Potential of a novel long-acting glucagon analog, HM15136, for the treatment of obesity

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ABSTRACT

Obesity is considered as a main risk factor for metabolic syndrome. Although there are several anti-obesity drugs, their main mode of action (MoA) is appetite suppression. Thus, body weight loss (BWL) efficacy is limited with benefits fading when the drugs stopped. Glucagon (GCG) has been used to treat hypoglycemia. Recent studies indicated a stimulatory effect of GCG on energy expenditure, suggesting its utilization as an anti-obese drug. Since BWL is a key for insulin resistance (IR) reversal and blood glucose (BG) normalization, we hypothesized that sustained GCG treatment may reduce hyperglycemic risk via IR improvement following efficient BWL. To investigate this hypothesis, we developed a novel long-acting GCG analog, HM15136, and evaluated the effect of HM15136 on BW and BG *in vivo*

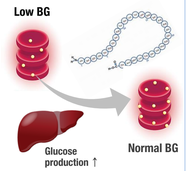
Firstly, we demonstrated that HM15136 had improved solubility (≥150 *vs.* 0.03 mg/mL) and stability at pH7.0, compared to native GCG. Regarding *in vitro* biological activity, HM15136 selectively activated GCG receptor (GCGR), and showed similar maximal potency with native GCG (*data not shown*). In addition, extended half-life and improved bioavailability was observed in mice, rats, and dogs. PK simulation further demonstrated the once-weekly potential of HM15136 in human. Next, the *in vivo* efficacy of HM15136 in obesity was investigated in DIO mice. Chronic treatment of HM15136 showed body weight loss (BWL) in a dose-dependent manner. Of note, unlike GLP-1RA, food intake (FI)-independent BWL could provide more BWL and fat mass reduction than GLP-1RA. White adipose tissue (WAT) browning suggests enhanced energy expenditure by HM15136

In conclusion, our results demonstrate the potential for prolonged GCGR stimulation with agent like HM15136 as a novel therapeutic option for obesity treatment. Human studies are needed to confirm these findings and to evaluate the potential safety of HM15136

BACKGROUND

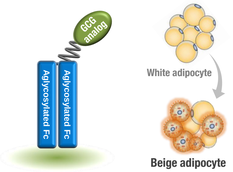
Poor solubility and stability of native GCG limited the investigation of long-term pharmacologic effects. To overcome these limitations, HM15136 was developed as a stable long-acting GCGR agonist

Acute GCGR activation condition



➢ **Hepatic glucose output ↑**
➢ Insufficient for
: Lipid metabolism improvement
: Energy expenditure induction

Sustained GCGR activation in obese condition



➢ Enhanced lipolysis & energy expenditure by fat browning → **Efficient BWL**
➢ Hepatic lipid clearance ↑
→ **Blood lipotoxicity improvement**
➢ BG production sources ↓ (glycogen, lipid)
➢ INS sensitivity improvement
→ **BG normalization**

Optimized for
: *Long-term use for obesity*

METHODS

- PK of HM15136 was investigated in ICR mice, SD rats, and beagle dogs after single subcutaneous or intravenous administration of HM15136. The blood samples were collected at indicated time points, and the blood HM15136 concentration was determined; Based on PK results, human PK was simulated
- To evaluate the therapeutic potential of HM15136 in obesity, DIO mice were chronically administered with HM15136, and body weight (BW) was monitored. To clarify food intake-independent BWL mechanism, BWL was compared under pair-fed condition. At the end of treatment, fat mass and thermogenic marker change were determined
- To evaluate the nausea and vomiting incidence of HM15136, conditioned taste aversion (CTA) test was performed. Briefly, HM15136 was administered into normal mice supplied with water at specific time for 3 days prior to CTA test. After drug treatment, saccharin water was subsequently supplied, and its intake was measured

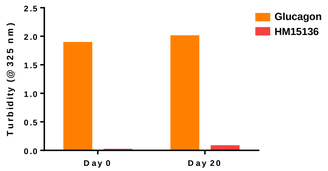
RESULTS

Improved solubility and physical stability of HM15136

Table 1. Solubility of HM15136

Test article	Solubility at pH 7.0
Glucagon	0.03 mg/mL
HM15136	**≥ 150 mg/mL**

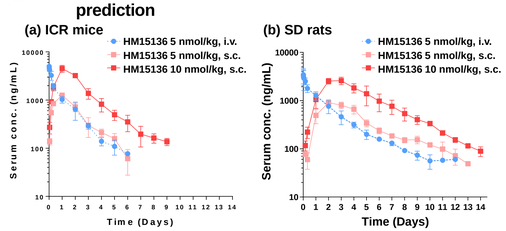
Figure 1. Physical stability of HM15136 in PBS (pH 7.0) at 25°C



