Anti-fibrotic effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in BDL-induced liver fibrosis mice

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Presenter Disclosure

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Background

Essential role of hepatic stellate cell (HSC) in liver fibrosis
Proposed modes of action (MoA) for direct anti-fibrotic effect by HM15211

*Potent hepatic lipid lowering and MoAs presented (2018 ADA, 1106-P)

*Anti-inflammatory effect and MoAs presented (2020 ADA, 1804-P)

Inhibition of HSC activation

Inhibition of activated HSC fibrogenesis

LAPSTriple agonist (HM15211)
Experimental scheme

C57BL/6 mice (n = 10/group)

BDL: Bile-duct ligation

Drug treatment for 2 wks

Fibrosis onset and progression

Model | Key highlights | Poster #
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AMLN/TAA mice | Anti-inflammatory effect and MoA; Anti-fibrotic effect | 1804-P |
BDL mice | Direct anti-fibrotic effect and MoA | 1803-P |
CDHFD mice | BW loss-independent efficacy in NASH and fibrosis | 1830-P |
Figure 1. HM15211 effect on hepatic hydroxyproline and fibrosis score

- Significant reduction both in hepatic hydroxyproline contents and fibrosis score by HM15211 in BDL mice
- Greater efficacy than obeticholic acid (OCA) suggests more therapeutic benefits of HM15211 in fibrosis

(a) Hepatic hydroxyproline contents
- Study #1
- Study #2

(b) Fibrosis score
- Study #1
- Study #2

Significant reduction both in hepatic hydroxyproline contents and fibrosis score by HM15211 in BDL mice. Greater efficacy than obeticholic acid (OCA) suggests more therapeutic benefits of HM15211 in fibrosis.

- Sham, Vehicle
- BDL, Vehicle
- BDL, Obeticholic acid 30 mg/kg, QD
- BDL, HM15211 1.3 nmol/kg, Q2D (2 mg/wk in human)
Figure 2. HM15211 effect on hepatic collagen deposition (study #1)

- HM15211 treatment was associated with greater reduction in Sirius red positive area than OCA, confirming anti-fibrotic effect of HM15211 in BDL mice

(a) Representative image for Sirius red staining

(b) Sirius red positive area

- Sham, Vehicle
- BDL, Vehicle
- BDL, Obeticholic acid 30 mg/kg, QD
- BDL, HM15211 1.3 nmol/kg, Q2D (2 mg/wk in human)

[Scale bar: 300 μm]

† Similar reduction in Sirius red positive area was observed in study #2 (data not shown)
Consistently, improvement at blood fibrosis surrogate markers further supports anti-fibrotic effect of HM15211. Decrease in blood TGF-β level suggests the mitigation of HSC activation by HM15211.

Figure 3. HM15211 effect on blood surrogate marker level (study #1)

- (a) TGF-β
- (b) TIMP-1
- (c) Hyaluronic acid

Sham, Vehicle
BDL, Vehicle
BDL, Obeticholic acid 30 mg/kg, QD
BDL, HM15211 1.3 nmol/kg, Q2D (2 mg/wk in human)

††† Similar reduction in blood fibrosis surrogate marker was observed in study #2 (data not shown).
Figure 4. HM15211 effect on collagen secretion in HSC

HM15211, but not OCA, reduced TGF-β induced collagen secretion both in LX2 cells and rat primary HSCs, demonstrating direct inhibitory effect of HM15211 on fibrogenesis of activated HSC.

(a) LX2 cells
(b) Rat primary HSCs
Conclusion

• HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist, is designed to treat NASH and fibrosis

• In BDL mice, HM15211 confers significant improvement in fibrosis regardless of model induction period

• Hence, better efficacy than OCA highlights anti-fibrotic effect of HM15211

• HM15211, but not OCA, not only reduced TGF-β production, but also inhibited collagen secretion by HSC in the presence of TGF-β, clarifying negative modulation of HSC activation as a MoA for anti-fibrotic effect by HM15211

• For human efficacy translation, clinical studies in biopsy-proven NASH and fibrosis patients are on-going