Mechanistic Insights into the Potent Anti-Obesity Effects of HM15275, a Novel Long-Acting GLP-1/GIP/Glucagon Triple Agonist

Yohan Kim, Seon Myeong Lee, Dahae Lee, Eunjin Park, Jeong A. Kim, SungHee Hong, Sungmin Bae, Sang Hyun Lee, In Young Choi
Hanmi Pharmaceutical Co., Ltd., Seoul, Republic of Korea

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Introduction

Background and aims: Obesity is increasingly recognized as a global health crisis due to its association with various metabolic diseases, emphasizing the urgent need for effective treatment. To address this, HM15275, a long-acting GLP-1/GIP/GCG triple agonist, was developed and has demonstrated significant body weight loss (BWL) and improved glycemic control in preclinical studies. This study aimed to further evaluate the anti-obesity effects of HM15275 in comparison with other incretin drugs and to explore its mechanisms of action (MoA) in mouse models of obesity.

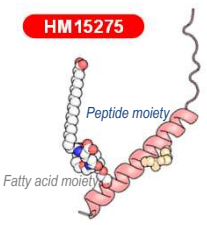
Materials and methods: The effects of HM15275 on BWL and body composition were evaluated in DIO mice, including a switching study for SEMA or TZP to HM15275. GLP-1R KO mice were utilized for target engagement study. To understand a underlying mechanism for its potent BWL, pair-fed and energy expenditure studies were conducted, and histologic analysis was followed in mesenteric white adipose tissue (mWAT). Semaglutide (SEMA), tirzepatide (TZP), and/or in-house synthesized retatrutide (RETA) served as comparative controls.

Results: In DIO mice, a 3-week treatment with HM15275 resulted in greater BWL (-39.9% vs. baseline) compared to SEMA (-14.9%) and TZP (-25.3%). Importantly, despite a greater reduction in fat mass, HM15275 led to less lean mass loss than TZP, suggesting improved weight loss quality. Potent BWL effect of HM15275 was further demonstrated when switching from SEMA or TZP. Notably, in GLP-1R KO mice, HM15275 still induced significantly greater BWL (-24.5% vs. baseline) than SEMA (no reduction) and TZP (-4.2%) along with improved ipGTT profile, suggesting an optimized GIP and glucagon engagement of HM15275 for both BWL and favorable glycemic control. Pair-fed and energy expenditure studies revealed that in addition to food intake regulation, enhanced energy expenditure contributed to potent BWL by HM15275. Consistently, the expression of PGC-1α and UCP-1 in mWAT was significantly increased by HM15275 treatment compared to vehicle or TZP. Furthermore, a 6-week treatment with HM15275 resulted in significantly greater BWL and fat mass loss compared to RETA with no difference in lean mass, highlighting its improved weight loss potency and quality.

Conclusion: In DIO mice, HM15275 demonstrated BWL primarily driven by fat mass reduction, with greater effects than other incretin drugs. In addition, comprehensive MoA studies elucidated the underlying mechanism for its potent BWL. These findings highlight the potential of HM15275 to enable both quantitatively and qualitatively improved obesity management. The clinical translation of these results will be further explored in planned phase 2 studies.

Background

HM15275 is a novel long-acting GLP-1/GIP/Glucagon triple agonist conjugated with fatty acid moiety, optimally designed for treatment of obesity and relative complications.



- Designed and optimized to maximize body weight reduction (activity balance)
- The extended half-life is sufficient for weekly dosing
- Additional CVRM benefits expected by proper utilization of glucagon
- P1 study in United States completed

GLP-1 GIP
- Weight loss by appetite regulation
- Indirect effects from BW loss and BG control for CVRM benefits

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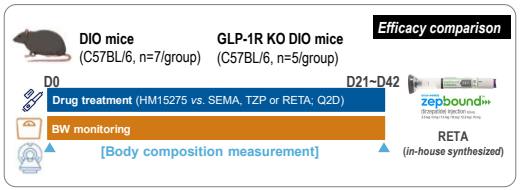
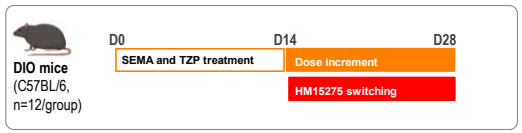
Glucagon
- Weight loss by energy expenditure
- Direct tissue effect for CVRM benefits

Experimental methods

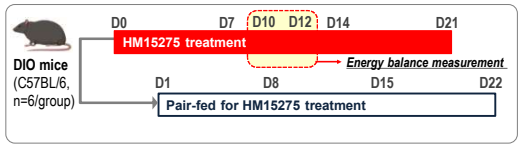
(a) Body weight efficacy study design



(b) Switching study design



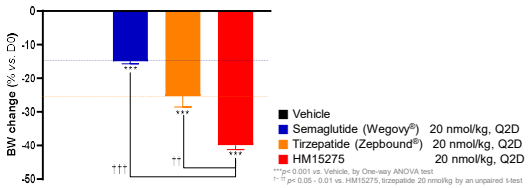
(c) Energy expenditure (EE) study design



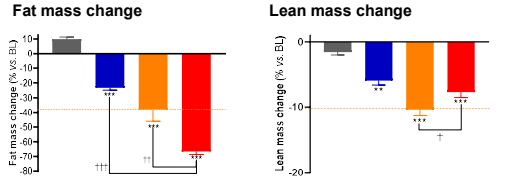
Superior weight loss and quality in DIO mice

