Abstract #757

Beneficial effects on metabolic disorders by a long-acting glucagon analogue, HM15136, in pre-clinical models

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Presenter Disclosure

Employee of Hanmi Pharm. Co., Ltd.

Proposed working mechanism for CKD improvement by HM15136

HM15136: “Long-acting glucagon analog”

Favorable metabolic effects
: **Indirect mechanism**

Inhibitory effects on EMT and apoptosis by metabolic stress
: **Direct mechanism**

Obesity

Hyperlipidemia

High blood pressure

Risk factors of kidney health

CKD
(Chronic kidney disease)

EMT* of tubular epithelial cell

*Epithelial to mesenchymal transition

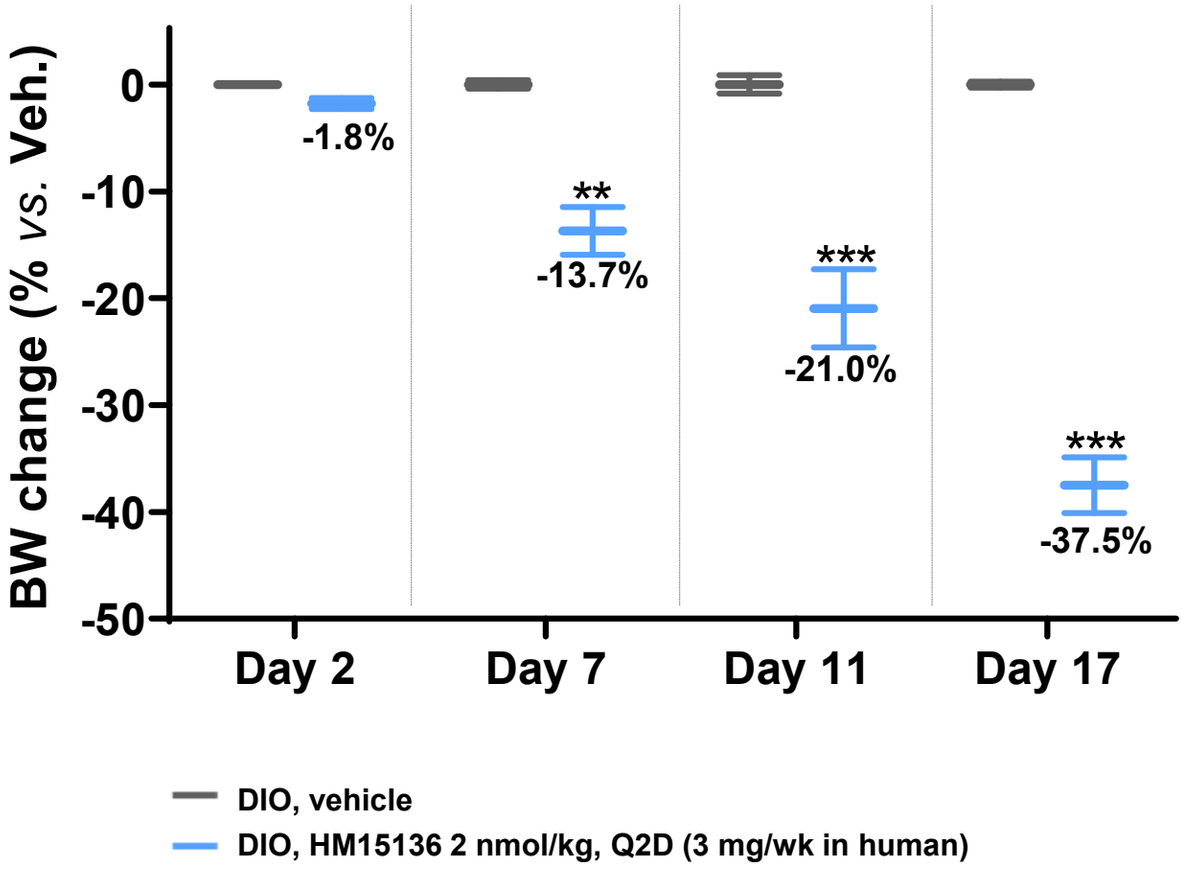
Podocyte apoptosis

Main etiologies of CKD onset & progression

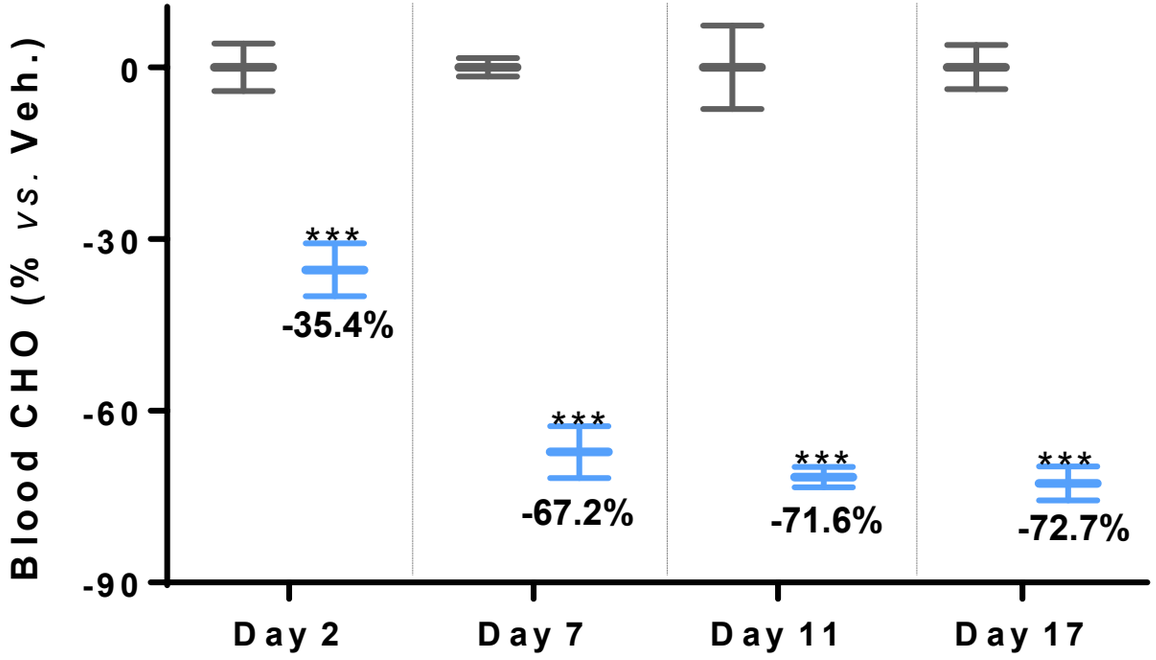
Figure 1. HM15136 effect in DIO mice

➢ Over the course of the study, HM15136 treatment continuously decreased the risk factors of CKD such as BW and blood cholesterol in DIO mice

(a) Change in BW over time



(b) Change in blood cholesterol (CHO) over time



DIO, vehicle

DIO, HM15136 2 nmol/kg, Q2D (3 mg/wk in human)

