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Potent weight loss mechanism of a novel long-acting glucagon analog, HM15136, in animal models of obesity

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Presenter Disclosure

Employee of Hanmi Pharm. Co., Ltd.

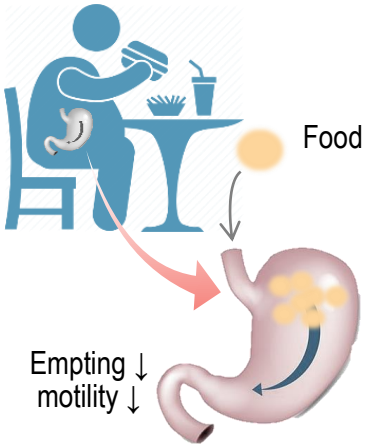
Background

HM15136 might have therapeutic potential on obesity management via various mode of actions (MoAs)

✓Expected benefits of HM15136 for obesity treatment

Food intake regulation

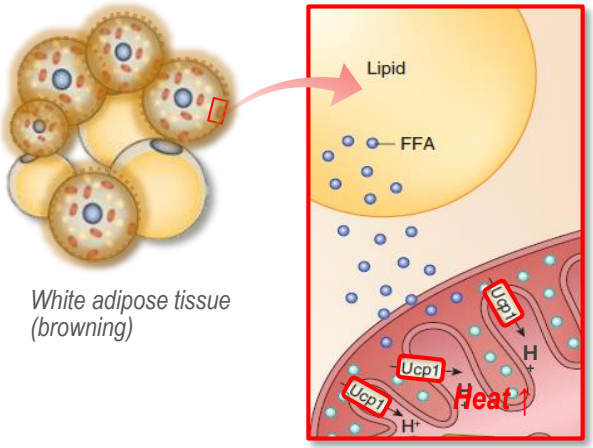
1) Food intake inhibition
(gastric emptying ↓, intestinal motility ↓)



Metabolic phenotype change

1) Browning
(Mitochondria biogenesis)

2) Energy expenditure
(Thermogenesis)

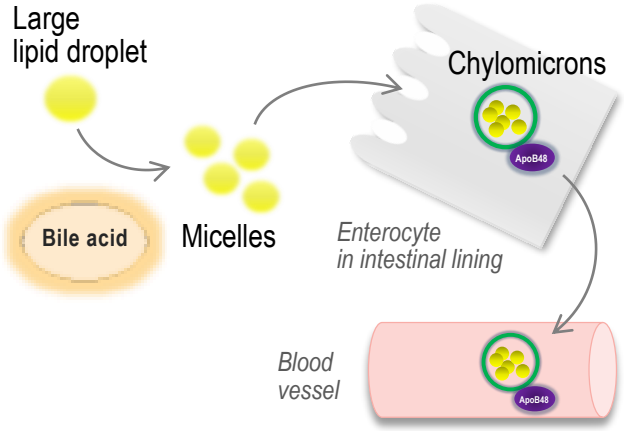


White adipose tissue (browning)

Lipid absorption inhibition

1) Lipid digestion
(Lipase or Bile acid ↓)

2) Lipid absorption
(ApoB48 ↓)



