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The novel long acting GLP-1/Glucagon dual agonist HM12525A reduces body weight and improves glycermic control in rodent models

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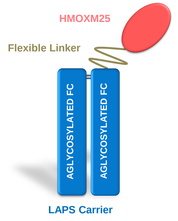
Abstract

Oxyntomodulin is released from the L cells of the small intestine in response to a meal, and is believed to exert its biological effects by activating both the GLP-1 receptor and the glucagon receptor. The combined mechanism of food intake inhibition and increased energy expenditure is expected to enhance body weight loss. In addition, lipid metabolism is also expected to improve via the lipolytic effects of glucagon. HM12525A was developed by conjugating a novel GLP-1/Glucagon dual agonist with the constant region of the human immunoglobulin via a non peptidyl linker. HM12525A is a potent dual agonist with well balanced affinities for the individual receptors. It also has a pharmacokinetic profile compatible with once weekly or less frequent dosing regimens. The pharmacological effects of HM12525A were studied in high fat diet induced obese mice and in *db/db* mice. The high fat fed obese mice were treated once weekly sc with HM12525A (1, 3, and 5 nmol/kg) for 2 weeks, and 100 nmol/kg of liraglutide was treated daily as an active comparator. HM12525A induced dose dependent body weight loss (-3, -10, -31%) compared to liraglutide (-17%), while showing less inhibition of food intake. An glucose tolerance test showed that HM12525A lowered glycemic excursion significantly. The glucose lowering efficacy was also evaluated in *db/db* mice after once-a-week administration of 6 nmol/kg HM12525A for 4 weeks, in comparison with 60 and 100 nmol/kg of liraglutide administered daily. The results showed that 6 nmol/kg of weekly HM12525A had comparable HbA1c reduction to the 100 nmol/kg of daily liraglutide. In conclusion, the long acting GLP-1/Glucagon dual agonist HM12525A showed potent body weight loss as well as glucose lowering efficacy in rodent models

Introduction

- Obesity is an major health issue. According to the WHO, approximately 1.6 billion adults are overweight, and by 2015, this number is projected to rise to 2.3 billion, with over 700 million classified as obese.
- Oxyntomodulin is released from the L cells of the small intestine in response to meal ingestion, and is believed to exert its biological effects by activating both the GLP-1 receptor and the glucagon receptor. The combined mechanism of food intake inhibition and increased energy expenditure would be expected to enhance weight loss and reductions of fat mass, exceeding that of a pure GLP-1R agonist, as well as improved glucose control. However the short circulating half-life (~12 min) limits its clinical potential.
- HMOXM25 created by amino acid modification in the oxyntomoulin sequence that improved GLP-1R and GlucaogonR potency. HM12525A is the site-specific conjugated form of HMOXM25 and the constant region of human globulin G4 fragment (LAPS carrier) linked via a non-peptidyl PEG linker based on a novel strategy for developing long-acting proteins.



- In the present study, HM12525A showed that it has superior long-acting and therapeutic profile regard to body weight and glycemic control. These findings suggest that HM12525A might use a once-weekly regimen and be a potential therapeutic candidate for the treatment of obese diabetic obese patients.

Methods

- The dual receptor activation of HM12525A were identified using human GLP-1 receptor and human Glucagon receptor transformed CHO cell lines. The cAMP levels of individual cell lines were measured using commercially available cAMP assay kits.
- 26 weeks HFD induced C57BL/6J mice (n=6) were treated (s.c) with HM12525A once a week, or with liraglutide once daily for 2 weeks respectively. The body weight and food intake was monitored daily and an IPGTT was performed at the end of the treatment period.
- Energy Expenditure as well as home-cage activity were assessed by using a combined indirect calorimetry system for 1 week after the first administration in DIO mice. O2 consumption and CO2 production were measured every 10 min for a total of 7 days to determine the respiratory quotient and energy expenditure. Home-cage locomotor activity was determined using a multidimensional infrared light beam system with beams scanning the bottom.
- *Db/db* mice (n=7) were treated (s.c) with HM12525A once a week, or liraglutide once daily, for 4 weeks respectively. we measured blood glucose levels at each time points using a glucometer. Blood samples were collected and HbA_{1C} levels were measured. Data was compared by 1-way ANOVA followed by Dunnett's multiple comparison test: *p<0.05, **p<0.01 vs. vehicle

Results

Synergystic Effects of GLP-1 and Glucagon in Obesity

GLP-1/Glucagon dual-agonist enable superior weight control induced food intake inhibition by GLP-1 and increased energy expenditure and direct lipolysis by Glucagon

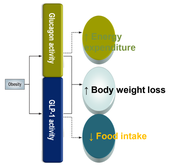


Table 1. Dual agonist benefit as obesity drug

	GLP-1	Glucagon	Dual-agonist
Food Intake ↓	O	Δ	O
Energy expenditure ↑	X	O	O
Glucose lowering	O	X	O
Cholesterol ↓	Δ	O	O
Hyperglycemia	X	O	X

