Bone protective effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in the obese-osteoporosis rodent model

500-P

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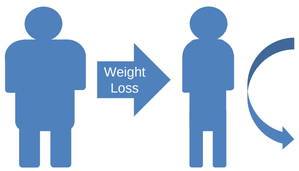
BACKGROUND

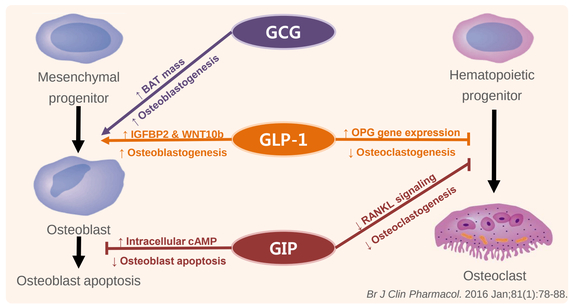
- **Increased fracture risk associated to weight loss[1]**



Bone mass loss
↓ Mechanical effect
↓ Insulin and IGF-1
↓ Estrogen, Adiponectin and Ghrelin
↓ Calcium absorption

Increased Fall Risk
Disorder of bone quality
Mineralization disorder
Bone mass loss

- **Bone homeostasis effects of GCG[2], GLP-1[3] and GIP[4]**



Br J Clin Pharmacol. 2016 Jan;81(1):78-88.

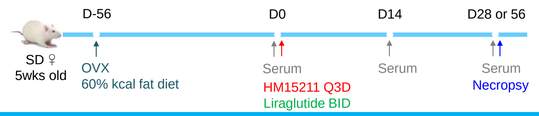
AIMS

This study investigated whether treatment with HM15211 prevents bone loss under a severe weight loss condition, and the underlying mechanism of action.

METHODS

- To investigate MoA for bone protection of HM15211, MC3T3-E1 cells were treated with HM15211. Osteoblast differentiation related markers (RUNX2, OCN, ALP and Col1α) were analyzed using real-time PCR. Additionally, collagen protein expression change and anti-apoptotic effect were evaluated using commercial kit.

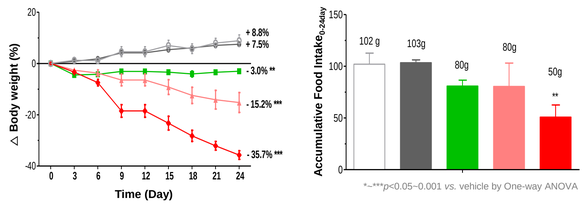
- Diet induced obesity (DIO) osteoporosis rat model was induced by surgical oophorectomy (OVX) and fed 60% kcal fat diet to immatured 5 weeks old female sprague dawley (SD) rats for 8 weeks. Serum levels of bone biochemical markers (Glu-OC ; Glu-Osteocalcin, OPG ; Osteoprotegerin and PINP ; Procollagen type I propeptides) were measured by commercial ELISA kits. BMD (Bone mineral density) of femurs were monitored using a high resolution in vivo μ-CT system (n = 7 /group). Food restricted group was supplied limited amount of daily food to be had same weight loss with HM15211 2.2 nmol/kg treated group.



RESULTS

Reduction of body weight and food intake

Figure 1. Body weight change and accumulative food intake



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

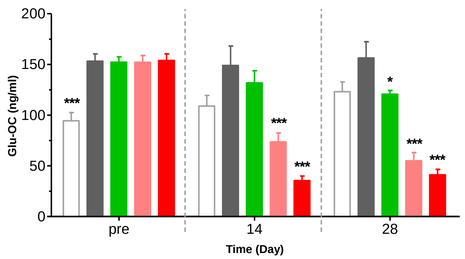
➢ HM15211 administration significantly decreased body weight and food intake, respectively.

