Potent Weight Loss Effect and Mechanism of a Novel Long-acting GLP-1/GIP/GCG Triple Agonist, HM15275, in Animal Model of Obesity

Poster-335

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ABSTRACT

Introduction & Objective: Obesity is a major public health concern linked to numerous metabolic diseases, including T2DM and CVD. In previous nonclinical studies, HM15275, a novel long-acting GLP-1/GIP/Glucagon triple agonist, showed optimized activity balance for potent weight loss and glycemic control. The present studies further investigate to (1) confirm the beneficial effect of HM15275 on body weight and metabolic parameters, and (2) elucidate the underlying mechanism.

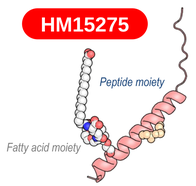
Method: Potential effects of HM15275 on body weight, body composition and lipid profile were evaluated in DIO mice. To reveal the weight loss mechanism by HM15275, pair-fed and energy balance studies were conducted, and mesenteric white adipose tissue (mWAT) was subjected to immunohistochemistry. Tirzepatide (TZP) was used as a comparative control.

Results: In DIO mice, 3 weeks of HM15275 treatment led to greater weight loss (-39.9% vs. D0) than TZP (-25.3% vs. D0), and similar benefits were also observed in lipid profile. Notably, despite of more fat mass reduction, less lean mass change was observed for HM15275 (vs. TZP), suggesting improved weight loss quality. As to the underlying mechanism, pair-fed study indicated food intake inhibition-dependent and -independent weight loss mechanism by HM15275, latter of which was mediated by enhanced energy expenditure. Furthermore, expression of PGC-1α and UCP-1 were increased in mWAT and these effects were even greater than TZP, suggesting more potent fat browning effect of HM15275. In line with this, TZP to HM15275 switching showed an additional weight loss compared to TZP maintenance.

Conclusion: In DIO mice, more therapeutic benefits of HM15275 were well corroborated than TZP. Importantly, compared to TZP (GLP-1/GIP), HM15275 (GLP-1/GIP/GCG) could induce more fat browning, which clearly explains how HM15275 substantially enhances energy expenditure and thus highlights the essential role of GCG engagement. A Phase 1 clinical study is ongoing to assess the clinical relevance of these findings.

BACKGROUND

HM15275 is a novel long-acting GLP-1/GIP/GCG 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
- On-going for P1 study in United States

GLP-1 **GIP**

➢Weight loss by appetite regulation
➢Indirect effects from BW loss and BG control for CVRM benefits

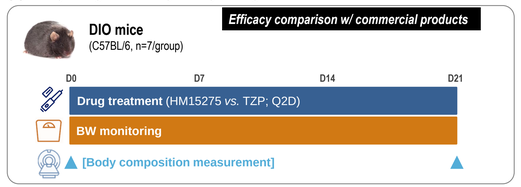
+

Glucagon

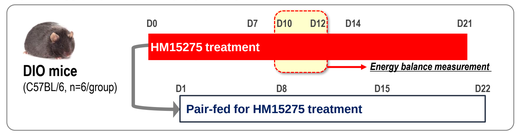
➢Weight loss by energy expenditure
➢Direct tissue effect for CVRM benefits

METHODS

(a) Body weight efficacy study design



(b) Energy expenditure (EE) study design



(c) Switching study design

RESULTS

Body weight loss effect & quality in DIO mice

Figure 1. Changes in body weight over time in DIO mice

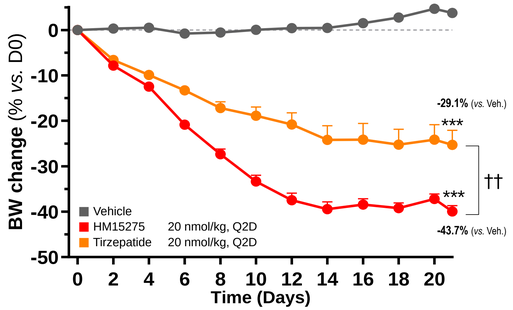


Figure 2. Changes in body composition at the end of treatment

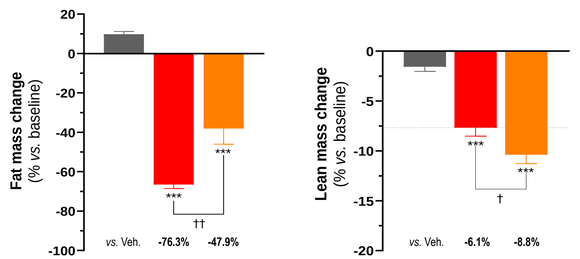
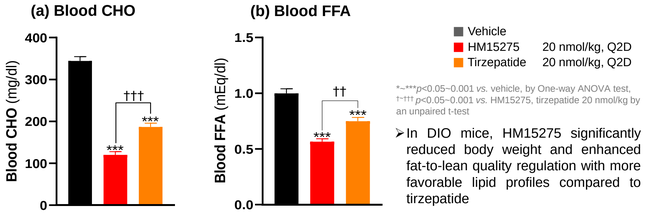