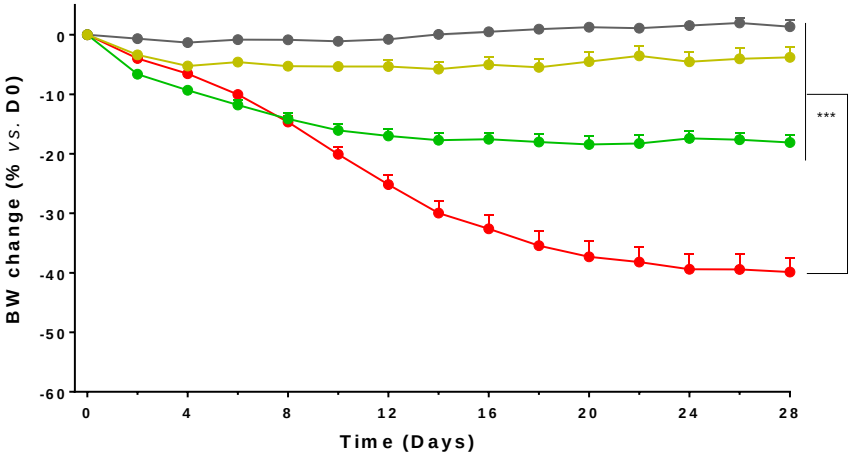
Method

- To compare the BWL efficacy between HM15136 and GLP-1RAs, either HM15136 or various GLP-1RAs (liraglutide, dulaglutide) was subcutaneously administered into diet-induced obesity (DIO) mice for 4 weeks.
- To assess the FI inhibition-independent BWL mechanism, BW change in DIO mice was compared with liraglutide under pair-fed controlled condition. At the end of treatment, blood lipid profiles and fat mass were determined. Then, the white adipose tissue (WAT) samples were subjected to immunohistochemistry to examine the thermogenic marker expression (PGC-1α and UCP-1) and adiposity, respectively
- To measure energy expenditure and respiratory exchange ratio (RER), each DIO mouse was subjected to indirect calorimetry, followed by VO_2 and VCO_2 monitoring
- To investigate the effect of HM15136 on lipid absorption, oral lipid tolerance test (oLTT) was performed after HM15136 3 weeks treatment in DIO mice. At the end of treatment, blood TG (at 0, 2, 4 hr after corn oil treatment), blood bile acid and ApoB48 level was analyzed.

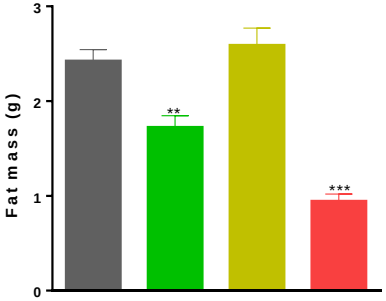
Figure 1. Efficacy comparison of HM15136 and GLP-1RAs in DIO mice

- HM15136 showed greater BWL, fat mass reduction, and blood CHO reduction than other GLP-1 receptor agonists, suggesting the therapeutic potential of HM15136 in obesity management

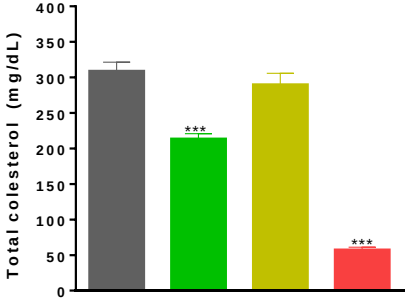
(a) BW change



(b) Fat mass



(c) Blood CHO



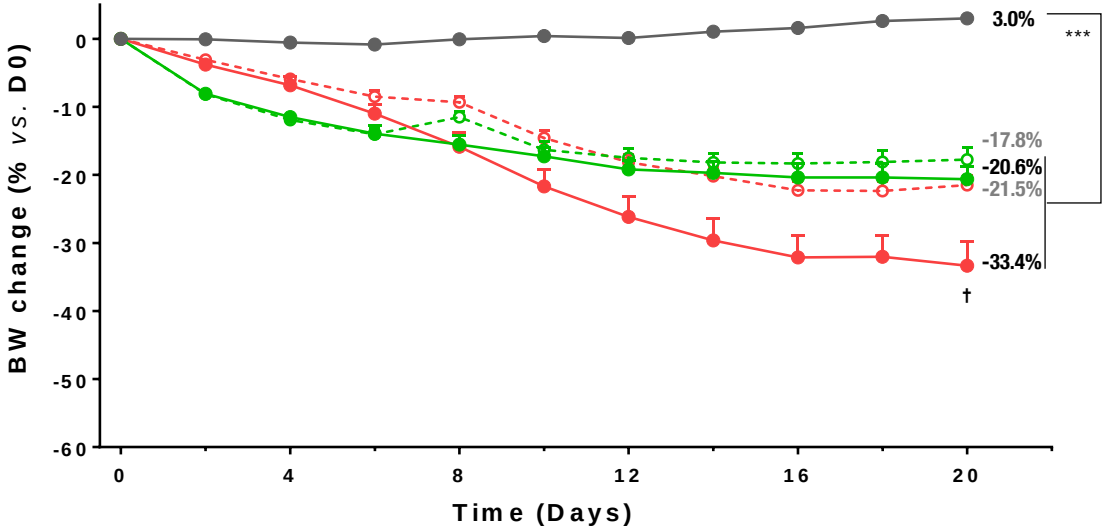
** ~ ***p<0.01 ~ 0.001 *vs.* DIO mice, vehicle by One-way ANOVA,