- Sham vehicle, Q2D
- OVX vehicle, Q2D
- OVX Liraglutide 25 nmol/kg, BID (3 mg/day in human)
- OVX HM15211 2.2 nmol/kg, Q2D (4 mg/week in human)
- OVX HM15211 4.4 nmol/kg, Q2D (8 mg/week in human)

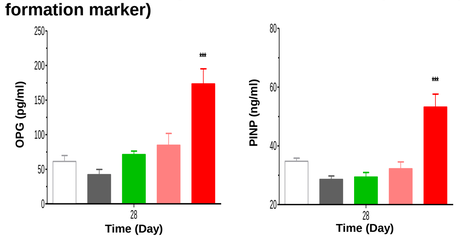
Improvement of bone biochemical markers

Figure 2. Serum levels of Glu-OC, OPG and PINP

(a) Glu-OC (bone resorption marker)



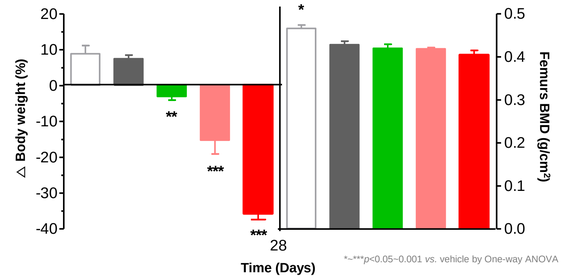
(b) OPG (osteoclastogenesis inhibition marker) & PINP (bone formation marker)



➢ Bone bio chemical markers (Glu-OC, OPG and PINP) were dose dependently improved on HM15211 dosing group, respectively.

Prevention of BMD loss following weight loss

Figure 3. Weight loss and femurs BMD



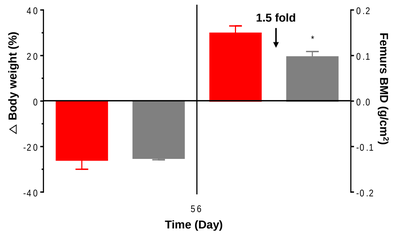
*~***p<0.05~0.001 vs. vehicle by One-way ANOVA*

➢ Even in a severe weight loss condition, HM15211 prevented BMD loss of femurs

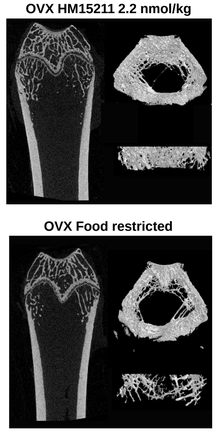
Protection of bone health in same weight loss

Figure 4. Bone health profiles while weight loss matching

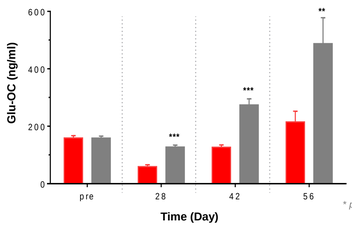
(a) Weight loss and femurs BMD



(b) μ-CT image of Femurs



(c) Glu-OC (bone resorption marker)



** p<0.05 vs. food restricted group by t-Test*

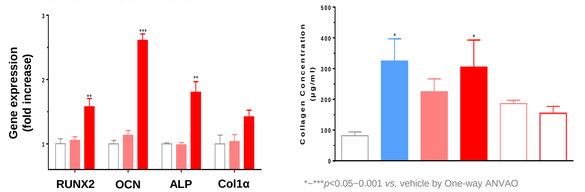
- OVX HM15211 2.2 nmol/kg, Q2D (4 mg/week in human)
- OVX Food restricted

➢ During the same weight loss, HM15211 prevented the decline of bone health

MoA studies for bone protection

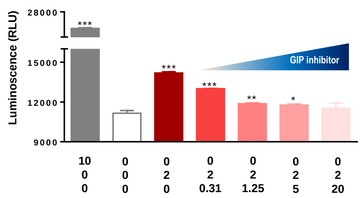
Figure 5. Bone protection mechanism in MC3T3-E1 cell

(a) Osteoblast differentiation marker genes & Collagen expression in conditioned media



*~***p<0.05~0.001 vs. vehicle by One-way ANVAO*

(b) Inhibition of osteoblast apoptosis



➢ HM15211 improved osteoblast differentiation and showed anti-apoptotic effect. Additionally, GIP antagonist reversed the beneficial effect of HM15211 on bone protection.