Figure 1. Changes in body weight and body composition in DIO mice

(a) Changes in BW (D21)



(b) Changes in body composition

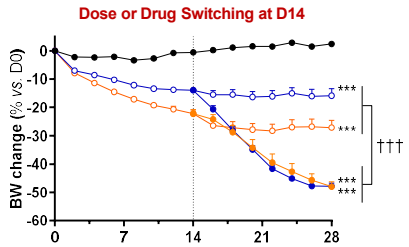


➢In DIO mice, HM15275 mainly attributed to more fat mass reduction and notably, despite greater body weight loss than SEMA and TZP, more favorable weight loss quality (WLQ) was demonstrated by HM15275.

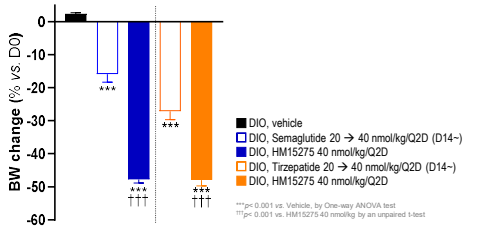
Switching promoted additional weight loss benefits

Figure 2. Changes in body weight after switching in DIO mice

(a) Changes in BW over time



(b) Changes in BW (D28)

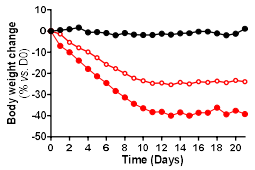


➢In DIO mice, additional weight loss was observed when SEMA or TZP treatment was switched to HM15275 at D14, while dose escalation of SEMA or TZP only showed marginal additive effects.

Mode of action – Energy expenditure

Figure 3. Mechanism evaluation for body weight reduction by pair-fed DIO mice

(a) Changes in BW over time



(b) Energy expenditure over time (D10-12)

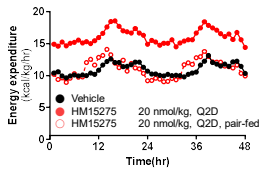
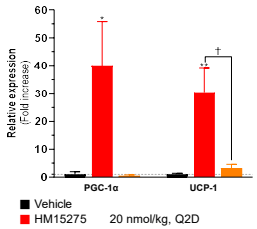
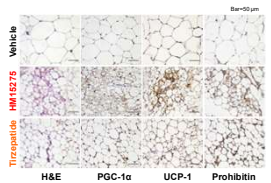


Figure 4. Immunohistochemistry and gene expression for energy expenditure

(a) Marker gene expression levels



(b) Immunohistochemistry

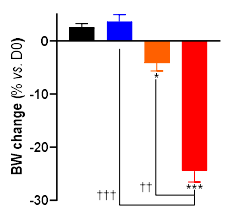


➢Both FI inhibition-dependent and -independent mechanisms of weight loss were demonstrated for HM15275, with the latter attributed to enhanced energy expenditure associated with GCG engagement.

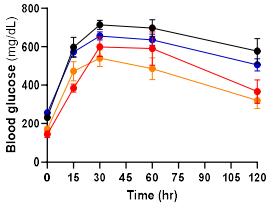
Target engagement in GLP-1R KO DIO mice

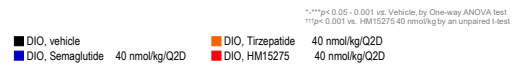
Figure 5. Changes in body weight and blood glucose by ipGTT

(a) Changes in BW (D28)



(b) BG level in ipGTT (D28)



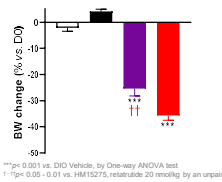


➢In GLP-1R KO DIO mice, GCG engagement of HM15275 was reaffirmed as critical for potent weight loss, while favorable BG control highlighted its optimized triple agonist profile.

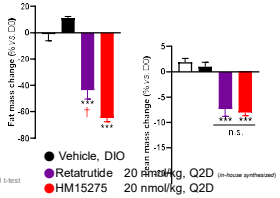
Long-term weight loss effect in DIO mice

Figure 6. Changes in body weight and body composition over time in DIO mice

(a) Changes in BW (D42)



(b) Changes in body composition



➢Notably, HM15275 achieved greater weight and fat loss than retatrutide, with similar lean mass change, highlighting its optimized triple agonism

Concluding Remarks

- A novel long-acting GLP-1/GIP/Glucagon triple agonist with fatty acid conjugation, designed for obesity and related complications.
- Induces potent body weight reduction compared with other incretin drugs, via appetite suppression and **especially glucagon-mediated energy expenditure** (adipose browning).
- **Critical role of glucagon in potent body weight reduction reaffirmed in GLP-1R knockout models, with a favorable glucose profile.**
- Superior efficacy compared with retatrutide in reducing body weight and fat mass, with similar lean mass, **highlighting its optimized triple agonist profile.**
- **Human relevance to be evaluated in Phase 2 clinical study initiating 4Q 2025 (US).**
- **Please note Hanmi's additional obesity & metabolism related presentations:**
  HM17321 (long-acting UCN2 analog) – 669, 730, 819 (Short oral), 226 (Oral)
  Oral GLP1 receptor agonist – LBA 47 (Short oral)