HM15912, a novel long-acting GLP-2 analog, improves intestinal growth and absorption capacity in rat model of short bowel syndrome

#P6852

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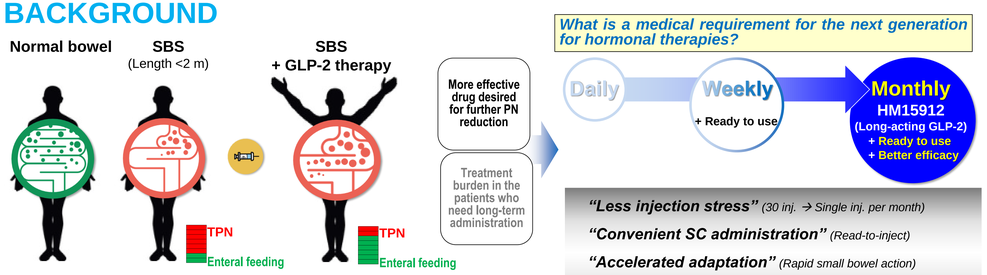
ABSTRACT

Short bowel syndrome (SBS) with intestinal failure requires partial or total parenteral nutrition (PN) to maintain health and growth. However, long-term use of PN may lead to life-threatening complications. Although teduglutide was firstly approved, the widespread use of it is still limited due to insufficient efficacy and leading to a significant burden for patients by daily administration. Hence, there is a medical unmet needs for more effective and longer lasting GLP-2 analog drugs. Here, we investigated the potential therapeutic effect of HM15912, which is currently under clinical development for once a month use, in small bowel resected rat model of SBS.

To evaluate *in vitro* activity of HM15912, cAMP accumulation in CHO cells overexpressed human GLP-2 receptor (GLP-2R) was measured, and HM15912 was potently activated GLP-2R with a full agonistic activity as native human GLP-2 (EC_{50}= 0.327 *vs* 0.173 nM, relative activity= 52.5%). Next, to demonstrate that GLP-2R stimulation by HM15912 results in the production and release of insulin-like growth factor-1 (IGF-1) as a known mechanism of GLP-2, HM15912 was treated to mice primary intestinal subepithelial myofibroblasts (ISEMF). mRNA transcription and protein secretion levels of IGF-1 was dose-dependently increased by treatment of HM15912 ($p < 0.05$ and $p < 0.001$, respectively). Longer-lasting property was evaluated in rats after single administration, and HM15912 exhibited 70-fold extended elimination half-life (42.4 h) compared to teduglutide (0.6 h). Based on this prolonged mode of action with the potent in vitro activity, intestinotrophic effect of HM15912 was investigated in 80% of small intestine (SI) resected jejuno-ileal anastomosis model rats. The SBS rats given HM15912 every week for 2 weeks significantly increased wet weight of jejunum compared to resection vehicle or b.i.d treatment of teduglutide. In addition, HM15912 treated group was associated with a significant increase in absorption capacity of SI such as serum D-xylose concentrations. Furthermore, the mice given HM15912 with various administration intervals for 2 weeks significantly increased SI weight compared to b.i.d treatment of teduglutide (35% over vehicle). In Q2D, Q4D and Q1W dosing intervals of HM15912, SI weights were dose-dependently increased 66~112% ($p < 0.001$), 91~103% ($p < 0.001$) and 55~74% over vehicle ($p < 0.05$~0.001), respectively.

The results supported that small bowel hypertrophic effect of HM15912 are well-correlated with functional improvement of SI in short bowel condition, and superior efficacy to teduglutide was still observed even after once weekly administration in mice. Therefore, HM15912 could be a novel therapeutic option for SBS by providing remarkable small bowel tropic effect with extended administration interval.

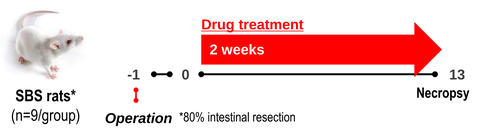
BACKGROUND



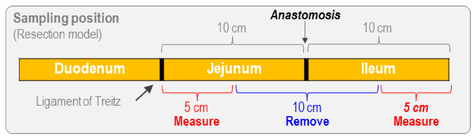
METHODS

Experimental scheme

Study #1 : Intestinotrophic effect in SBS model rats



Study #2 : Intestinotrophic effect according to various dosing regimens in mice



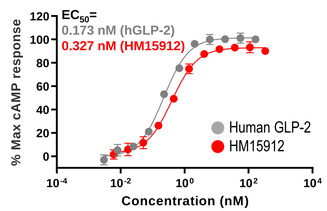
- In study #1, to induce short bowel syndrome, SD rats were resected 80% of small intestine. In this jejuno-ileal resected rats, teduglutide (s.c., BID) or HM15912 (s.c., Q2D) were subcutaneously administered for 2 weeks.
- In study #2, to further investigate benefit of extended dosing interval supporting once monthly administration in human, C57BL/6 mice were treated with teduglutide or weekly GLP-2 analogs by their respective treatment regimen considering the typical treatment regimen in human, or HM15912 by various administration regimens, every other day or once weekly for 2 weeks.

