Therapeutic Potential of HM15275, a Novel Long-Acting GLP-1/GIP/GCG Triple Agonist, in Animal Models of Heart Failure

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ABSTRACT

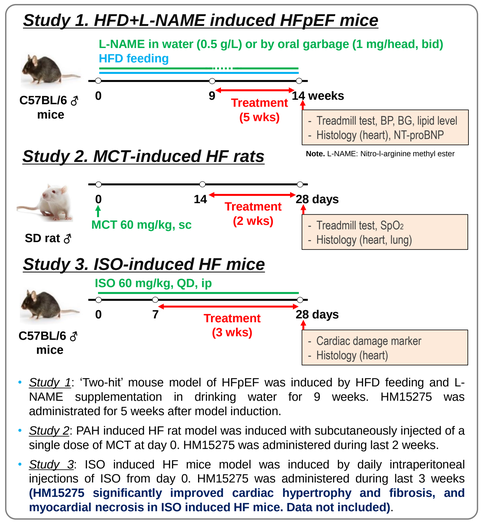
Introduction & Objective: Obesity significantly increases the risk of cardiovascular death and is a leading cause of heart failure with preserved ejection fraction (HFpEF). Considering these outcomes, the purpose of this study is to evaluate whether HM15275, a novel long-acting GLP-1/GIP/GCG triple agonist, could alleviate heart failure (HF)-related symptoms in various animal models of HF.

Methods: To investigate therapeutic effects of HM15275 in HF animal models, we used a high fat diet (HFD) + nitro-l-arginine methyl ester (L-NAME) mouse model of HFpEF, induced by obesity and hypertension. Second, we used the monocrotaline (MCT)-induced HF rat model to induce HF caused by pulmonary arterial hypertension (PAH). Finally, isoproterenol (ISO)-induced HF mouse model was used to induce HF with cardiac dilation and ventricular dysfunction. HM15275 was administrated for 2 to 5 weeks after model induction. Semaglutide (Sema) and tirzepatide (TZP) were used as comparative control.

Results: In three HF animal models, HM15275 significantly improved cardiac hypertrophy compared to other incretin drugs, Sema and TZP. Interestingly, HM15275 significantly improved exercise capacity and arterial oxygen saturation and reduced myocardial fibrosis and cardiomyocytes size compared to Sema and TZP in MCT-induced HF rat model. Also, in HFD + L-NAME mouse model, HM15275 remarkably changed multiple biomarkers of cardiovascular risk, including body weight, blood glucose, levels of lipids, and physical limitations.

Conclusion: HM15275 significantly improved exercise intolerance, cardiac hypertrophy, and fibrosis in HF murine models, compared to Sema and TZP, supporting that it could be a novel therapeutic option for HF patients.

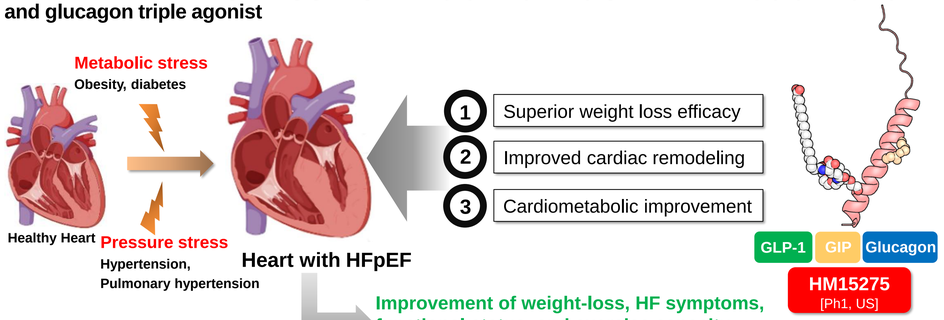
METHODS



- *Study 1*: 'Two-hit' mouse model of HFpEF was induced by HFD feeding and L-NAME supplementation in drinking water for 9 weeks. HM15275 was administrated for 5 weeks after model induction.
- *Study 2*: PAH induced HF rat model was induced with subcutaneously injected of a single dose of MCT at day 0. HM15275 was administered during last 2 weeks.
- *Study 3*: ISO induced HF mice model was induced by daily intraperitoneal injections of ISO from day 0. HM15275 was administered during last 3 weeks **(HM15275 significantly improved cardiac hypertrophy and fibrosis, and myocardial necrosis in ISO induced HF mice. Data not included)**.

