A Novel UCN2 Analog HM17321 With HM15275 Improves Body Composition In Mouse Model Of Obesity

Hyunjoo Kwon*, Jeong A Kim, Seon Myeong Lee, Jung Kuk Kim, Sang Hyun Lee and In Young Choi
Hanmi Pharmaceutical Co., Ltd., Seoul, Republic of Korea

Hanmi

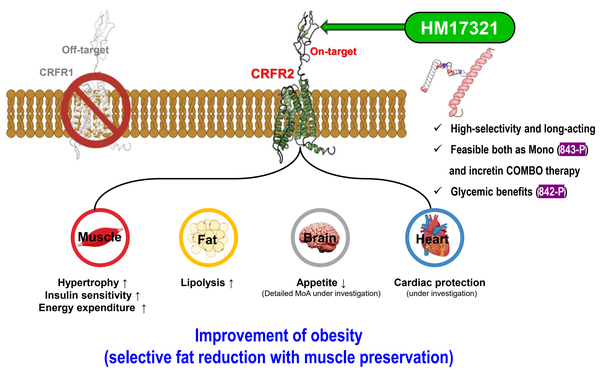
Poster
886-P

Introduction

Introduction and Objective: Incretin drugs have shown remarkable efficacy in body weight reduction and metabolic improvements. However, concerns remain regarding lean mass loss and long-term outcomes. Urocortin-2 (UCN2) is a corticotropin-releasing factor receptor2 (CRFR2) agonist and has been known to regulate glucose metabolism, insulin sensitivity and skeletal muscle hypertrophy. In current study, we explore the anti-obesity effects of HM17321, a novel CRFR2 selective UCN2 analog, in combination with HM15275 (a GLP-1/GIP/Glucagon triple agonist) or semaglutide (a GLP-1 agonist) in DIO mice.
Methods: DIO mice were treated with vehicle, HM17321 or HM15275 for 3 weeks, followed by HM17321 switching or add-on in HM15275-treated mice for an additional 3 weeks. In a second study, DIO mice were subcutaneously treated with vehicle, HM17321, semaglutide or the combination for 4 weeks. Body weight and body composition were assessed throughout the study.
Results: HM17321 significantly reduced body weight and fat mass while simultaneously increasing lean mass in DIO mice. Switching from HM15275 to HM17321 maintained body weight and fat loss while preserving lean mass. Add-on of HM17321 further reduced fat mass without additional lean mass loss. Notably, HM17321-treated and switching groups showed skeletal muscle hypertrophy as confirmed by fiber type-specific CSA analysis of TA and soleus. Serum metabolic parameters were significantly improved in all treatment groups. Similar results were observed with the combination of HM17321 and semaglutide.
Conclusion: HM17321 and its combination with HM15275 or semaglutide leads to favorable body composition during weight loss and improved metabolic parameters in DIO mice, supporting its potential as a monotherapy and in combination with incretin drugs for obesity.

Background

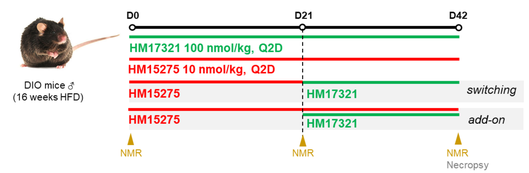
HM17321, a novel long-acting CRFR2 selective and biased UCN2 analog, is optimally designed to selectively reduce fat while simultaneously increasing muscle mass during weight loss, maximizing weight loss quality (WLQ) and metabolic improvement.



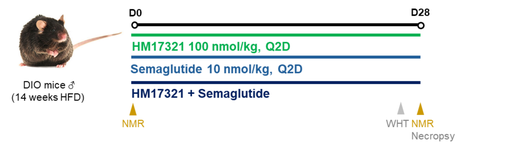
Improvement of obesity
(selective fat reduction with muscle preservation)

Study Design

Study 1. Combination efficacy of HM17321 and HM15275 (switching or add-on strategy)