RESULTS

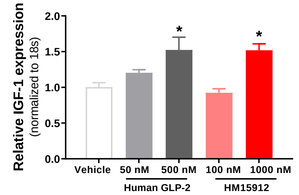
Pharmacological characteristics of HM15912

Fig. 1 *In vitro* activity of HM15912 and its IGF-1 related mode of action

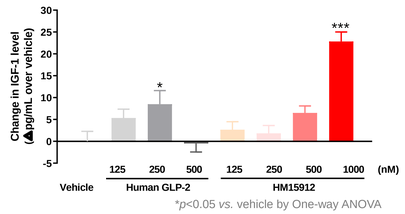
(a) *In vitro* activity of HM15912



(b) IGF-1 mRNA expression



(c) IGF-1 protein secretion

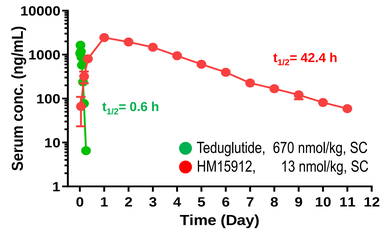


*p<0.05 vs. vehicle by One-way ANOVA

➢ (a) GLP-2 analogs increased intracellular cAMP level in dose-dependent manner with maximal efficacy similar to the native human GLP-2. (b) Both human GLP-2 (500 nM) and HM15912 (1000 nM) significantly increased the levels of IGF-1 mRNA expression by approximately 1.5 fold compared to vehicle. (c) After 180 minutes of treatment, both human GLP-2 (250 nM) and HM15912 (1000 nM) showed a significantly increased secreted protein levels of IGF-1.

Prolonged duration of action

Fig. 2 Pharmacokinetics in rats

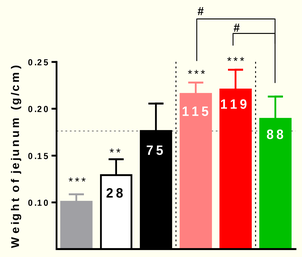


➢ HM15912 exhibited 70-fold extended elimination half-life (42.4 hours) compared with teduglutide in SD rats (0.6 hours).

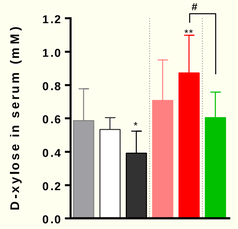
Study #1, Intestinotrophic efficacy in SBS model rats

Fig. 3 Significant intestinotrophic effect compared to teduglutide in SBS model rats

(a) Weight of jejunum



(b) Serum D-xylose level



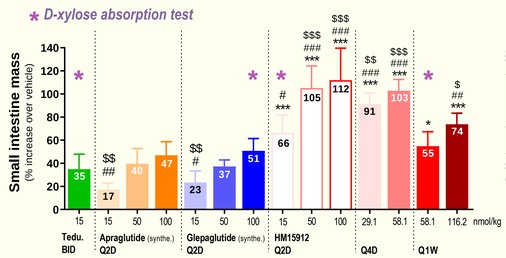
Non-operation vehicle
Sham-operation vehicle
Resection vehicle
Teduglutide, 30.0 nmol/kg/BID, SC **[0.05 mg/kg/day HED]**
HM15912, 4.5 nmol/kg/Q2D, SC **[0.06 mg/kg/week HED]**
HM15912, 30.0 nmol/kg/Q2D, SC **[1.0 mg/kg/week HED]**

➢ (a) In 80% jejuno-ileal resected rats, HM15912 treatment significantly increased wet weight of jejunum compared to resection vehicle or teduglutide treated group, but this is not the case of ileum (*Not shown*). (b) HM15912 treated group was associated with a significant increase in absorption capacity of small intestine based on serum D-xylose concentrations. *HED= Human equivalent dose considering body surface area*

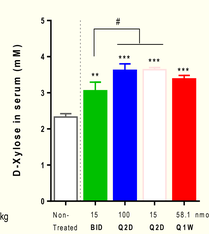
Study #2, Intestinotrophic efficacy via various dosing intervals

Fig. 4 Significant intestinotrophic effect compared to daily and weekly GLP-2 analogs in C57BL/6 mice

(a) Small intestine mass



(b) Serum D-xylose level



Teduglutide 15.0 nmol/kg/BID, SC **[E_{max}]**
Apraglutide (Synthesized) ~100 nmol/kg/Q2D, SC **[~10 mg/week HED]**
Glepaglutide (Synthesized) ~100 nmol/kg/Q2D, SC **[~10 mg/week HED]**
HM15912 (weekly) ~100 nmol/kg/Q2D, SC **[~1.5 mg/kg/week HED]**
HM15912 (Biweekly) ~58.1 nmol/kg/Q4D, SC **[~0.9 mg/kg/bi-weekly HED]**
HM15912 (Monthly) ~116.2 nmol/kg/QW, SC **[~ 2 mg/kg/month HED]**

*, Significantly differ. *vs.* Teduglutide
#, Significantly differ. *vs.* Apraglutide
$, Significantly differ. *vs.* Glepaglutide
by one way ANOVA test

➢ (a) In normal mice, all administration regimens of HM15912 significantly increased small intestine (SI) mass than teduglutide and weekly GLP-2 analogs. At equimolar dose with Q2D, HM15912 significantly increased SI mass than weekly GLP-2 analogs (112% vs 47% and 51% over vehicle). Even after weekly administration of HM15912 mimicking once a month in human, it also significantly increased SI mass (74% over vehicle) than weekly GLP-2 analogs (47% and 51% over vehicle).

CONCLUSIONS

- **HM15912, novel long-acting GLP-2 analog, significantly improved not only small intestinal growth but also nutrition absorbing capacity than teduglutide as well as weekly GLP-2 analogs, which are currently under clinical development, even with a less dosing frequency, supporting that HM15912 will provide a better treatment option to SBS patients in terms of remarkable small bowel tropic effect and more extended administration interval.**