# Anti-fibrotic potential of a novel long-acting Glucagon/GIP/GLP-1 triple agonist, HM15211, in preclinical models of fibrosis

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## ABSTRACT

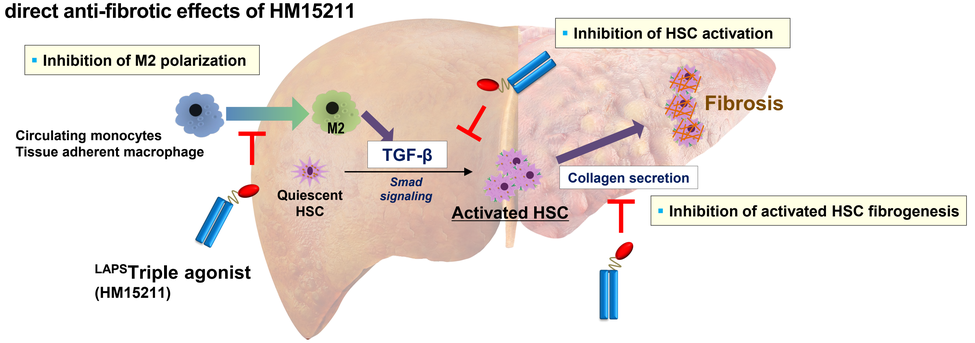

Fibrosis due to nonalcoholic steatohepatitis (NASH) remains a major cause of liver-related mortality. Since complex biological pathways are involved in fibrosis progression, multi-disciplinary therapeutic approaches should be required to effectively deliver treatment effects on fibrosis. For this purpose, we developed a novel long-acting Glucagon/GIP/GLP-1 triple agonist, HM15211. Here, we evaluated the anti-fibrotic effect of HM15211 in various animal models of fibrosis, and investigated underlying mechanism in vitro.

Mice fed with AMLN diet were concomitantly treated with thioacetamide (AMLN/TAA mice) for 16 weeks, and HM15211 was administered during last 8 weeks. HM15211 treatment significantly reduced hepatic (-53.9, -41.4 and -51.9 % vs. vehicle for α-SMA, TIMP-1 and collagen1a1 expression) and blood (-49.3, -48.0 and -49.1% vs. vehicle for TIMP-1, PIIINP and hyaluronic acid level) surrogate markers for fibrosis. HM15211 treatment was also associated with significant reduction in hepatic hydroxyproline (-53.1% vs. Veh) and sirius red positive area (-70.6% vs. Veh) in AMLN/TAA mice. Next, anti-fibrotic effect of HM15211 was further evaluated in choline-deficient and high fat diet (CD-HFD) mice. Strikingly, greater reduction in hepatic hydroxyproline and collagen contents (-4.2, -10.0, -31.2% vs. vehicle for acylated GLP-1, acylated GLP-1/GIP, HM15211) was observed compared to acylated GLP-1 or acylated GLP-1/GIP in CD-HFD mice. Additional in vitro studies in LX2 cell and rat primary hepatic stellate cell (HSC) unveiled that HM15211 could negatively affect multiple steps of TGF-β signaling in HSC.

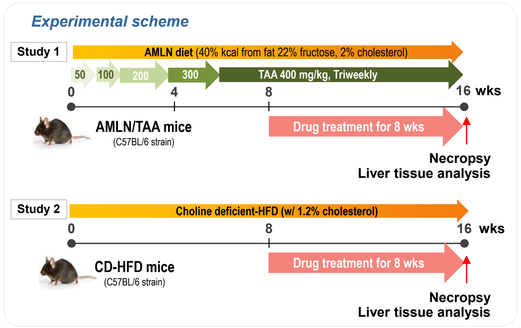
Based on these results, HM15211 may be a novel therapeutic option for liver fibrosis in addition to NASH itself. Hence, related mechanistic studies further highlight direct inhibitory effect of HM15211 on HSC activation. On-going human efficacy study will assess the clinical relevance of these findings.


## BACKGROUND

**Liver fibrosis by hepatic stellate cell (HSC) activation, and proposed modes of action (MoA) for direct anti-fibrotic effects of HM15211**




