Potential effect of a novel combination of GLP-1RA (efpeglenatide) and long-acting glucagon analog (HM15136) in animal models of metabolic disorder

657-P

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ABSTRACT

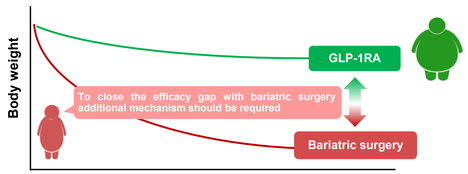
In addition to glycemic control, GLP-1RA efficacy is established in obesity. However, more efforts are still required to close efficacy gap with bariatric surgery. Recent studies demonstrate the favorable effect of glucagon (GCG) receptor activation on energy expenditure and hepatic lipid metabolism. So, combination of GCG with GLP-1RA not only enhances body weight loss (BWL) barely achieved by current therapy, but also expands its therapeutic utility to various metabolic disorders. Previously, we confirmed the long-acting GCG properties of HM15136 from animal to human. In addition, GLP-1 class effect of efpeglenatide (Efpe), once-weekly GLP-1RA, was confirmed in clinical studies. Thus, to develop a novel combination therapy, we investigated potential effects of Efpe and HM15136 combination in animal models of metabolic disorders.

In DIO mice, 4 weeks treatment of Efpe and HM15136 combination (COMBO) showed more BWL than Efpe mono treatment. Of note, greater BWL was also confirmed for COMBO treatment compared to acylated GLP-1/GIP co-agonist (-18.5, -55.9, -44.9% *vs.* vehicle for Efpe, COMBO, GLP-1/GIP). Similar results were observed when measuring fat mass (-19.5%, -83.8%, -77.2% *vs.* vehicle for Efpe, COMBO, GLP-1/GIP) and blood lipid profiles (total cholesterol: -41.8%, -82.0%, -63.2% *vs.* vehicle for Efpe, COMBO, GLP-1/GIP) in DIO mice. To further demonstrate benefits of this novel COMBO, additional study was performed in DIO/STZ rats, and COMBO treatment consistently showed more BWL than Efpe (-5.1, -12.1% *vs.* vehicle for Efpe, COMBO) along with numerically more HbA1c reduction (-1.0, -1.5% *vs.* vehicle for Efpe, COMBO).

Therefore, HM15136 might be a novel COMBO partner for Efpe, providing enhanced BWL and favorable metabolic profiles. These results warrants further evaluation for therapeutic potential of this novel COMBO in various metabolic disorders including dyslipidemia and NASH.

BACKGROUND

Unmet-needs of GLP-1RA for obesity management



[Benefits of efpegleantide and HM15136 COMBO]

Efpeglenatide (Long-acting GLP-1)		(1) Ratio optimized and individualized		HM15136 (Long-acting GCG)
	O	Satiety regulation	O	
		Energy expenditure ↑	O	
	O	Glycemic control	Transient BG elevation	
		(2) Enhanced BW loss		
		(3) Indication expansion to more metabolic diseases e.g. Dyslipidemia, CKD, & NASH		
		Direct benefits on CVR*	O	
	O	Anti-inflammation	O	
		Anti-fibrosis	O	

*CVR: Cardiovascular renal

METHODS

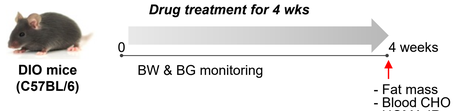
- To evaluate combination effect of GLP-1RA (efpeglenatide) and glucagon analog (HM15136) on obesity, efpeglenatide and its combination with HM15136 was subcutaneously administered into diet-induced obesity (DIO) mice. Changes in body weight (BW) and blood glucose (BG) were monitored, and blood lipid profile, fat mass and HOMA-IR were determined after 4 weeks treatment
- To explore optimal combination ratio of efpeglenatide and HM15136, additional efficacy study was performed in DIO/STZ rats. Efpeglenatide and HM15136 COMBO with various ratio (same total dose) were administered for 4 weeks, and BW and BG were monitored. At the end of treatment, HbA1c was determined

RESULTS

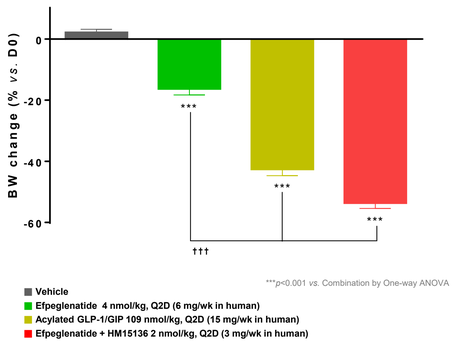
Beneficial effects of combination therapy on metabolic disorders in DIO mice

Figure 1. Effects of combination on BW, fat mass and blood CHO in DIO mice (n=7)

