1925-P

Beneficial effects of a novel long-acting glucagon analog, HM15136, on obesity and obesity related metabolic disorders in animal models

Jong Suk Lee, Seon Myeong Lee, Jae Hyuk Choi, Eun Jin Park, Jong Soo Lee, Sang Don Lee, Sung Min Bae, Dae Jin Kim and In Young Choi

Hanmi Pharm. Co., Ltd., Seoul, Republic of Korea

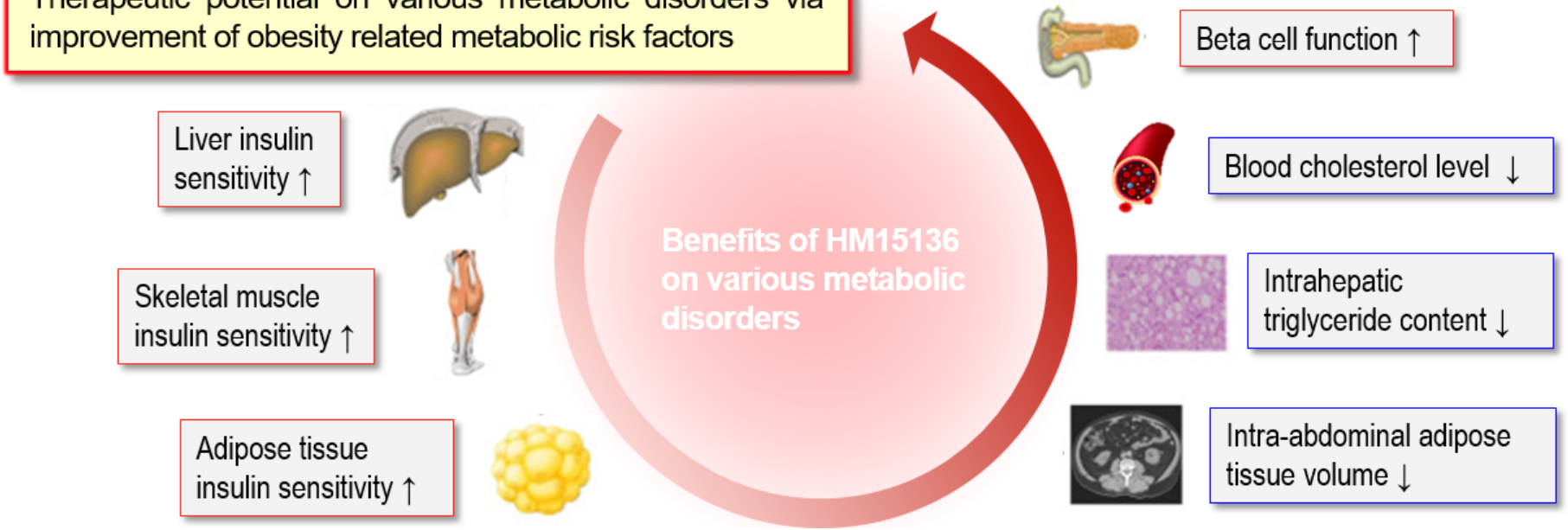
Presenter Disclosure

Employee of Hanmi Pharm. Co., Ltd.

Background

Since obesity is major risk factor for various metabolic disorders (hyperlipidemia, fatty liver, diabetes, and insulin resistance)**, potent BWL effect of HM15136 could provide a therapeutic potential on various metabolic disorders via improvement of obesity related metabolic risk factors**

Therapeutic potential on various metabolic disorders via improvement of obesity related metabolic risk factors



