Therapeutic effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in a NASH and fibrosis animal model

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ABSTRACT

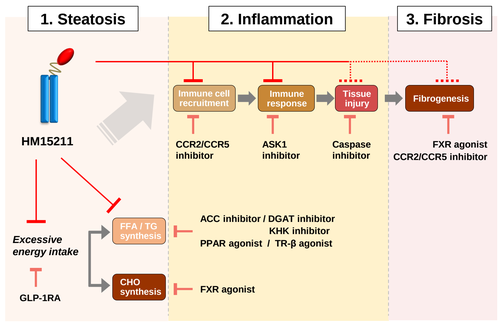
NASH, a severe form of NAFLD, can lead to end stage liver disease such as cirrhosis. Despite increasing prevalence and as a burden for public health, advances in the development of therapeutics are slow with yet no approved drug for NASH treatment. Since liver fat accumulation and inflammation are associated with NASH progression, targeting both aspects may contribute to NASH resolution and fibrosis improvement. Thus, to directly aid those aspects, we developed a novel long-acting, GLP-1/GIP/Glucagon triple agonist, HM15211. With a unique activity profile, HM15211 showed a liver preferential distribution, and exerted potent hepatic triglyceride (TG) reduction in addition to efficient body weight loss (BWL) in DIO mice, suggesting HM15211 as a novel therapeutic option for NASH treatment. Here, we evaluated the therapeutic potential of HM15211 in NASH and fibrosis animal models including monkeys

In MCD-diet mice (6 weeks induction), HM15211 treatment led to significant decrease in hepatic TG content (-82.6% *vs.* vehicle). Time course MRI confirmed the progressive steatosis resolution. Histological analysis further indicated a significant reduction both in hepatic inflammatory gene expression and NAFLD activity score (NAS) (1.3 for HM15211, 3.4 for liraglutide, and 3.0 for vehicle). Next, to evaluate the therapeutic potential in fibrosis, MCD-diet mice were used for an extended period (up to 12 weeks induction) for overt liver fibrosis induction. In line with NASH improvement, HM15211 reduced hepatic hydroxyproline and the fibrosis score. Finally, obese and NASH monkeys were administered with HM15211, and predominant fat mass reduction, and improvement of blood lipid profiles and histological NASH/fibrosis markers were consistently observed in these primates too

Based on these results, HM15211 may provide efficacy for the treatment of NASH and fibrosis. Further studies are needed to assess the clinical relevance of these findings

BACKGROUND

Modulation of multiple aspects of NASH and liver fibrosis by HM15211 in comparison to the action of other drug candidates for NASH



METHODS

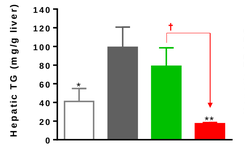
- Therapeutic potential of HM15211 in NASH and fibrosis was evaluated in MCD-diet mice (6 or 12 weeks induction). After 4 ~ 5 weeks treatment of HM15211, liver tissue samples were prepared to measure hepatic TG, TBARS (oxidative stress marker), Inflammation & HSC activation related marker gene expression (TNF-α, F4/80, TGF-β and α-SMA) and fibrosis related marker gene expression (Collagen-1α, and TIMP-1). To non-invasively monitor the changes in hepatic lipid contents, each mouse was subjected to MRI analysis every 2 weeks
- To investigate the therapeutic effects of HM15211 in more human relevance disease model, biopsy-proven obese, NASH, and fibrosis monkeys (BMI >40 kg/m², NAS + fibrosis score > 7) induced by high fat diet for 1 ~ 3 years were utilized. After 12 weeks treatment of HM15211 including 3 weeks titration period, body weight and blood lipid profiles were determined, and liver biopsy samples were subjected to histologic analysis. Liver fat contents were determined by MRI-PDFF
- To determine NAS (NAFLD activity score), the same region of each liver tissue was subjected to H&E staining. For fibrosis analysis, Sirius red staining and hepatic hydroxyproline analysis were performed

