A Novel Long-Acting GLP-1/Glucagon Dual Receptor Agonist: Potent Weight Loss Mechanism and Improvement of NASH by HM12525A

ABSTRACT

HM12525A is a long-acting GLP-1/glucagon dual agonist for once-weekly administration. In a preclinical study, oral co-administration of a 1 μg/kg dose of HM12525A in HFD-fed ob/ob mice induced significant weight loss and reduction in liver steatosis, compared to 1 mg/kg doses of GLP-1 (1-37, amide) or glucagon. Potent weight loss effect by HM12525A was also confirmed in human volunteers. In this study, we investigated the effects of HM12525A on adipose tissue mass and liver histology in diet-induced obesity models. Our data suggests that HM12525A may be an effective treatment for obesity and NASH.

RESULTS

Figure 1. Body weight loss in DIO rats (n=7, J6wk)
(a) Body weight change
(b) Cumulative Food Intake

Figure 2. Increase of serum FGF21 and UCP mRNA level
(a) Serum FGF21
(b) UCP1 mRNA

Figure 3. Body weight loss effect by human weekly and monthly mimic condition in DIO rats
(a) BWL by human GWQ mimetic
(b) BWL by human GMQ mimetic

Figure 4. Body composition change in DIO mice (n=10, 4 wks)
(a) Body weight
(b) Body fat mass
(c) Lean body mass

Figure 5. Lipid change in DIO mice (null, 2 wks)
(a) Total cholesterol change
(b) LDL change
(c) HDL change

Figure 6. Therapeutic potential in ALIOS diet mice (n=7, 4 wks)
(a) Hepatic TG level
(b) Collagen-1 mRNA
(c) Steatosis score

Figure 7. Therapeutic potential in MCD mice (n=7, 4 wks)
(a) TNF-α mRNA
(b) Collagen-1 mRNA
(c) NAPLD activity score

METHODS

Animal study

RESULTS

• HM12525A showed superior body weight loss compared with Liraglutide
• Potent BWL effect of HM12525A is twofold that of pair-fed animals indicating increase of EE
• HM12525A reduced BW and fat mass without a change in lean body mass indicating fast increasing BMI as the driving force for the potent BWL

CONCLUSIONS

• In addition to benefits in glycemic control, HM12525A showed potent body weight loss which was driven by regulating both appetite and energy expenditure in animal models.
• The glucagon-FGF21 axis plays an essential role in weight loss effect of HM12525A, even at human monthly mimetic condition in DIO mice.
• The new reduction mechanism is that HM12525A, which was well correlated with reduced cholesterol and LDL.
• In further rodent models, HM12525A reduced hepatic TG accumulation and expression of inflammation, and fibrosis-related marker along with improved histological score.
• Our results suggest that the novel GLP-1/glucagon dual agonist HM12525A may have clinical potential for the treatment of obesity and obesity-related liver disease.

REFERENCES