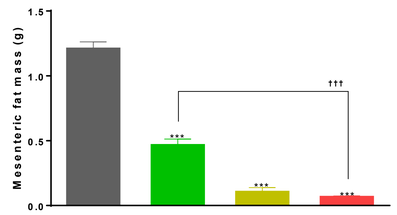
(a) Study design in DIO mice



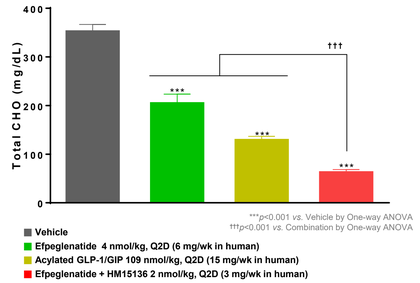
(b) BW change at week 4



(b) Fat mass at week 4



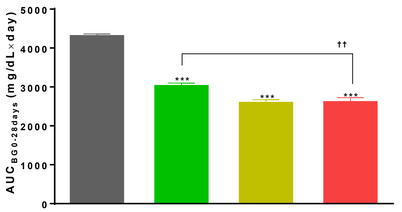
(c) Blood total cholesterol (CHO) at week 4



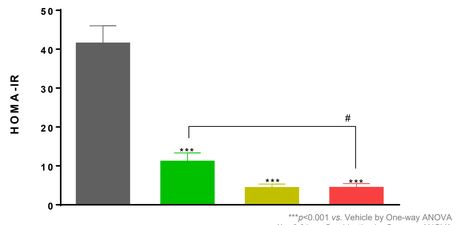
➢ In DIO mice, combination treatment of efpeglenatide and HM15136 showed greater reduction in BW, fat mass, and blood CHO. More benefits over acylated GLP-1/GIP further rationalized combination of efpeglenatide and HM15136

Figure 2. Effects of combination on glycemic control in DIO mice

(a) BG AUC for 4 weeks



(b) HOMA-IR at week 4



***p<0.001 *vs.* Vehicle by One-way ANOVA
††p<0.01 *vs.* Combination by One-way ANOVA
#p<0.05 *vs.* Combination by unpaired t-test

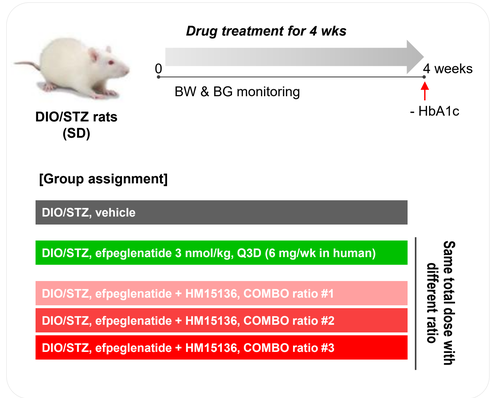
Vehicle
Efpeglenatide 4 nmol/kg, Q2D (6 mg/wk in human)
Acylated GLP-1/GIP 109 nmol/kg, Q2D (15 mg/wk in human)
Efpeglenatide + HM15136 2 nmol/kg, Q2D (3 mg/wk in human)

➢ Combination of efpeglenatide and HM15136 had additional BG lowering rather than increasing BG elevation risk. Improved insulin sensitivity secondary to potent BWL might contribute to this favorable BG control

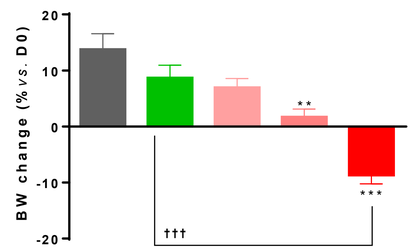
Beneficial effects of combination therapy on metabolic disorders in DIO/STZ rats

Figure 3. Effects of combination on BW and glycemic control in DIO/STZ rats (n=6)

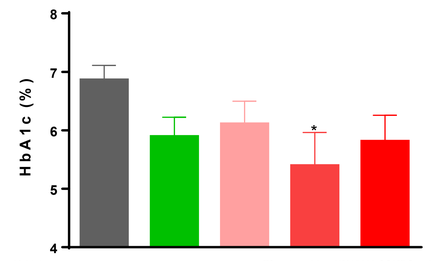
(a) Study design in DIO/STZ rats



(b) Body weight change at week 4



(c) HbA1c at week 4



-*p<0.01 ~ 0.001 *vs.* Vehicle by One-way ANOVA
†††p<0.001 *vs.* Combination by On

➢ In DIO/STZ rats, efpeglenatide and HM15136 COMBO ratios showing [1] more benefits in both BW and BG control than efpeglenatide, and [2] maximized BWL with BG neutral effect were confirmed

CONCLUSIONS

- **Efpeglenatide and HM15136 are novel long-acting GLP-1RA and glucagon analog, respectively**
- **In DIO mice, efpeglenatide and HM15136 COMBO showes more BWL, fat mass reduction and blood lipid lowering than efpegleantide mono**
- **In DIO/STZ rats, the COMBO ratios with optimal efficacy in both obesity and T2DM, and maximized anti-obesity effects are identified, which will give valuable information for future clinical studies with various metabolic disease background**
- **Therefore, HM15136 might be a suitable combination partner of GLP-1RAs such as efpeglenatide for metabolic disease management**