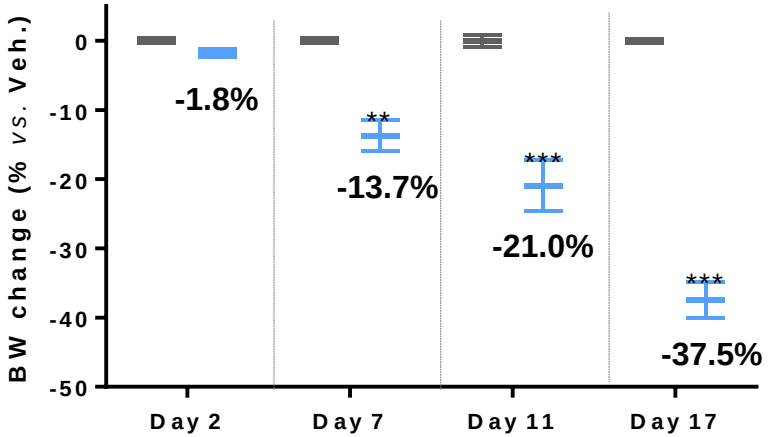
Method

- To confirm the beneficial effects of HM15136 on obesity and obesity related metabolic disorders, HM15136 was subcutaneously administered into diet-induced obesity (DIO) mice for 17 days. The tested doses of HM15136 were 2.0 nmol/kg, 4.0 nmol/kg, once every 2 days (Q2D, 3 mg/week in human, 6 mg/week in human)
- To investigate the time-course pharmacologic action of HM15136 in the liver, blood, liver fat contents, blood lipid were determined at D2, D7, D11, and D17
- To assess the potential impact of HM15136 in insulin sensitivity, 4hr FBG and blood INS level were measured during necropsy
- To investigate the glycemic control efficacy of HM15136, oGTT was performed and FBG, INS level was measured at D2, D8, D14 in DIO mice

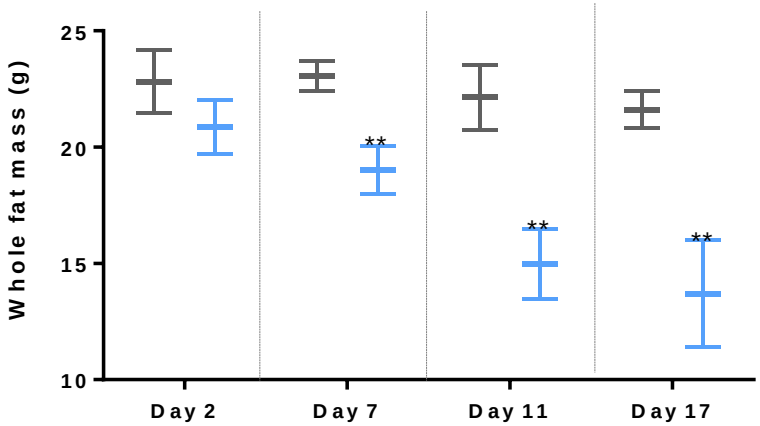
Figure 1. Efficacy of HM15136 for fat reduction and FBG in DIO mice

- At D7, D11 and D17, HM15136 3 mg treatment continuously decreased BW and whole body fat mass despite plateau of blood CHO and liver TG, suggesting lipid profile improvement of liver and blood might be occurred via both BWL dependent mechanism by HM15136 and direct mechanism by HM15136

(a) BW change



(b) Fat mass change



DIO, Vehicle

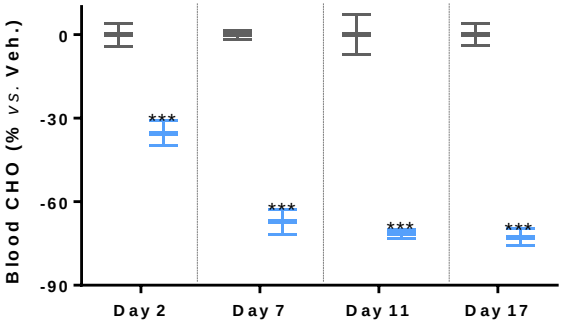
HM15136 2 nmol/kg, Q2D (3.0 mg/wk HED)

$^{**}p<0.01$, $^{***}p<0.001$ *vs.* DIO, vehicle by t-test

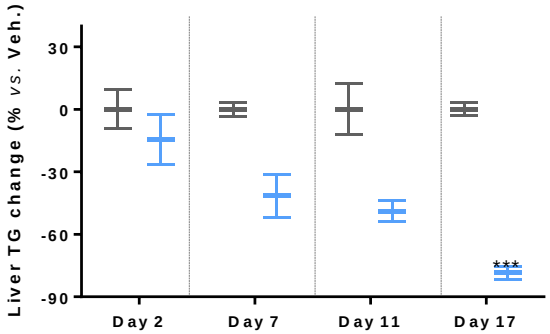
Figure 1. Efficacy of HM15136 for fat reduction and FBG in DIO mice