Figure 3. Lipid profiles at the end of treatment

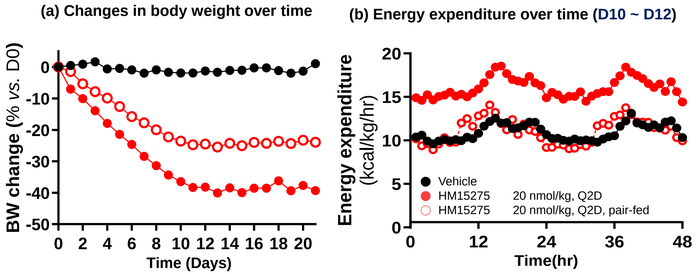


*~***p<0.05~0.001 vs. vehicle, by One-way ANOVA test, †~†††p<0.05~0.001 vs. HM15275, tirzepatide 20 nmol/kg by an unpaired t-test

➢In DIO mice, HM15275 significantly reduced body weight and enhanced fat-to-lean quality regulation with more favorable lipid profiles compared to tirzepatide

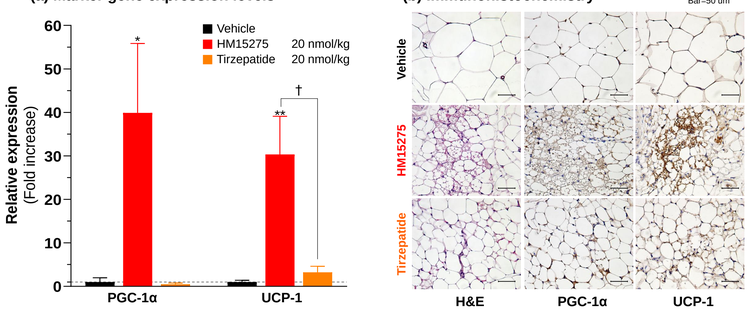
Mode of action – Energy expenditure

Figure 4. Mechanism evaluation for BW reduction by pair-fed DIO mice



➢In DIO mice, HM15275 exhibited food intake inhibition-dependent and -independent BW loss. The latter case resulted from increase in energy expenditure, demonstrating the essential role of glucagon engagement

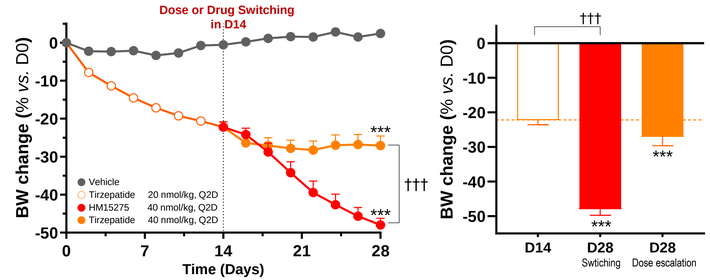
Figure 5. Immunohistochemistry and gene expression for energy expenditure



➢ In DIO mice, HM15275 substantially reduced lipid droplet size of white adipose tissue. Additionally, PGC-1α and UCP-1 expression and tissue staining indicated that HM15275 could provide more potent fat browning effect than tirzepatide.

Additional body weight loss by switching

Figure 6. Changes in body weight over time under switching conditions



➢ Switching from TZP to 275 showed additional BW loss while TZP dose escalation only showed marginal additive effect.

CONCLUSIONS

- **HM15275, a novel long-acting triple agonist, is designed to treat obesity via optimized activity balance of GLP-1, GIP, and GCG**
- **In DIO mice, HM15275 showed greater BW loss and improved weight loss quality compared to GIP/GLP-1 co-agonist. Potent BW loss resulted from both food intake inhibition and energy expenditure enhancement.**
- **Notably, compared to TZP (GLP-1/GIP), HM15275 (GLP-1/GIP/GCG) induced more fat browning, highlighting the essential role of GCG engagement in favorable metabolic phenotype change**
- **Phase 1 study (SAD/MAD, US) is on-going for the clinical relevant of these findings**

***Please note additional posters presenting Hanmi's novel obesity pipeline for high quality obesity management (Poster-504) and its incretin COMBO (Poster-329)**