RESULTS

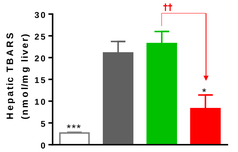
Steatosis and inflammation improvement in MCD mice

Figure 1. Effect of HM15211 on steatosis in MCD-diet mice (n=7)

(a) Hepatic TG



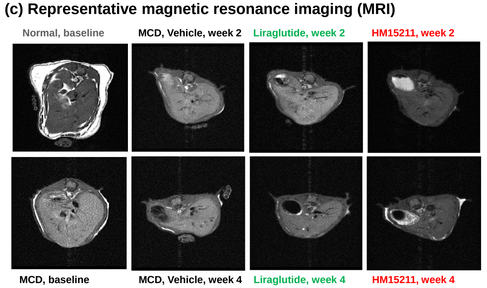
(b) Hepatic TBARS§



* ~ ***p<0.05 ~ 0.001 *vs.* MCD mice, vehicle by One-way ANOVA, † ~ †† p<0.05 ~ 0.01 *vs.* liraglutide by One-way ANOVA

§ TBARS: Thiobarbituric acid reactive substances, oxidative stress marker

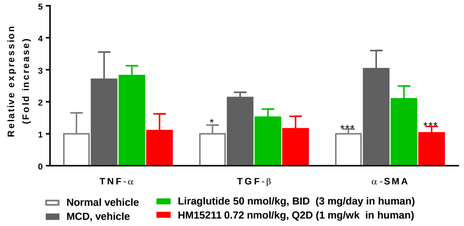
(c) Representative magnetic resonance imaging (MRI)



➢ HM15211 significantly reduced liver TG and TBARS independent of BWL (*data not shown*) in MCD-diet mice, suggesting its direct liver effect on steatosis improvement

Figure 2. Effect of HM15211 on inflammation markers in MCD-diet mice (n=7)

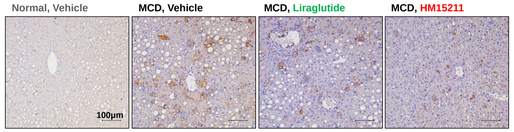
(a) Inflammation and HSC§ activation marker gene expression



* ~ ***p<0.05 ~ 0.001 *vs.* MCD mice, vehicle by One-way ANOVA

§ HSC: Hepatic stellate cell involved in hepatic fibrosis

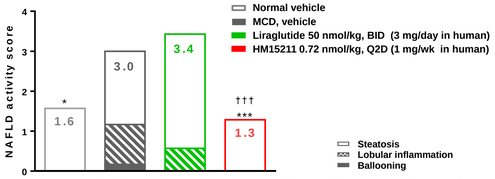
(b) F4/80 staining



➢ HM15211 reduces hepatic inflammation and HSC activation related marker expression, suggesting the anti-inflammatory effects of HM15211

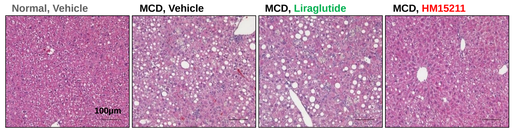
Figure 3. Effect of HM15211 on NASH in MCD-diet mice (n=7)

(a) NAS



* ~ ***p<0.05 ~ 0.001 *vs.* MCD mice, vehicle by One-way ANOVA, †††p<0.001 *vs.* liraglutide by One-way ANOVA

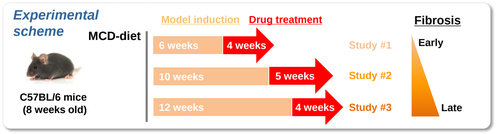
(b) H&E staining



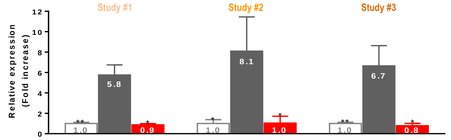
➢ Consistently, HM15211 reduced steatosis, inflammation and ballooning score, thereby completely reversing NAS to normal level in MCD-diet mice