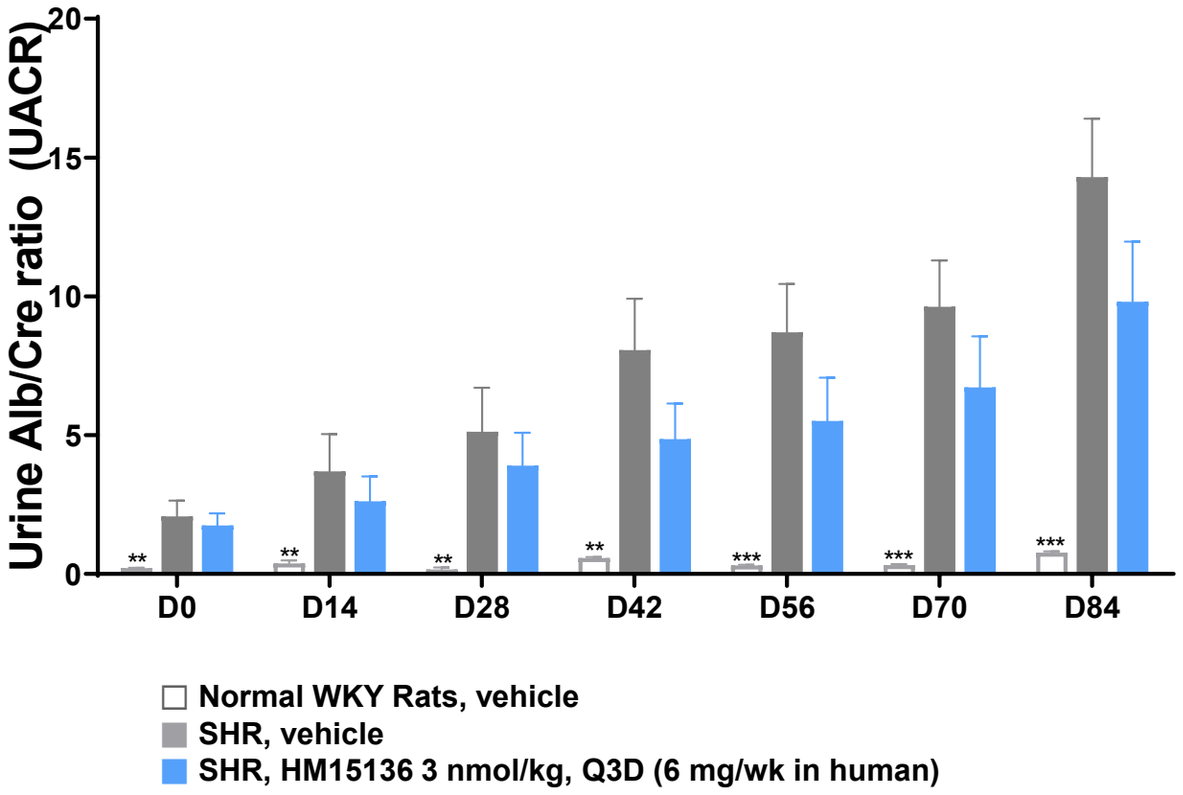
***p<0.001 *vs.* DIO, vehicle at indicated time points by t-test

