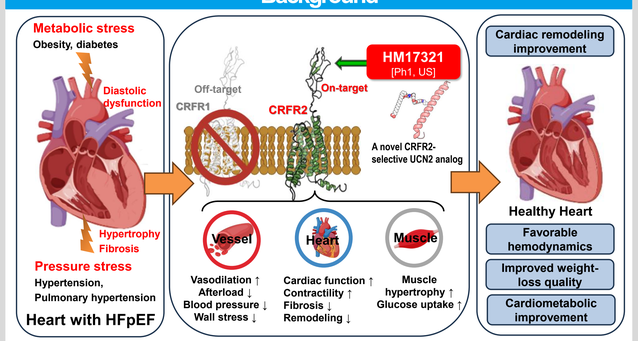
Introduction and Objective: Heart failure (HF) is a major global cause of mortality, and its prevalence is increasing with rising obesity rates, particularly in HFpEF. Urocortin-2 (UCN2) exerts beneficial cardiovascular effects, including vasodilation and improved cardiac function in HF. HM17321 is a CRFR2-selective UCN2 analog currently in phase 1 clinical development as an anti-obesity therapy with improved weight loss quality (WLQ). This study evaluated the therapeutic potential of HM17321 in rodent HF models and a translational non-human primate model.

Methods: Cardioprotective effects of HM17321 were evaluated in three preclinical models, including an obesity and hypertension driven HFpEF mouse model (HFD/L-NAME), a monocrotaline (MCT)-induced HF rat model, and middle-aged obese rhesus monkeys. HM17321 was administered for 2 to 5 weeks in rodents and for 13 weeks in non-human primates. Cardiac structure and function (echocardiography) and exercise capacity were assessed.

Results: In HFpEF mice, HM17321 significantly reduced left ventricular (LV) hypertrophy with decreased LV mass and wall thickness compared to vehicle (LV mass: 132.2 mg vs. 177.6 mg; wall thickness: 0.88 mm vs. 1.05 mm). HM17321 also decreased MV E/E′ ratio and shortened IVRT compared to vehicle, suggesting improved diastolic function (MV E/E′ ratio: 22.8 vs. 28.7; IVRT: 16.2 ms vs. 20.5 ms). In MCT-induced HF rat model, HM17321 markedly improved exercise capacity, arterial oxygen saturation, and myocardial fibrosis. In obese rhesus monkeys, HM17321 significantly reduced systolic and diastolic blood pressure (114/54 mmHg vs. 140/69 mmHg, vehicle) without increasing heart rate.

Conclusion: HM17321 improved cardiac function and attenuated pathological cardiac remodeling in rodent HF models and a non-human primate model. These findings suggest that HM17321, developed as an anti-obesity therapy for improved WLQ, may also represent a novel therapeutic option for HF, supported by cardiovascular effects observed in primates.

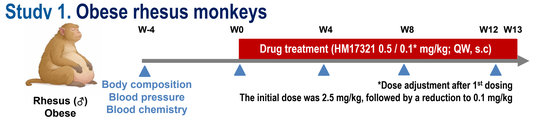
Background



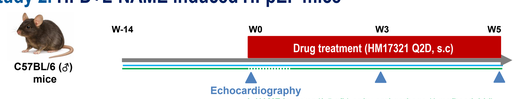
- HM17321, a novel long-acting CRFR2-selective UCN2 analog, is designed to selectively reduce fat while increasing muscle mass. It also provides favorable hemodynamic and cardioprotective benefits across multiple heart failure models.