- At D7, D11 and D17, HM15136 3 mg treatment continuously decreased BW and whole body fat mass despite plateau of blood CHO and liver TG, suggesting lipid profile improvement of liver and blood might be occurred via both BWL dependent mechanism by HM15136 and direct mechanism by HM15136

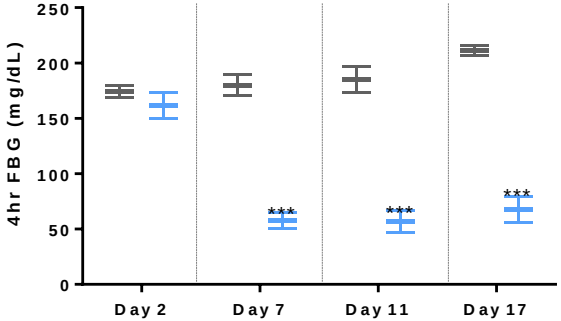
(c) Blood cholesterol



(d) Liver triacylglycerol



(e) Fasting blood glucose



DIO, Vehicle

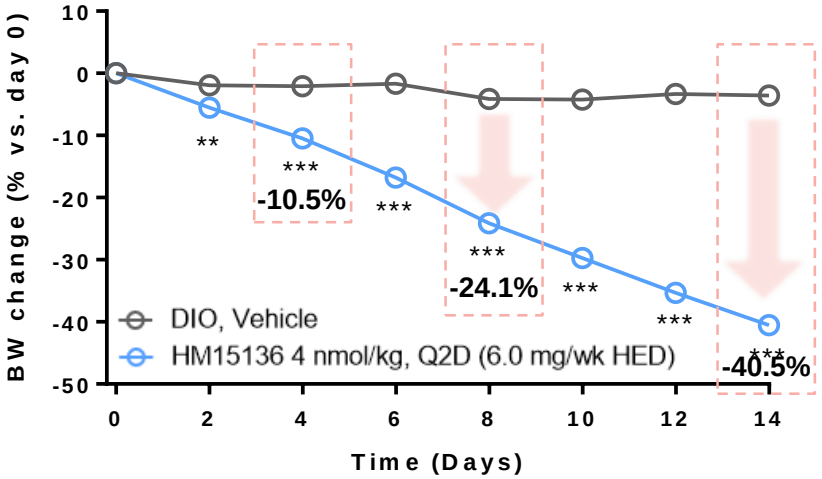
HM15136 2 nmol/kg, Q2D (3.0 mg/wk HED)

****p*<0.001 *vs.* DIO, vehicle by t-test

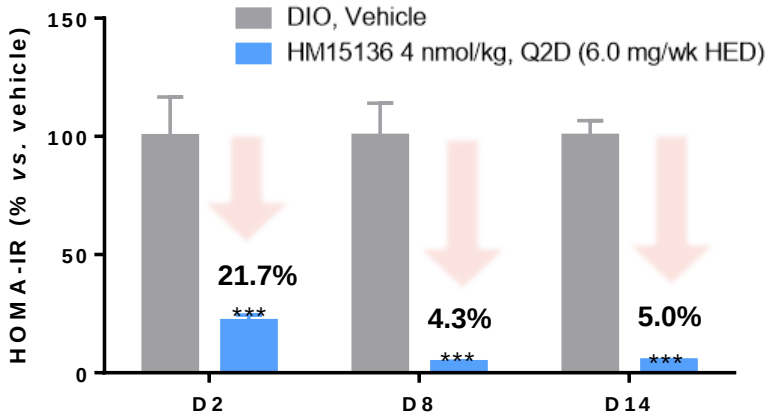
Figure 2. Time-dependent effect of BWL on glycemic control in DIO mice

- HM15136 significantly lowered fasting serum insulin levels (data not shown), and HOMA-IR at D2, suggesting the direct effects of HM15136 on improvement in fasting insulin sensitivity in DIO mice