Figure 2. HM15136 effect on kidney function in SHR* mice

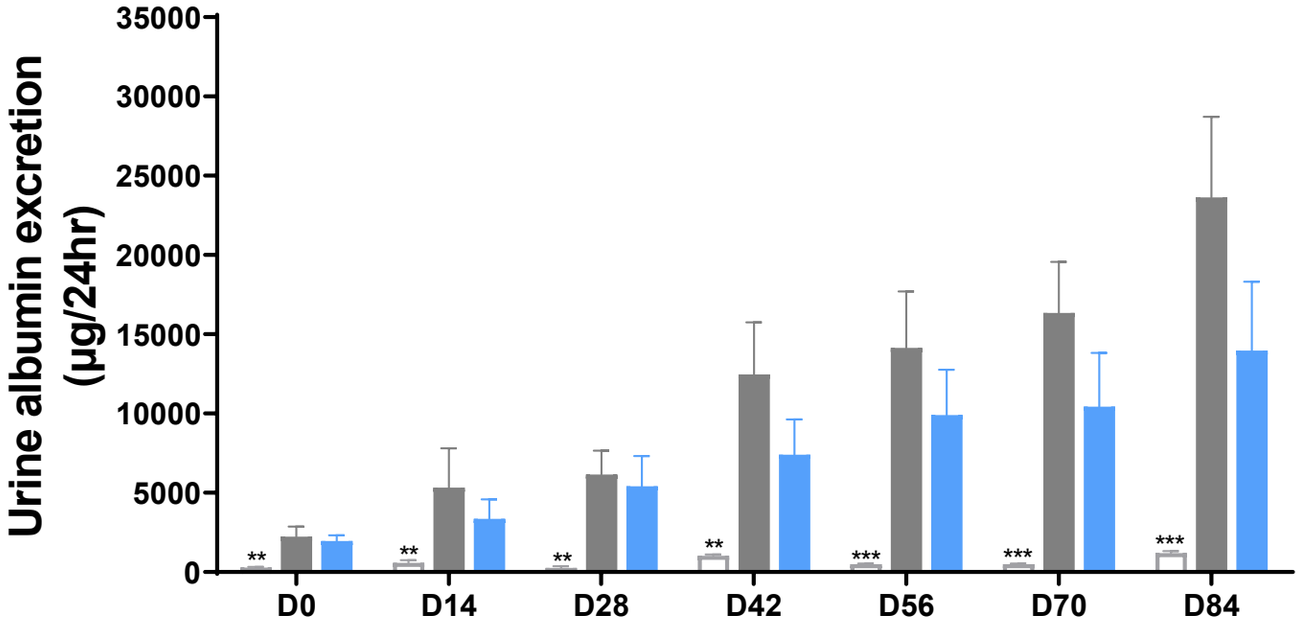
*SHR: Spontaneously hypertensive rat

- In SHR, HM15136 treatment continuously improved kidney function as indicated by UACR and urinary albumin excretion level, suggesting therapeutic potential of HM15136 on CKD

(a) Change in UCAR over time



(b) Change in albumin excretion over time



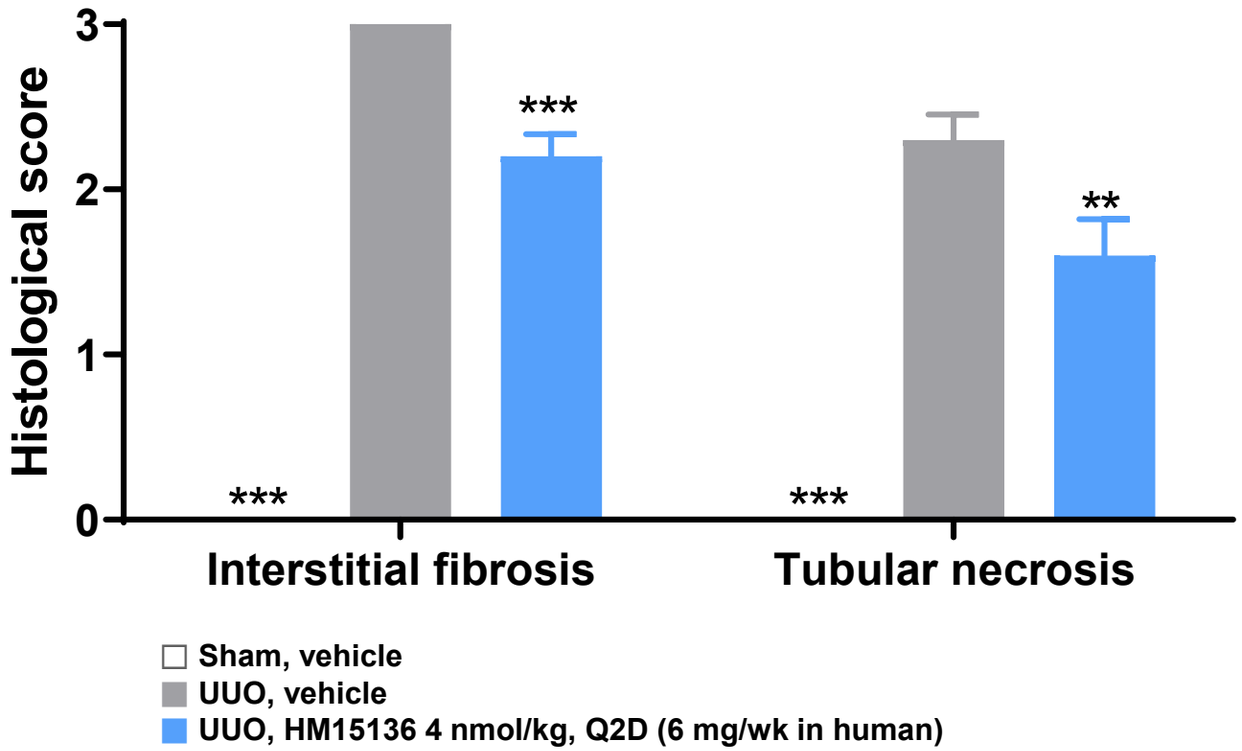
~*p<0.01 ~ 0.001 *vs.* SHR, vehicle at indicated time points by One-way ANOVA