- Vehicle
- Liraglutide 50 nmol/kg, BID (3 mg/day in human)
- Dulaglutide 2.7 nmol/kg, Q2D (4.5 mg/week in human)
- HM15136 2 nmol/kg, Q2D (3 mg/week in human)

Figure 2. FI inhibition dependent and independent WL effect in DIO mice

- Unlike liraglutide, more body weight loss was observed even under pair-feeding conditions, indicating the appetite regulation-independent body weight loss by HM15136.

(a) BW change



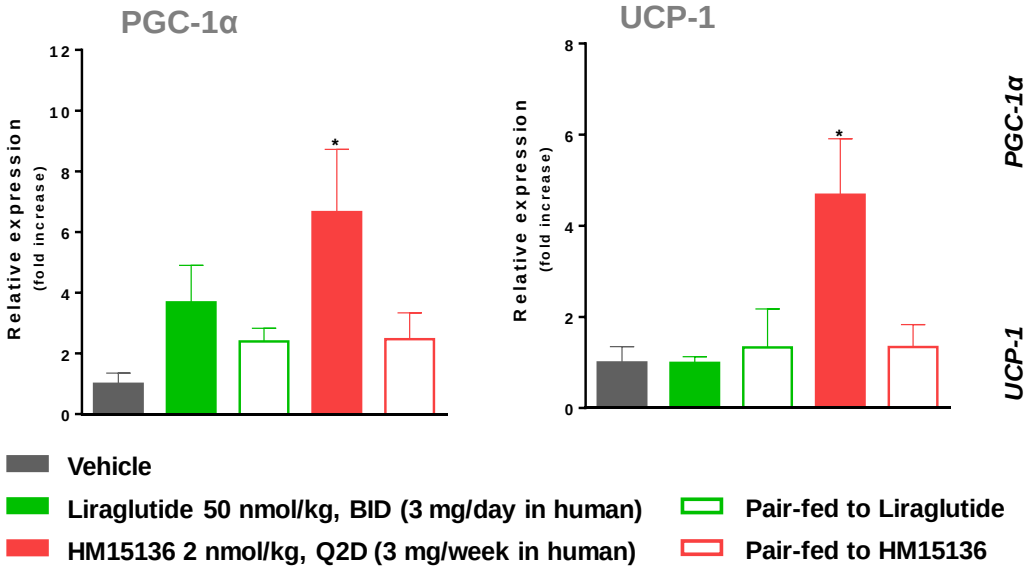
Vehicle
Liraglutide 50 nmol/kg, BID (3 mg/day in human)
HM15136 2 nmol/kg, Q2D (3 mg/week in human)
Pair-fed to Liraglutide
Pair-fed to HM15136

***p< 0.001 *vs.* DIO mice, vehicle by One-way ANOVA
† p<0.05 *vs.* each pair-fed group by t-test

Figure 2. FI inhibition dependent and independent WL effect in DIO mice

- Compared to liraglutide, HM15136 showed more increase in PGC-1α & UCP-1 expression in WAT, suggesting additional satiety-regulation independent BWL MoA