Methods

Study 1. Obese rhesus monkeys



Study 2. HFD+L-NAME induced HFpEF mice

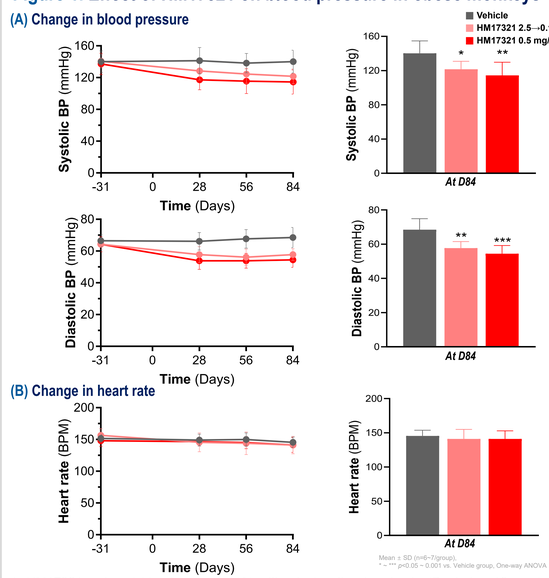


Study 3. MCT-induced HF rats

- *Study 1*: Obese rhesus monkeys (10–18 years, mean BW 18.0 kg, BMI 49.3 kg/m², n=6–7/group) were studied at Primed. Animals received once-weekly subcutaneous injections of HM17321 for 13 weeks. Body weight was measured weekly, while body composition, blood pressure, and heart rate were assessed at 4-week intervals.
- *Study 2*: 'Two-hit' mouse model of HFpEF was induced by HFD feeding and L-NAME supplementation in drinking water for 14 weeks. HM17321 was administrated for 5 weeks after model induction.
- *Study 3*: PAH-induced HF rat model was established by a single subcutaneous injection of MCT on Day 0. HM17321 was administered during last 2 weeks.

Hemodynamic benefits in obese monkey

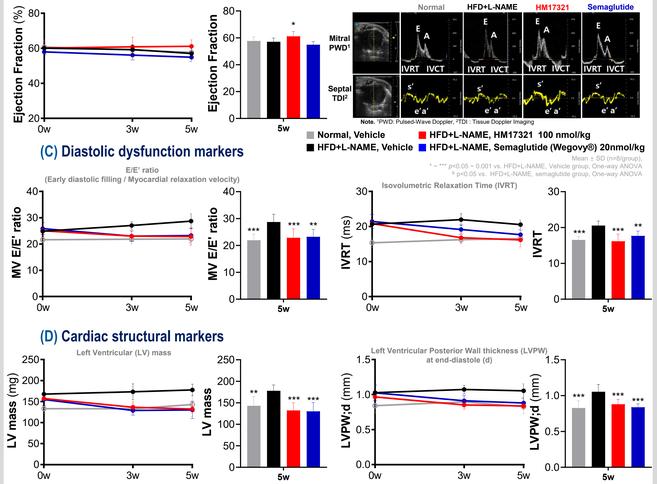
Figure 1. Effect of HM17321 on blood pressure in obese monkeys



➢ HM17321 reduced blood pressure (A) without elevating heart rate (B) during 13 weeks of treatment in obese monkeys

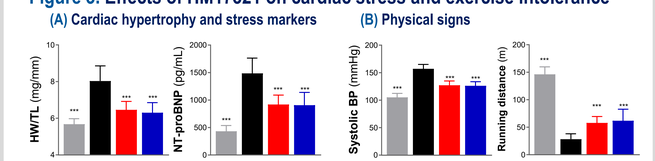
Efficacy in HFD+L-NAME induced HFpEF mice

Figure 2. Effects of HM17321 on echocardiography



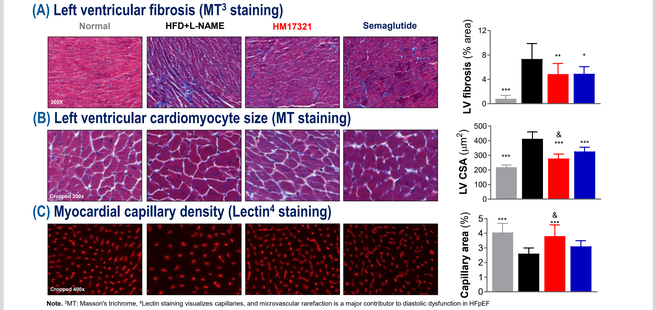
➢ In HFD+L-NAME induced HFpEF mice, HM17321 markedly increased ejection fraction at week 5 (A) and improved diastolic dysfunction (B, C) and cardiac structural remodeling (D).

