Potent Weight Loss and Favorable Glycemic Control Effects of a Novel Long-Acting GLP-1/GIP/GCG Triple Agonist, HM15275, in Animal Models

776-P

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ABSTRACT

Introduction & Objective: The prevalence of obesity is increasing worldwide, urging development of obesity drugs with better efficacies and weight loss qualities. HM15275 is a GLP-1/GIP/Glucagon triple agonist designed to have well-harmonized activities and long-acting property for maximized body weight reduction. To elaborate the effects, a series of studies were conducted to evaluate (1) proper target engagement, (2) pharmacokinetics, and (3) body weight loss effects in DIO mice.

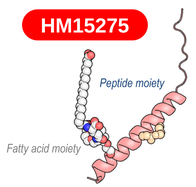
Method: Target receptor engagement of HM15275 was tested by cAMP assay with or without antagonist for each receptor. Plasma concentrations of HM15275 in rat and mouse were measured after a single subcutaneous dosing of HM15275. In DIO mice, body weight loss by HM15275 was compared with semaglutide and tirzepatide after 3 weeks treatment.

Results: Maximal *in vitro* activities of HM15275 significantly reduced in the presence of selective GLP-1, GIP, or Glucagon antagonist (hGLP-1R: 94.56% to 0.81%, hGIPR: 97.85% to 14.07%, hGlucagonR: 95.16% to 4.14%), indicating proper target engagement. In addition, protracted pharmacokinetic profiles were observed in rodent models, (half-life in mouse: 12 ~ 16 hr and rat: 17 ~ 19 hr). In DIO mice, HM15275 remarkably decreased body weight compared to semaglutide or tirzepatide at week 3 (-39.9%, -15.0%, and -25.3% *vs.* baseline). Furthermore, pair-fed study showed both food intake inhibition dependent and independent weight loss by HM15275. Energy balance evaluation revealed enhanced energy expenditure by HM15275. ipGTT results indicated favorable glycemic control of HM15275.

Conclusion: As a novel long-acting triple agonist, the molecular characteristics of HM15275 had been elucidated, demonstrating superior weight loss compared to currently available anti-obesity drugs. Therefore, HM15275 could be a valuable therapeutic option for weight control and human study is ongoing to assess clinical relevance of such 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
  *For more details, visit poster 798-P, 799-P, and 1872-LB
- On-going for P1 study in United States

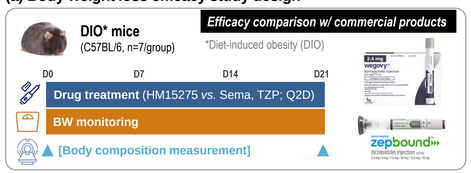
GLP-1 **GIP**
- Weight loss by appetite regulation
- Indirect effects from BW loss and BG control for CVRM benefits

+

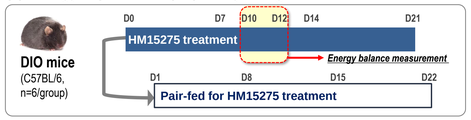
Glucagon
- Weight loss by energy expenditure
- Direct tissue effect for CVRM benefits

METHODS

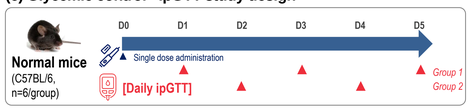
(a) Body weight loss efficacy study design



(b) Energy expenditure (EE) study design



(c) Glycemic control - ipGTT study design



In vitro & PK PROPERTIES

Table 1. *In vitro* characterization

Study	Models	Outcomes
Target receptor engagement (SPA)	^{125}I labelled native peptides with hGLP-1R, hGIPR, and hGCGR	Dose-dependent binding with all three receptors
Receptor-mediated activities (cAMP assay)	CHO cells stably expressing either hGLP-1R, hGIPR, or hGCGR	Full agonistic activities of GLP-1, GIP, and GCG
Long-acting evaluation (SPR)	Interaction with (1) purified serum albumin and (2) plasma from rodent and non-rodent	Dose-dependent binding with albumin and plasma protein binding