(b) PGC-1α and UCP-1 mRNA level in WAT



(c) Immunohistochemistry in WAT

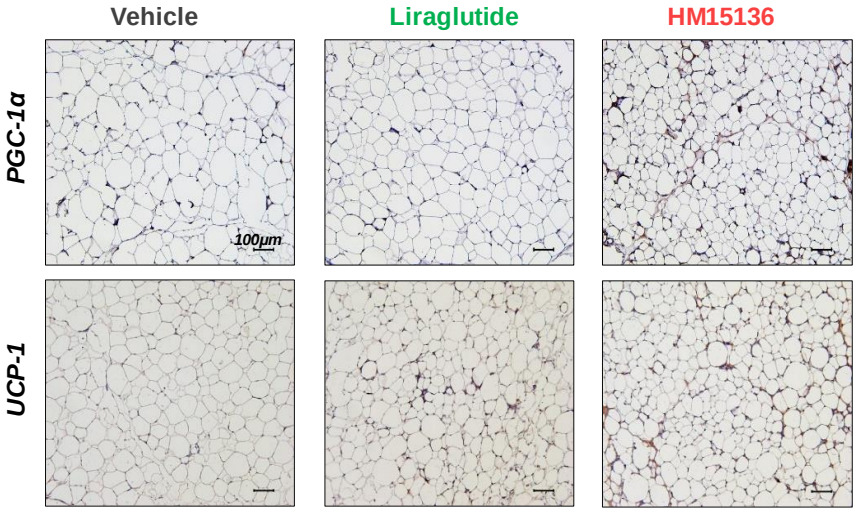
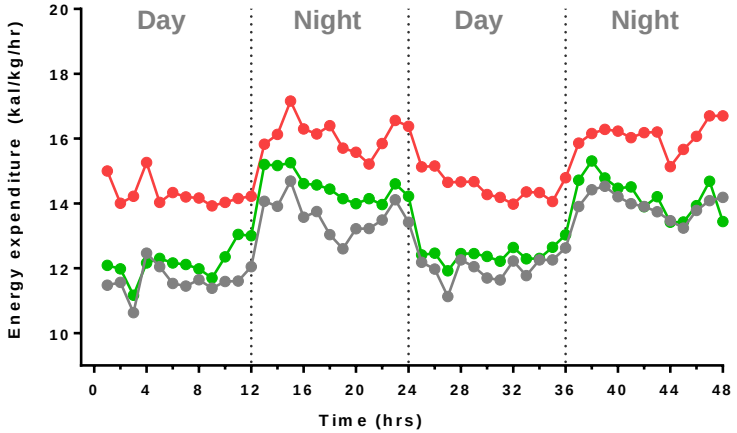


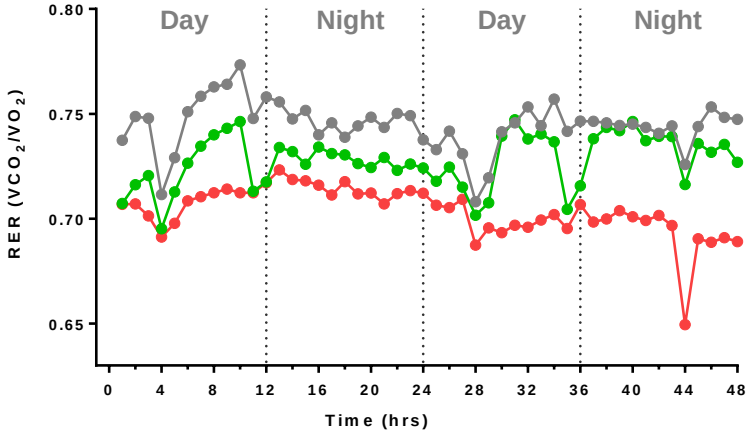
Figure 3. Effect of HM15136 on energy expenditure and RER in DIO mice

- HM15136 increased energy expenditure in DIO mice. Reduced RER (value closed to 0.7) suggests exclusive fat burning by HM15136 treatment.