(a) BW change



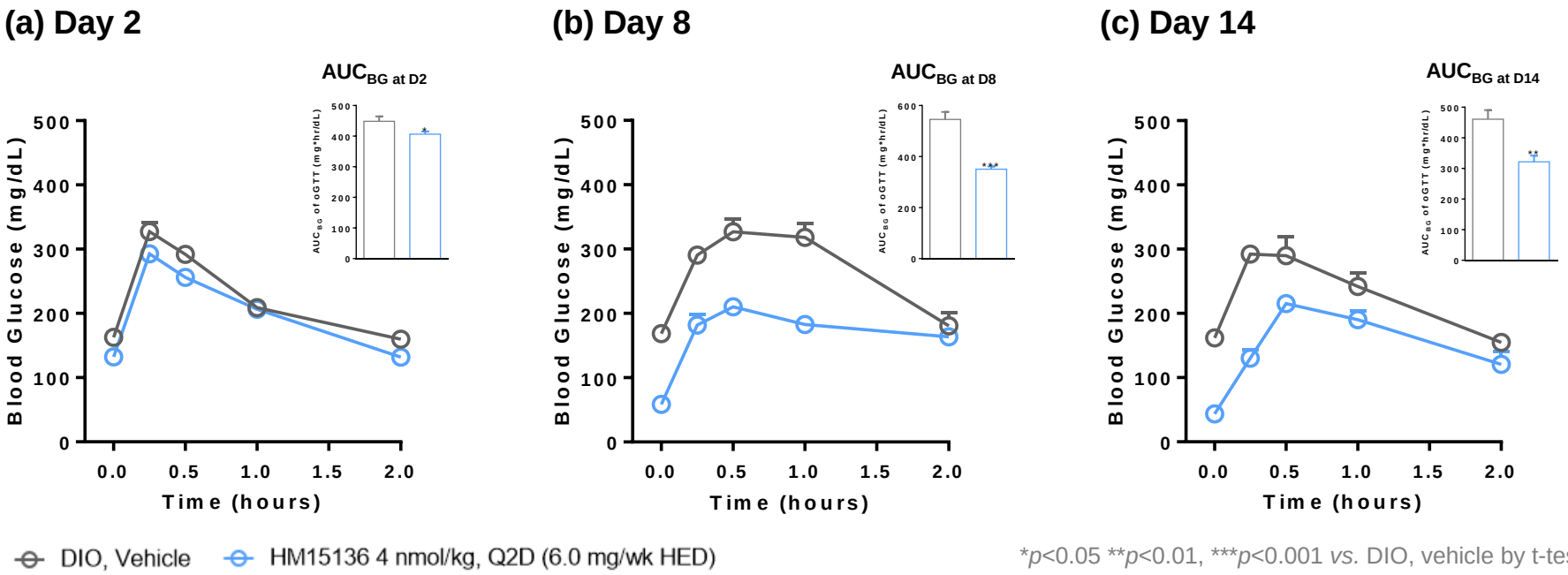
(b) HOMA IR



***p<0.001 *vs.* DIO, vehicle by t-test

Figure 3. Oral glucose tolerance test in DIO mice

- In DIO mice, HM15136 showed restoration of glucose intolerance at day 8, suggesting continued treatment of HM15136 might improve glycemic control via improved insulin sensitivity and glucose source depletion



Conclusion

- HM15136 is a novel long-acting glucagon analog developed for the treatment of obesity
- Chronic treatment of HM15136 showed time dependently increased BWL
- Interestingly, BWL effect of HM15136 was correlated with improvement of obesity related metabolic risk factors
- At D7, D11 and D17, HM15136 6 mg treatment continuously decreased BW and whole body mass despite plateau of blood CHO and liver TG, suggesting lipid profile improvement of liver and blood precedes and then BWL and fat mass is continuously improved, suggesting WL-independent action for lipid lowering and steatosis improvement
- In addition, HM15136 improved insulin sensitivity and glucose tolerance
- Therefore, HM15136 might be a novel therapeutic option for obesity and obesity related disorders