BACKGROUND

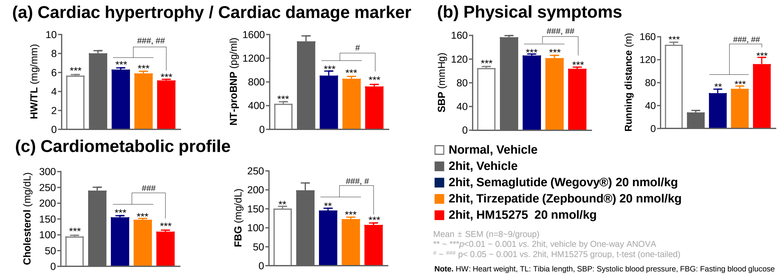
HM15275 is a novel long-acting glucagon-like peptide (GLP-1), gastric inhibitory peptide (GIP) and glucagon triple agonist



RESULTS

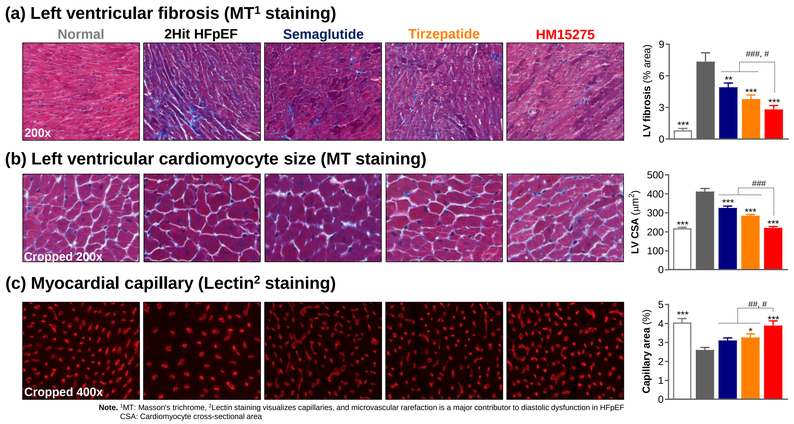
Efficacy in HFD+L-NAME induced HFpEF mice

Figure 1. Effects of HM15275 on key feature of heart failure



➢ HM15275 significantly improved cardiac hypertrophy and cardiac damage marker (a), physical symptoms (b), and cardiometabolic profiles (c) more effectively than Sema and TZP in HFpEF mice.

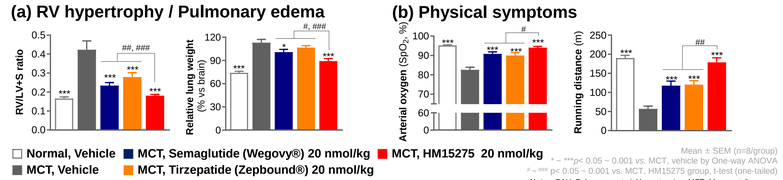
Figure 2. Effect of HM15275 on cardiac remodeling in HFpEF mice



➢ HM15275 treatment significantly leads to histological improvement of left ventricular (LV) fibrosis (a), hypertrophy (b), and myocardial capillary rarefaction (c) compared to Sema and TZP in HFpEF mice.

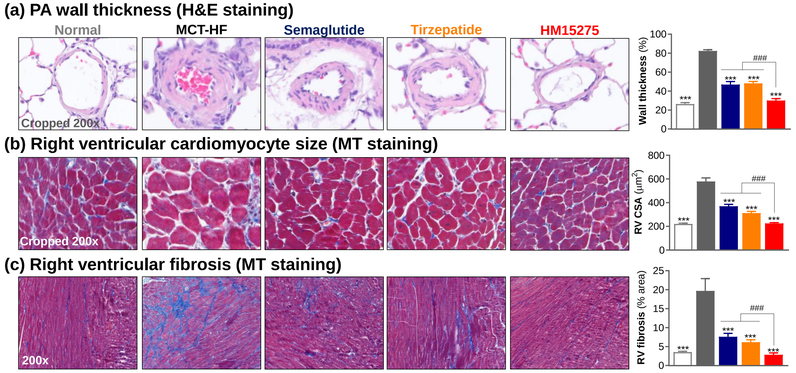
Efficacy in MCT induced heart failure rats

Figure 3. Effect of HM15275 on PAH symptoms



➢ HM15275 markedly reduced right ventricular (RV) hypertrophy and pulmonary edema (a) represented by weight ratio, and improved physical symptoms (b) more effectively than Sema and TZP in MCT-HF rats.

Figure 4. Effect of HM15275 on cardiac and vascular remodeling in MCT-HF rats



➢ HM15275 significantly improved pulmonary artery (PA) wall thickness (a), right ventricular (RV) hypertrophy (b), and fibrosis (c), compared to Sema and TZP in MCT-HF rats

CONCLUSIONS

- **HM15275, a novel long-acting GLP-1/GIP/GCG triple agonist, significantly ameliorated heart failure-related symptoms by regulating cardiac remodeling, blood pressure, body weight, and cardiometabolic profile in HFpEF mice compared to Sema and TZP**
- **The benefits of HM15275 in MCT induced HF rats highlight its potential to enhance heart failure treatment through pulmonary vascular remodeling**
- **In addition to the superior weight loss efficacy (please visit 776-P), renal and cardioprotective effect (please visit 798-P, 799-P) of HM15275 were shown**

American Diabetes Association's (ADA) 84th Scientific Sessions, Orlando, FL; June 21-24, 2024

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