(a) Energy expenditure



(b) Respiratory exchange ratio (RER)



Vehicle

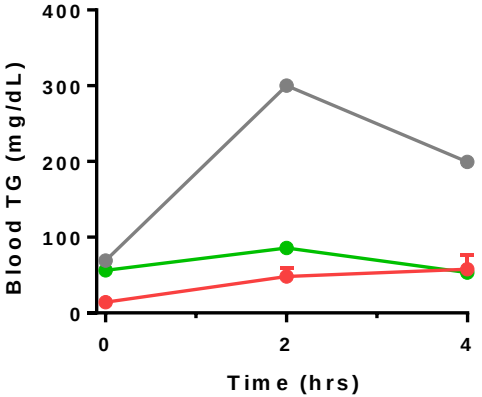
Liraglutide 50 nmol/kg, BID (3 mg/day in human)

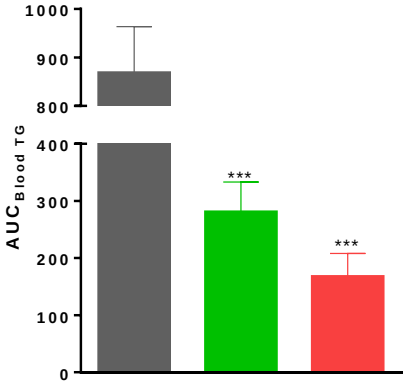
HM15136 2 nmol/kg, Q2D (3 mg/week in human)

Figure 4. Lipid absorption inhibition effect of HM15136 in DIO mice

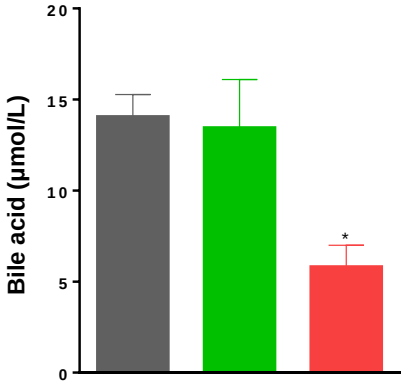
- HM15136 reduced blood TG during oLTT. Decreased blood bile acid and ApoB48 level suggests the potential inhibitory effect of HM15136 on lipid absorption

(a) Blood TG during oLTT

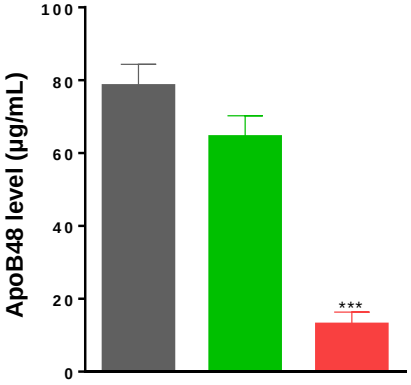




(b) Blood bile acid



(c) Blood ApoB48 level



* ~ ***p<0.05 ~ 0.001 *vs.* DIO mice, vehicle by One-way ANOVA

Vehicle

Liraglutide 50 nmol/kg, BID (3 mg/day in human)

HM15136 2 nmol/kg, Q2D (3 mg/week in human)

Conclusion

- HM15136 shows greater BWL than other GLP-1 receptor agonists such as liraglutide and dulaglutide in DIO mice.
- Unlike liragluitde, HM15136 shows greater BWL than pair-fed group in DIO mice
- HM15136 increases both the expression of PGC-1α and UCP-1 in WAT of DIO mice and energy expenditure in DIO mice
- Additionally, HM15136 effectively inhibits the lipid absorption in DIO mice
- Based on these food-intake inhibition dependent and independent BWL MoAs, HM15136 might be a novel therapeutic option for obesity