Figure 3. HM15136 effect on kidney pathology in UUO* mice and MoA

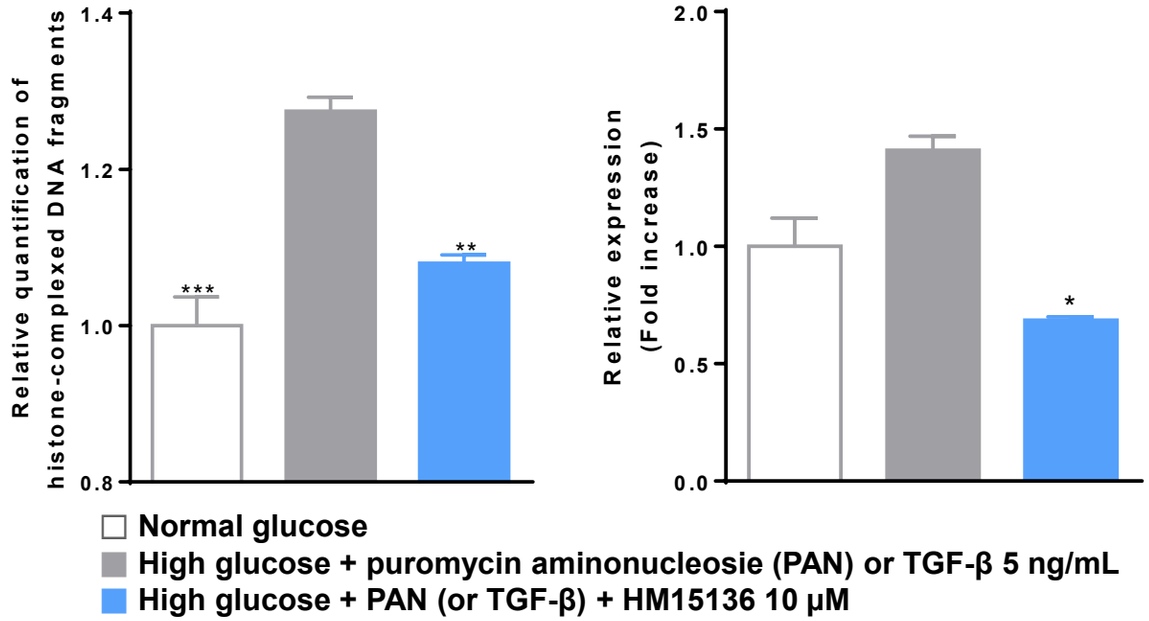
*UUO: Unilateral ureteral obstruction

- In UUO mice, HM15136 treatment effectively improved kidney pathologic scores. Mechanistically, stress-induced human podocyte apoptosis and TGF-β-induced EMT of HK-2 were prevented by HM15136, revealing underlying mechanism for CKD improvement by HM15136

(a) Kidney pathologic score



(b) Apoptosis of primary podocyte (left) **and EMT marker expression in HK-2 cells** (right)



*~***p<0.05 ~ 0.001 *vs.* UUO, vehicle or stimulation by One-way ANOVA

Summary & Conclusions

- **HM15135 is the first long-acting glucagon analog with once-weekly dosing potential for the management of various metabolic disorders**

- **Chronic treatment of HM15136 showed time-dependent BW loss, which correlates with improvement of obesity related CKD risk factors such as blood CHO and liver TG**

- **In SHR, HM15136 treatment was associated with kidney function improvement**

- **In UUO mice, pathologic features of kidney such as tubular necrosis and interstitial fibrosis were significantly improved by HM15136. Additional *in vitro* studies showed protective effects of HM15136 from stress-induced podocyte apoptosis and tubular epithelial cell EMT**

Sustained glucagon engagement by HM15136 could confer beneficial effects on CKD in addition to anti-obesity effects. Additional investigation is required for clinical relevance of these findings

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