Fibrosis improvement in MCD mice

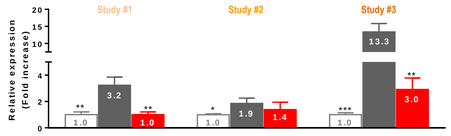
Figure 4. Effect of HM15211 on hepatic fibrosis in MCD-diet mice (n=7)



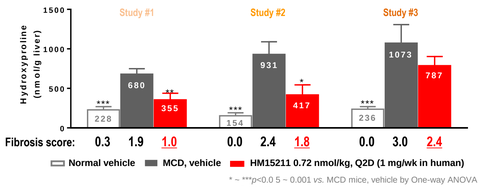
(a) Hepatic collagen-1α1 expression



(b) Hepatic TIMP1§ expression



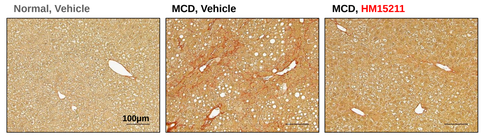
(c) Hepatic hydroxyproline and fibrosis score



* ~ ***p<0.05 ~ 0.001 *vs.* MCD mice, vehicle by One-way ANOVA

§ TIMP1: Tissue inhibitor of metalloproteinases, fibrosis marker

(d) Sirius red staining (from study #1)

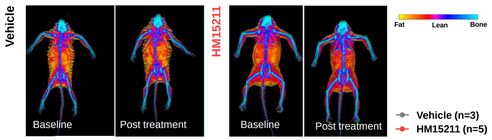


➢ HM15211 not only reduced hepatic expression of collagen-1α1 and TIMP-1, but also reduced hydroxyproline and fibrosis score in MCD-diet mice regardless of fibrosis stage

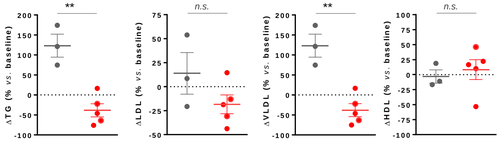
Therapeutic efficacy in obese/NASH monkeys

Figure 5. Effect of HM15211 on body composition and blood lipid profiles in obese/NASH monkeys

(a) DEXA image



(b) Changes in blood lipid profiles

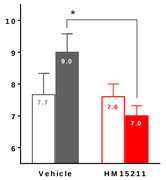


➢ In obese/NASH NHP, HM15211 provided BWL (*data not shown*) via fat mass reduction, and improved blood lipid profiles

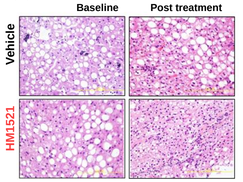
** p<0.01 *vs.* vehicle by un-paired t-test

Figure 6. Effect of HM15211 in obese/NASH monkeys

(a) NAS + Fibrosis score



(b) H&E staining



* p<0.05 *vs.* vehicle by un-paired t-test

Vehicle, baseline
Vehicle, post-treatment (n=3)
HM15211, baseline
HM15211, post-treatment (n=5)

➢ Relatively short-term treatment of HM15211 led to meaningful improvement in NAS + fibrosis score (*vs.* vehicle) in obese/NASH NHP

CONCLUSIONS

- **HM15211, a novel long-acting triple agonist, is designed to treat NASH and fibrosis by targeting both steatosis and hepatic inflammation**
- **In MCD-diet mice, HM15211 not only reduces liver fat and inflammation, but also improves fibrosis regardless of fibrosis stage**
- **Beneficial effects of HM15211 on NASH and fibrosis improvement are well-reproduced in obese/NASH NHP**
- **Therefore, HM15211 might be a novel therapeutic option for NASH and fibrosis**