➢HM15136 showed improved solubility and physical stability at physiological pH

PK properties of HM15136

Figure 2. PK in various animal species (n=3), and human PK prediction



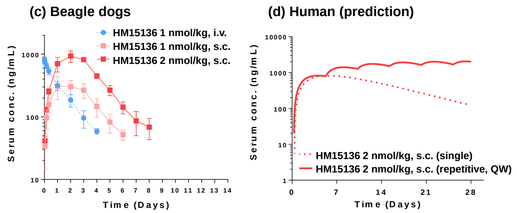


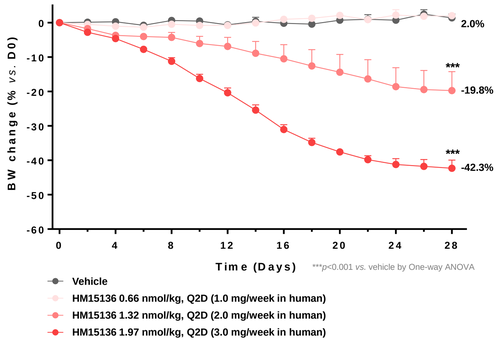
Table 2. PK parameters of HM15136

	ICR mice	SD rats	Beagle dogs	Human (prediction)
T_{max} (hr)	24 hr	48 ~ 64 hr	32 ~ 64 hr	129 hr
$T_{1/2}$ (hr)	32.3 ~ 56.2 hr	40.9 ~ 54.8 hr	26.6 ~ 34.9 hr	155.2 hr
BA (%)	≥ 76.9%	≥ 89.2%	> 100%	-

➢After LAPS-conjugation, HM15136 showed prolonged PK properties in various animal species. Simulated human PK suggests the once-weekly potential of HM15136

In vivo efficacy in an obesity animal model

Figure 3. Effect of HM15136 on body weight in DIO mice (n=7)

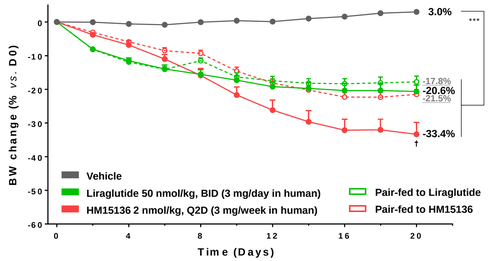


***p<0.001 *vs.* vehicle by One-way ANOVA

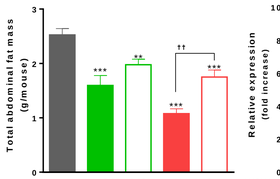
➢Chronic treatment of HM15136 led to dose-dependent BWL in DIO mice, demonstrating the anti-obese action of HM15136

Figure 4. Efficacy comparison of HM15136 and liraglutide in DIO mice under with pair feeding (n=7)

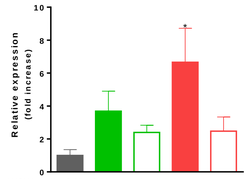
(a) BW change



(b) Fat mass



(c) PGC-1α§ gene level in WAT

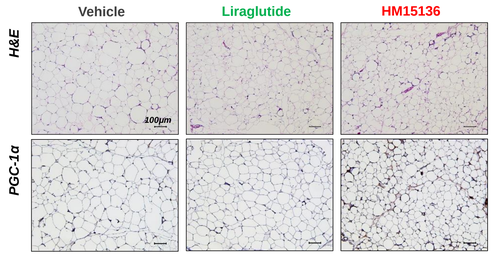


*~***p<0.05 ~ 0.001 *vs.* vehicle by One-way ANOVA, †~††p<0.05 ~ 0.01 *vs.* each pair-fed group by t-test

§ PGC-1α: Peroxisome proliferator-activated receptor gamma co-activator 1alpha

➢Unlike liraglutide, HM15136 provided more BWL, and fat mass reduction than pair-fed group, suggesting satiety-independent BWL mechanism

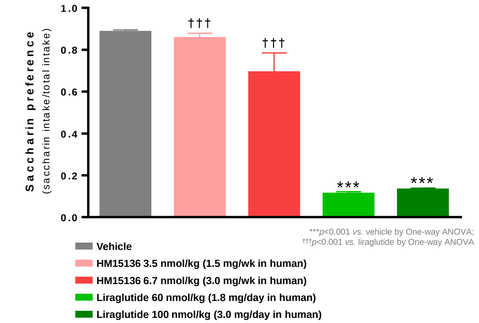
Figure 5. Effect of HM15136 on WAT phenotype in DIO mice



➢H&E staining and PGC-1α immunohistochemistry demonstrated obvious WAT browning by HM15136 in DIO mice

Safety assessment: G/I tolerability

Figure 6. Effect of HM15136 on saccharin water preference in normal mice (n=6)



***p<0.001 *vs.* vehicle by One-way ANOVA; †††p<0.001 *vs.* liraglutide by One-way ANOVA

➢HM15136 showed more saccharin water preference than liraglutide, suggesting reduced nausea and vomiting risk

CONCLUSIONS

- **HM15136 is a novel long-acting glucagon analog with improved solubility and stability at physiological pH**
- **In DIO mice, HM15136 shows dose-dependent BWL. BG elevation is observed only during initial treatment phase, which is rapidly normalized (*data not shown*)**
- **Unlike GLP-1RA, HM15136 shows food intake-independent BWL mechanism; WAT browning and enhanced energy expenditure might be involved**
- **Compared to daily GLP-1RA, HM15136 shows more saccharin water preference in mice, suggesting mitigated nausea and vomiting incidence**
- **Therefore, HM15136 might be a novel therapeutic option for the treatment of obesity**

REFERENCES

- Pocai A *et al.*, *Diabetes* **58**, 2258-66 (2009)
- Campbell JE and Drucker DJ., *Nat Rev Endocrinol.* **11**, 329-38 (2015)
- Muller TD *et al.*, *Physiol Rev.* **97**, 721-66 (2017)
- Kim T *et al.*, *Diabetes* **67**, 2157-66 (2018)

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