## METHODS

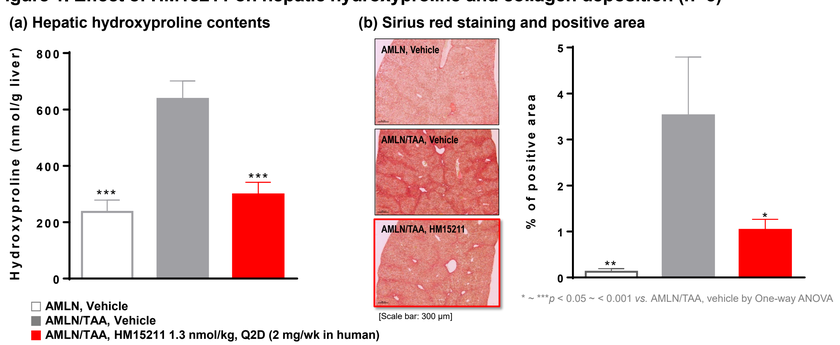



- To evaluate therapeutic effect of HM15211 on hepatic fibrosis, AMLN/TAA [Study 1] or CD-HFD [Study 2] induced hepatic fibrosis models were induced for 16 weeks, and HM15211 was administered during last 8 weeks. After 8 weeks drug treatment, the same region of each liver tissue sample was subjected to analysis related fibrotic conditions and the improvement
- In CD-HFD mice, for efficacy comparison, acylated GLP-1, GLP/GIP, and GLP/GCG [Study 2] were included
- To investigate mode of action (MoA) for direct anti-fibrotic effects of HM15211, TGF-β-induced hepatic stellate cell (HSC) activation was investigated in LX-2 cells (*in vivo*) and rat primary HSCs (*ex vivo*)
- In addition, IL-4/IL-13-induced M2 polarization (TGF-β level, a M2 marker) was determined in PMA-differentiated THP-1 macrophages

## RESULTS

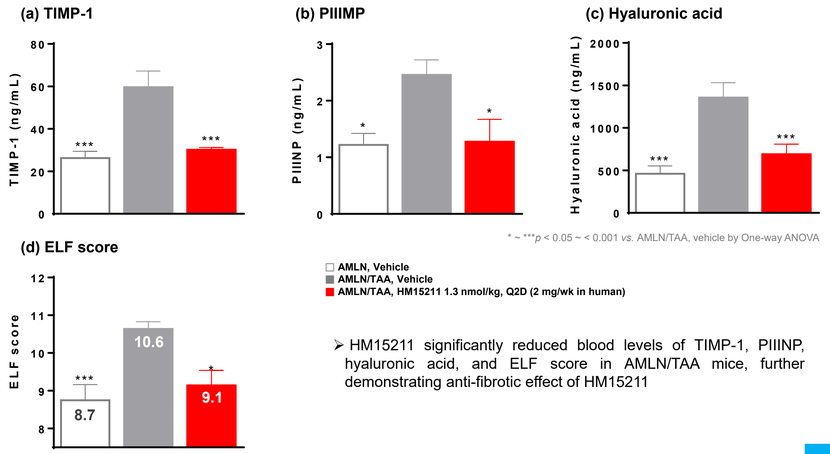
### Improvement of hepatic fibrosis in AMLN/TAA mice

**Figure 1. Effect of HM15211 on hepatic hydroxyproline and collagen deposition (n=5)**




➢ HM15211 treatment significantly reduced Sirius red positive area and hydroxyproline, demonstrating its anti-fibrotic effect

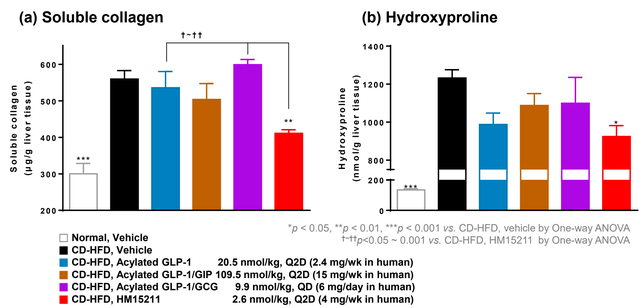
**Figure 2. Effect of HM15211 on blood fibrosis surrogate markers and ELF score**




➢ HM15211 significantly reduced blood levels of TIMP-1, PIIINP, hyaluronic acid, and ELF score in AMLN/TAA mice, further demonstrating anti-fibrotic effect of HM15211

### Fibrosis improvement in CD-HFD mice

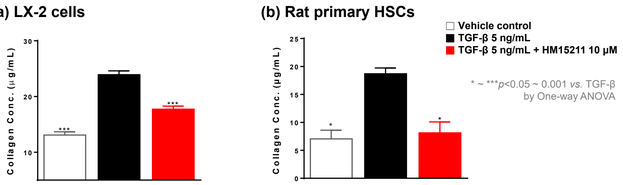
**Figure 3. Effect of HM15211 on hepatic collagen, and hydroxyproline (n=7)**




➢ Only HM15211, but not other incretins, showed robust reduction in hepatic level of soluble collagen, and hydroxyproline, demonstrating potent anti-fibrotic effects of HM15211

### MoAs for direct anti-fibrotic effects of HM15211

**Figure 4. Effect of HM15211 on collagen secretin of HSC**




➢ HM15211 significantly reduced TGF-β-induced collagen secretion both in LX2 cells and rat primary HSCs, indicating inhibitory effect of HM15211 on fibrogenesis of activated HSC

## CONCLUSIONS

- **HM15211 is designed to treat NASH and fibrosis by targeting multiple aspect of the disease**
- **In AMLN/TAA mice and CD-HFD mice, HM15211 shows robust anti-fibrotic effects, and more pronounced treatment benefits than acylated GLP-1RA, GLP/GIP, or GLP/GIP dual agonist were observed**
- **HM15211 inhibits collagen secretion by TGF-β in HSC, which explains direct anti-fibrotic effects of HM15211**
- **P2b study in biopsy-proven NASH subjects is on-going in US to assess clinical relevance of non-clinical findings (fast-track granted, US)**