CONCLUSIONS

- **Lower serum level of Glu-OC and higher serum levels of OPG and PINP were observed compared with those of vehicle and liraglutide treated groups in obese-osteoporosis rats model.**
- **HM15211 showed comparable BMD of femurs compare to vehicle while it showed greater weight loss compared to liraglutide in obese-osteoporosis rats model.**
- **HM15211 led to significant increase in collagen and Gla-OC expression, which were blunted by inhibition of GIPR-mediated signaling in osteoblast cell.**
- **These results suggest that HM15211 might provide potent weight loss without bone loss**

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Hanmi Pharm. Co., Ltd.

Novel combination of GLP-1/GIP/Glucagon triple agonist (HM15211) and once-weekly basal insulin offers improved glucose lowering and weight loss in a diabetic animal model

719-P

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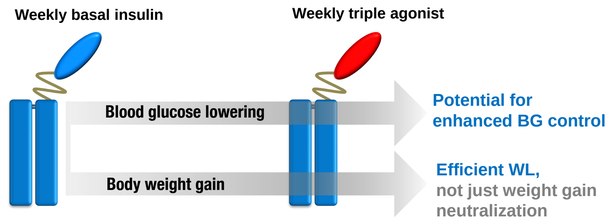
BACKGROUND

Despite improved glycemic control, no current combo therapies (i.e. Basal/bolus insulin and Insulin/GLP-1RA) **have consistent benefits in weight control.**

	Glycemic control (HbA1c change)	Total INS dose	Hypo. Risk	Weight control (BW change)
Basal /Bolus insulin	-1.46 %	84.1 U	1.66 episodes/PYE*	2.64 kg
Basal insulin /GLP-1RA COMBO	-1.3 ~ -2.0 %; -1.48 %	40.4 U	0.13 episodes/PYE	-2.7 ~ +2.0 kg; -0.93 kg

Diabetes Care. **41**, 1009-16 (2018) for DUAL VII; IR presentation 2Q, 2017 Novo nordisk. *PYE: patient years of exposure

Hypothesis



HM12460A [Ph1, US]
- Long-acting basal insulin
- Targeting once-weekly insulin
- Under efficacy evaluation in diabetic patients (P1b)

HM15211 [Ph1, US]
- Efficient WL effect in obese animals
- Expected for once-weekly regimen
- Under safety and PK evaluation in healthy volunteers (P1)

AIMS

- **We hypothesized that when combined with basal insulin, HM15211 could maximize the exogenous insulin response by providing potent BWL and following insulin sensitivity improvement.**
- **We investigated the therapeutic potential of HM15211 and long-acting basal insulin combination for T2DM treatment by evaluating drug-to-drug interaction (DDI), and glycemic and BW control efficacy in diabetic animal models**

METHODS

- *In vitro* human insulin receptor (hIR) phosphorylation potency by long-acting basal insulin (HM12460A) was evaluated in CHO cell stably expressing hIR in the presence or absence of HM15211. Similarly, cAMP accumulation potency by HM15211 was evaluated in CHO cells stably expressing respective receptors (human GLP-1R, GCGR, or GIPR) in the presence or absence of insulin counter partners.
- To evaluate the *in vivo* efficacy, db/db mice and DIO/STZ rats were chronically administered with HM15211 and/or HM12460A, and blood glucose and BW were monitored. At the end of the treatment, HbA1c levels were measured to determine overall glycemic control efficacy.

RESULTS

No pharmacologic drug-drug Interaction (DDI) between HM12460A and HM15211

Table 1. *In vitro* potency change by concomitant treatment

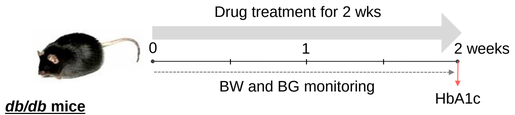
Test materials	% Activity vs. HM12460A or HM15211			
	hIR	hGLP-1R	hGCGR	hGIPR
HM12460A	100.0%	-	-	-
HM15211	-	100.0%	100.0%	100.0%
HM12460A (with HM15211)	126.1±29.0%	-	-	-
HM15211 (with HM12460A)	-	126.2±11.2%	91.1±3.5%	110.2±14.0%
Drug interference	No	No	No	No

➢hIR phosphorylation potency of HM12460A was not affected by concomitant treatment of HM15211. Similar results were also observed in cAMP accumulation potency of HM15211, suggesting no *in vitro* drug interference

