Intestinal hypertrophic and Anti-inflammatory potential of a Novel Combination of Long-acting GLP-2 analog (HM15912) and GLP-1RA (efpeglenatide) in Animal model of Inflammatory Bowel Disease

P-491

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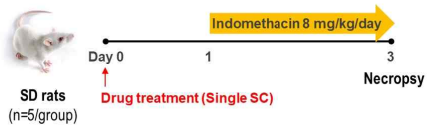
INTRODUCTION

- **Accumulating evidence implicates GLP-2 to have, beyond intestinal growth, a beneficial role in anti-inflammation, and GLP-1 to have, beyond glucose homeostasis, a beneficial role in intestinal growth and anti-inflammation**
- **Both incretin hormones also have beneficial effects on gastrointestinal tract, such as inhibition of gut motility**
- **Based on those pleiotropic actions of both incretins, we hypothesized that combination of HM15912 and efpeglenatide, which are long-acting version of GLP-2 and GLP-1RAs, respectively in our asset, may have synergistic effect on inflammatory bowel disease**

OBJECTIVES AND METHODS

[Study #1]

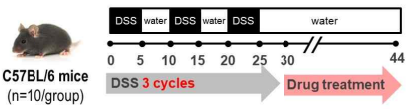
- **Preventive efficacy of HM15912/efpeglenatide combo on intestinal inflammation over anti-TNF-α in a representative animal model of Crohn's disease**
- **Benefit of HM15912/efpeglenatide combo on intestinal inflammation as an anti-TNF-α add-on regimen in a representative animal model of Crohn's disease**



- In the indometacin-induced Crohn's disease model rats, a day after single subcutaneous (SC) administration of HM15912 (3.1 mg/kg), efpeglenatide (0.18 mg/kg), rat anti-TNF-α mAb (0.2 mg/kg) individually or in combination, indometacin (7.5 kg/kg/day) was SC treated for 2 consecutive days to induce inflammation on intestine, and small intestine length, ulcer area (Evans blue staining) were evaluated on day 3.

[Study #2]

- **Therapeutic benefit of HM15912/efpeglenatide combo on intestinal inflammation over Cyclosporin A in a representative animal model of Ulcerative colitis**

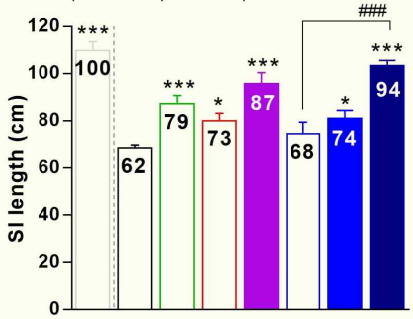


- In Dextran sulfate sodium (DSS)-induced ulcerative colitis model mice, C57BL/6 mice were orally treated with DSS (2% in water) for 5 days followed by stabilization period for next 5 days. This DSS treatment cycle was 2 more repeated before every other day treatment of HM15912 (1.76 mg/kg/Q2D, SC) and efpeglenatide (0.3 mg/kg/Q2D, SC) individually or in combination and daily oral administration of Cyclosporine A (20 mg/kg/QD). After 2 weeks treatment, cumulated disease activity index (DAI), and inflammation score in colon were evaluated.

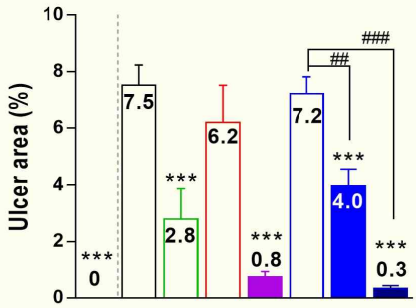
RESULTS

[Study #1] Preventive efficacy after combination with anti-TNF-α in idomethacin-induced IBD model rats (Crohn's disease)

Small intestine length
(Intestinotrophic effect)



Small intestine ulcer area
(Anti-inflammatory effect)