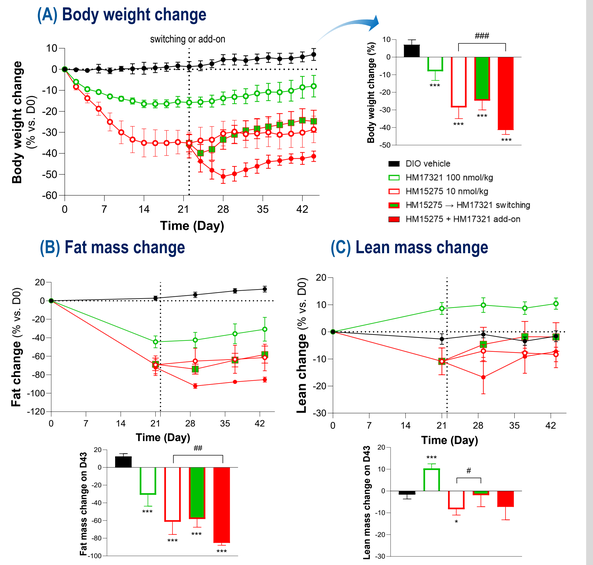


Study 2. Combination efficacy of HM17321 and semaglutide



Superior weight loss & favorable body composition

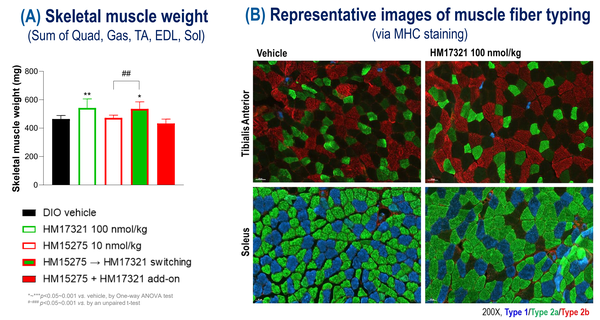
Figure 1. Efficacy of HM17321 switching or add-on strategy in HM15275 (a GLP-1/GIP/GCG triple agonist)-treated DIO mice



➢ Switching or add-on of HM17321 after 3 weeks of HM15275 treatment resulted in significant body weight and fat mass loss while preserving lean mass loss.

Skeletal muscle hypertrophy & fiber type composition

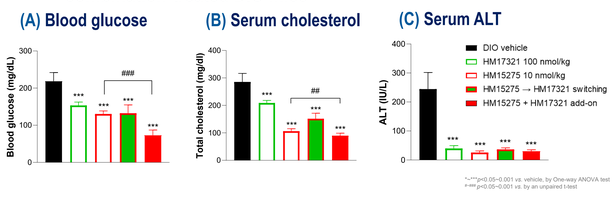
Figure 2. Evaluation of skeletal muscle hypertrophy and fiber type composition in HM17321/HM15275 combination-treated DIO mice



➢ HM17321 induced skeletal muscle hypertrophy as confirmed by increased skeletal muscle weight and cross-sectional area (CSA). Specifically, the average CSA of all muscle fibers (type I, IIa and IIb) were increased in HM17321-treated and switching groups.

Metabolic benefits

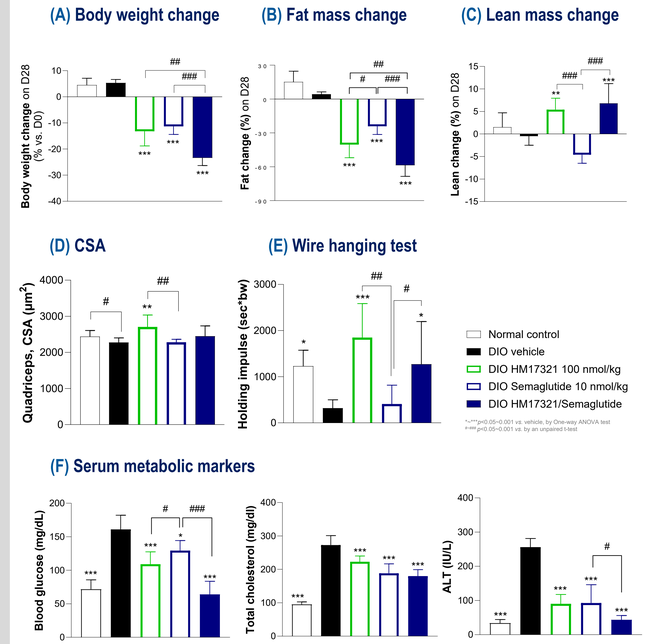
Figure 3. Improved serum metabolic parameters in HM17321/HM15275 combination-treated DIO mice



➢ Switching or add-on of HM17321 after 3 weeks of HM15275 treatment lowered fasting glucose, total cholesterol and ALT, suggesting improved metabolic parameters.

Combination efficacy of HM17321 with semaglutide

Figure 4. Efficacy of HM17321 and semaglutide combo in DIO mice



➢ HM17321/semaglutide combination resulted in additional body weight and fat loss, while increasing lean mass compared to semaglutide alone. HM17321/semaglutide combination restored cross-sectional area (CSA) and muscle endurance to levels of normal control. Moreover, the levels of blood glucose and ALT were synergistically decreased by HM17321/semaglutide treatment.

Concluding Remarks

- Switching from HM15275 to HM17321 treatment maintained fat mass loss while increasing lean mass compared to HM15275 monotherapy. Skeletal muscle weight and cross-sectional area (CSA) of all muscle fibers were significantly increased in HM17321 switching group comparable to those of HM17321-treated group.
- HM17321 add-on to HM15275 treatment led to further reductions in body weight and fat mass without additional lean mass loss. Moreover, synergistic improvement of blood glucose levels was observed in HM17321 add-on group.
- HM17321 significantly improved the efficacy of semaglutide as evidenced by greater weight and fat mass loss simultaneously increasing lean mass, suggesting HM17321 as an ideal combination partner for incretin-based therapy.
- Please note additional posters presenting Hanmi's pipeline, HM17321 (Poster, 843-P) and HM15275 (755-P, 774-P: Preclinical; 1980-LB: Phase 1 clinical).