Figure 1 . Individual and synergystic effects of GLP-1 and glucagon in obesity and pharamocotherapy

Receptor Pharmacology

Balanced potency (1:1) at the GLP-1R and GCGR elicited potent body weight loss and glucose lowering efficacy

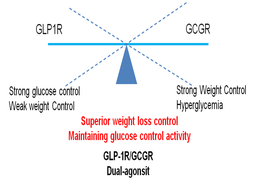


Figure 2. Optimal dual agonist profile

Table 2. Relative activity of HM12525A regard to native GLP-1 and Glucagon, respectively

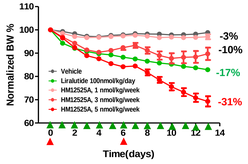
Test materials	Relative activity		GLP : Glucagon
	% of GLP-1	% of Glucagon	
GLP-1	100	---	
Glucagon	---	100	
HM12525A	30	37	1 : 1

The in vitro activity of HM12525A was identified using human GLP-1 receptor and human Glucagon receptor transformed cell lines

Body Weight Loss

HM12525A significantly decreases body weight in 26 weeks DIO mice for 2 weeks

(a) Body weight loss, DIO mice (n=6)



(b) Cumulative food intake in DIO mice (n=6)

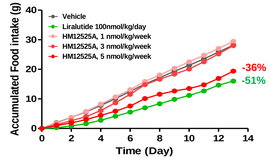
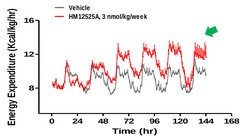


Figure 3. Dose dependent body weight loss (a) and cumulative food intake (b) of HM12525A in DIO mice

Energy Expenditure

HM12525A showed Increased Energy Expenditure without Locomotor Activity Change in DIO mice.

(a) Energy Expenditure , DIO mice (n=10/group)



(b) Locomotor activity, DIO mice (n=10/group)

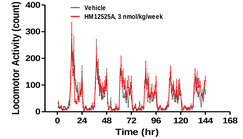
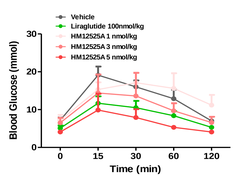


Figure 1. Energy expenditure of HM12525A in DIO mice (a) Energy expenditure (b) Locomoter activity

Glucose Tolerance (IPGTT)

HM12525A showed dose dependent reduction of glycemic excursion in DIO mice.

(a) blood glucose change, DIO mice (n=6)



(b) AUC of blood glucose, DIO mice (n=6)

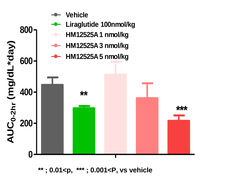
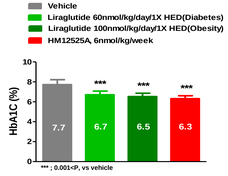


Figure 4. Change of blood glucose on IPGTT in DIO mice treated with HM12525A and liraglutide during for 2 weeks. The IPGTT was performed on the 24 hrs after 3 rd administration (day 15)

Glycemic Control

Weekly administration of HM12525A significantly improved blood glucose levels in *db/db* mice after 4 weeks treatment

(a) HbA1c, db/db mice (n=7)



(a) Body weight loss, db/db mice (n=7)

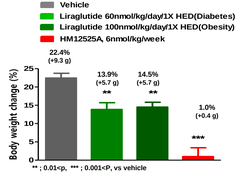


Figure 6. HbA1c reduction of HM12525A in *db/db* mice for 4 weeks

Conclusions

- **HM12525A is a novel fully potent and selective agonist on hGLP-1R and hGlucagonR which was developed by conjugating HMOXM25, a potent oxyntomodulin analog with the constant region of human globulin G4 fragment via non-peptidyl linker.**
- **HM12525 is well balanced agonism which shows improved glycemic control and superial weight loss compared to pure GLP-1R agonist.**
- **HM12525A shows an enhanced pharmacokinetic profile in rats and mice and is suited for once weekly treatment**
- **HM12525A, when injected once a week and based on its dual mode of action demonstrated more effective body weight control than a GLP-1R agonist in obese mice**
- **Increased energy expenditure was not associated with a change in spontaneously physical activity induced thermogenesis since locomotor activity did not differ between treatment groups and control**
- **HM12525A improves glycemic control in diabetic mice**
- **Based on our results, the dual GLP-1R/GlucagonR agonist HM12525A seems to have clinical potential for a once-weekly treatment of obesity and diabetes.**

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Further Information

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[Developmental Plans]

- Preclinical toxicity study implemented and will be completed until 3Q 2013
- Phase I clinical study (FIH) planned on 4Q 2013