In vivo efficacy studies for weekly Insulin/Triple agonist COMBO

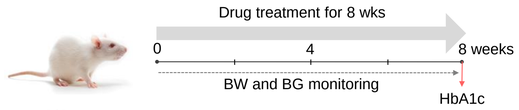
Figure 1. Experimental design for animal studies

a) Genetic diabetes model



***db/db* mice**
: Obesity and T2DM phenotype due to leptin receptor deficien

b) Acquired diabetes model

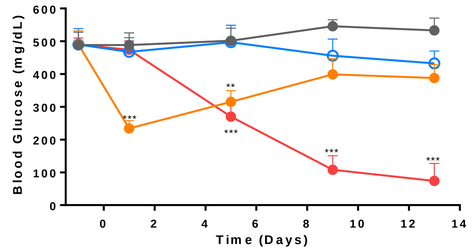


DIO/STZ rats
: Obesity and insulin resistance induced by high fat diet
: Partial β-cell destruction by low dose STZ administration

Glycemic and BW control by weekly Insulin/Triple agonist COMBO in *db/db* mice

Figure 2. BG, HbA1c and body weight change in *db/db* mice

(a) Non-fasting blood glucose profile



(b) HbA1c after 2 weeks treatment

(c) BWC after 2 weeks treatment

*~***p<0.05~0.001 *vs.* vehicle by one-way ANOVA
†p<0.05 *vs.* HM12460A mono by unpaired t-test

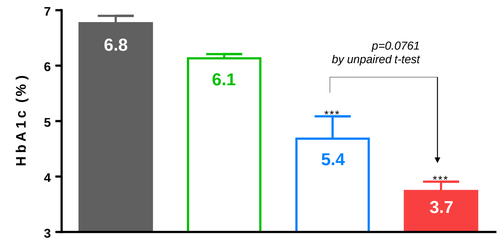
Vehicle
HM12460A 42.2 nmol/kg, Q2D (12 nmol/kg in human)
HM12460A 42.2 nmol/kg, Q2D + HM15211 2.6 nmol/kg, Q2D
IDeg 18.5 nmol/kg BID + Lirag 30 nmol/kg, BID (50 U + 1.8 mg in human)

➢In *db/db* mice, the HM12460A and HM15211 COMBO provided better glycemic control (vs. HM12460A mono) and greater weight loss than an HM12460A mono or IDeg/Lirag COMBO (insulin degludec/liraglutide COMBO)

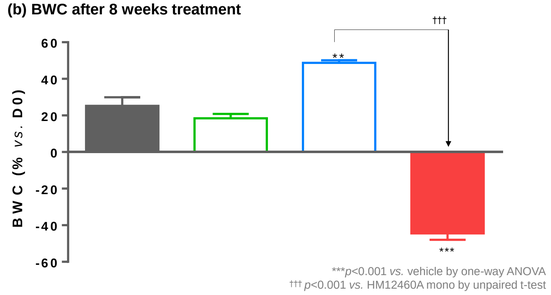
Glycemic and body weight control by weekly Insulin/Triple COMBO in DIO/STZ rats

Figure 3. HbA1c and Body weight change in DIO/STZ rats

(a) HbA1c after 8 weeks treatment



(b) BWC after 8 weeks treatment



***p<0.001 *vs.* vehicle by one-way ANOVA
†††p<0.001 *vs.* HM12460A mono by unpaired t-test

Vehicle
Liraglutide 15 nmol/kg, BID (1.8 mg in human)
HM12460A 16.2 nmol/kg, Q3D (6 nmol/kg in human)
HM12460A 16.2 nmol/kg, Q3D + HM15211 5.9 nmol/kg, Q3D

➢Combination treatment efficiently reduced BW and showed enhanced blood glucose lowering (data not shown) and more HbA1c reduction, compared to HM12460A mono or liragltutide mono in DIO/STZ rats

CONCLUSIONS

- **In diabetic animal models, weekly basal insulin and triple agonist COMBO provided better glycemic control (vs. insulin mono) and more weight loss than an INS/GLP-1RA COMBO**
- **In addition to prandial insulin and GLP-1RA, a triple agonist could be an additional COMBO partner for basal insulin resulting in improved glycemic control and particularly effective body weight loss exceeding what can be achieved by INS/GLP-1RA COMBO**

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