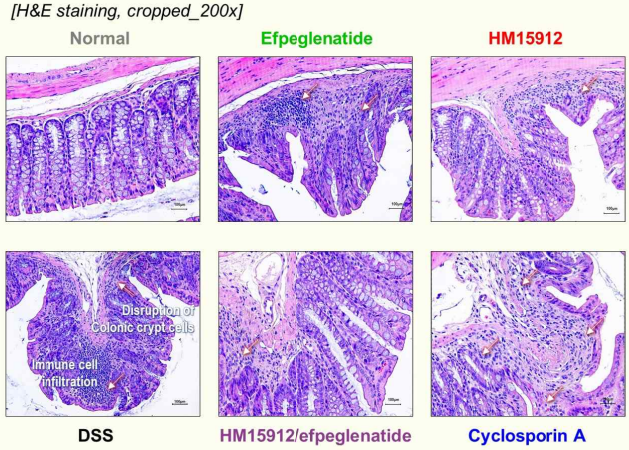
- Normal vehicle
- Indomethacin vehicle
- Efpeglenatide 0.18 mg/kg **[2 mg HED]**
- HM15912 3.1 mg/kg **[35 mg HED]**
- Efpeglenatide + HM15912
- Rat anti-TNF-α mAb 0.2 mg/kg
- Rat anti-TNF-α mAb + HM15912
- Rat anti-TNF-α mAb + HM15912 + Efpeglenatide

*, Significantly different *vs.* Indomethacin vehicle by one way ANOVA test
#, Significantly different *vs.* Rat anti-TNF-α mAb by one way ANOVA test

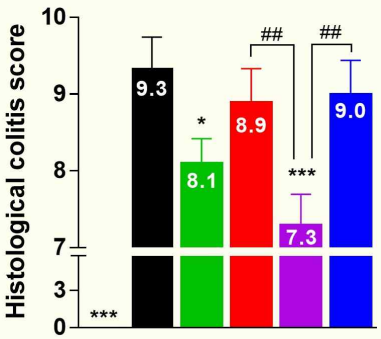
➢Significantly reduced small intestine length in indomethacin vehicle (62% of normal vehicle, $p<0.001$) was recovered by HM15912 and efpeglenatide (73 and 79% of normal vehicle), and fully recovered at normal condition (94% of normal vehicle) by triple combination of HM15912, efpeglenatide, and rat anti-TNF-α mAb. In line with this, ulcer area in small intestine was also drastically alleviated by the triple combination (0.3% *vs.* 7.5% of indomethacin vehicle, $p<0.001$). *HED= Human equivalent dose considering body surface area; 70kg per human*

[Study #2] Therapeutic efficacy in DSS-induced IBD model mice (Ulcerative colitis)

Histology of colon
[H&E staining, cropped_200x]

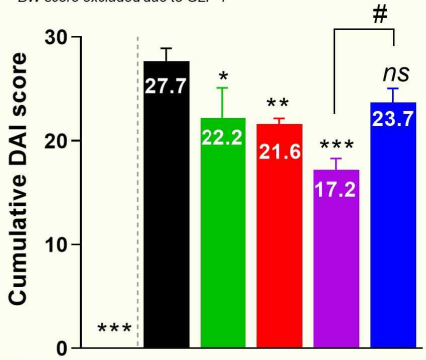


Histological colitis score
[Inflammation severity (3) + extent (3) + Crypt damage (4) + Percent involvement (4)]



- Normal vehicle
- DSS vehicle
- Efpelgenatide 0.3 mg/kg/Q2D **[6 mg/week HED]**
- HM15912 1.76 mg/kg/Q2D **[35 mg/week HED]**

Disease Activity Index
[Stool (4) + Blood (4) + BW scores(4)]
**BW score excluded due to GLP-1*



- HM15912 35 mg HED + Efpeglenatide 6 mg HED
- Cyclosporin A 20 mg/kg/QD

*, Significantly different *vs.*DSS by one-way ANOVA
#, Significantly different *vs.* Combo by one-way ANOVA

➢Cumulative DAI score was significantly reduced by HM15912 ($p<0.01$) or efpeglenatide ($p<0.05$), and further reduced by their COMBO (17.2 *vs* 27.7 in DSS veh., $p<0.001$), while showing non-significant effect in cyclosporine A treated group (23.7). Histological colitis score was also significantly reduced by combination (7.3 *vs* 9.3 in DSS veh., $p<0.001$), whereas cyclosporine A was not significantly effective (9.0).

CONCLUSIONS

A novel combination of long-acting GLP-2 analog, HM15912, and GLP-1RA, efpeglenatide, were additively mitigate inflammation in bowels and recover intestinal atrophy compared to individual treatments, rationally supporting that its combination may be alternative treatment option for IBD based on their intestinotrophic and anti-inflammatory effects.