Figure 3. Effects of HM17321 on cardiac stress and exercise intolerance



➢ HM17321 significantly improved cardiac hypertrophy, stress markers (A), and physical signs (B).

Figure 4. Effects of HM17321 on cardiac remodeling in HFpEF mice

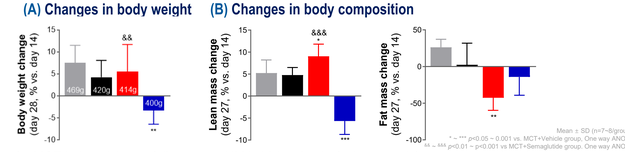


Note. ³MT: Masson's trichrome, ⁴Lectin staining visualizes capillaries, and microvascular rarefaction is a major contributor to diastolic dysfunction in HFpEF

➢HM17321 significantly reduced LV fibrosis (A), cardiac hypertrophy (B), and myocardial capillary rarefaction (C) in HFpEF mice, with significantly greater improvements in cardiac hypertrophy and capillary rarefaction versus semaglutide.

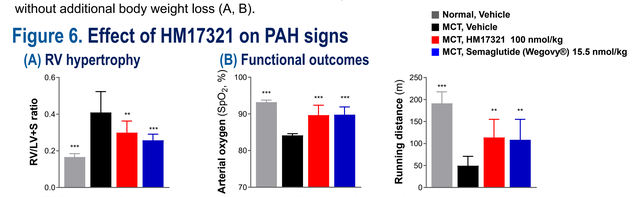
Efficacy in MCT induced heart failure rats

Figure 5. Effect of HM17321 on body weight and body composition



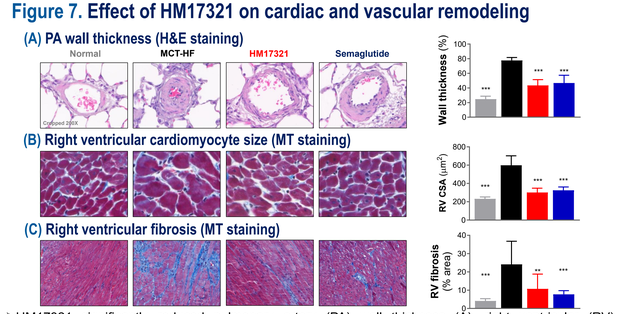
➢In MCT-induced heart failure rats, HM17321 selectively increased lean mass and reduced fat mass without additional body weight loss (A, B).

Figure 6. Effect of HM17321 on PAH signs



➢HM17321 efficiently reduced right ventricular (RV) hypertrophy (A) represented by weight ratio, and improved physical signs (B) in MCT-HF rats.

Figure 7. Effect of HM17321 on cardiac and vascular remodeling



➢HM17321 significantly reduced pulmonary artery (PA) wall thickness (A), right ventricular (RV) hypertrophy (B), and fibrosis (C) in MCT-HF rats

Concluding Remarks

- In obese non-human primates, HM17321 reduced blood pressure without increasing heart rate, supporting favorable hemodynamic properties.
- HM17321 improved diastolic dysfunction and cardiac remodeling, while modestly increasing ejection fraction in HFpEF mice.
- HM17321 improved heart failure phenotypes independent of additional body weight loss in MCT-induced HF rats, suggesting direct cardioprotective efficacy.
- Together, these findings highlight the potential of HM17321 as a distinct cardiometabolic therapeutic, broadly applicable across obesity and heart failure indications.
- Please also note Hanmi's additional presentations on our pipeline:
  HM17321, a UCN2 analog (1783-P, 1803-P, 2537-P, 2538-P, 2579-P, 3078-LB)
  HM500197, a peptide-based MSTN inhibitor (3073-LB)

References

1. Adão R et al. *Drug Discov Today. 2015* 20(7):906-14
2. Rademaker MT et al. *Hypertension.* 2011 57(6):1136-1144.