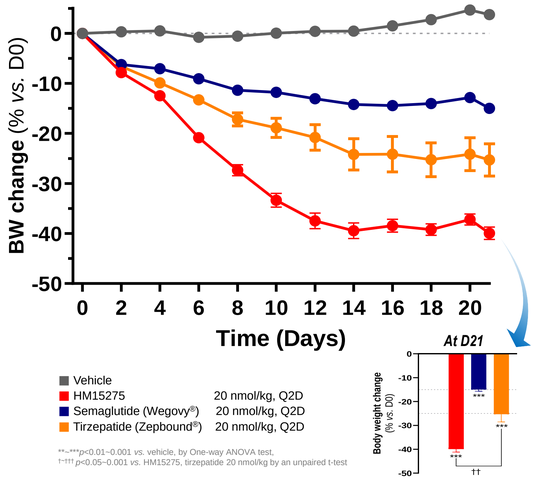
Table 2. Pharmacokinetics profiles

Species / Parameters	Mouse	Rat	Dog	Monkey
$t_{1/2}$ (h)	~16.3	~18.8	~91.9	~116.1

RESULTS

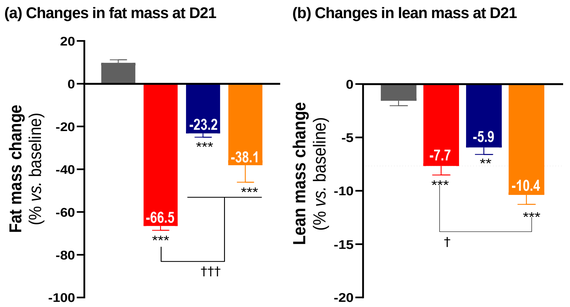
Superior weight loss effect & quality in DIO mice

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



**, ***p<0.01~0.001 *vs.* vehicle, by One-way ANOVA test,
†††p<0.05~0.001 *vs.* HM15275, tirzepatide 20 nmol/kg by an unpaired t-test

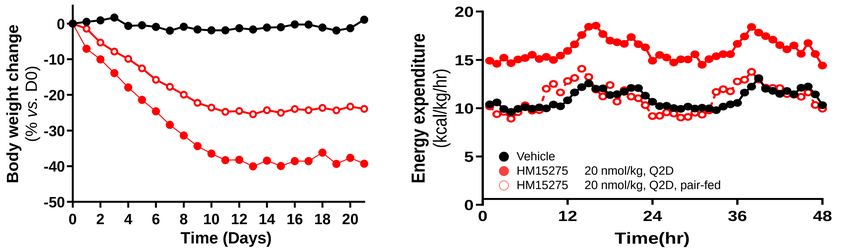
Figure 2. Changes in body composition at the end of treatment



➢In DIO mice, HM15275 significantly reduced body weight and enhanced fat-to-lean quality regulation with more therapeutic benefits compared to other incretin-based obesity drugs

Mode of action – Energy expenditure

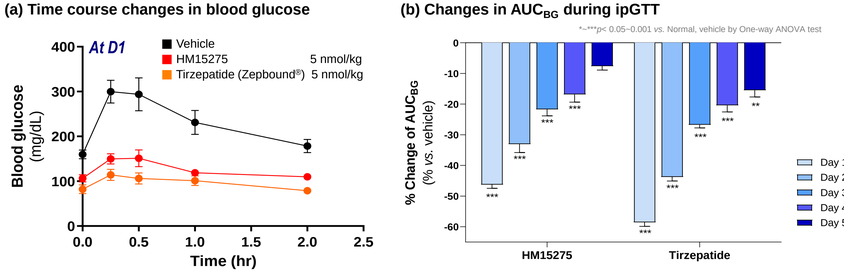
Figure 3. Mechanism evaluation for body weight reduction by pair-fed DIO mice



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

Favorable glycemic control - ipGTT

Figure 4. Blood glucose tolerance assessment



➢ ipGTT results in normal mice indicated glucose tolerance improvement effect of HM15275 comparable to tirzepatide

CONCLUSIONS

- **HM15275, a novel long-acting triple agonist, is designed to treat obesity by regulating the optimal activities of GLP-1, GIP, and GCG receptors**
- ***In-vitro* and PK studies demonstrated the proper target engagement and long-acting property**
- **In DIO mice, HM15275 showed significant body weight reduction and superior effect and quality compared to other incretin-based drugs. The weight loss was attributed to both inhibited food intake and elevated energy expenditure**
- **Favorable glycemic control was observed in time dependent manner and comparable with other compared drugs. For CVD benefits of HM15275, please visit 798-P, 799-P and 1872-LB for details**
- **Phase 1 study is on-going for the clinical relevant of these findings**

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