Beneficial effects of a long-acting GLP-2 analog, HM15912, after switching from daily or weekly GLP-2 analog drugs in animal model

#P95

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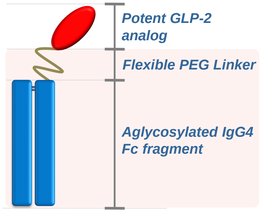
BACKGROUND

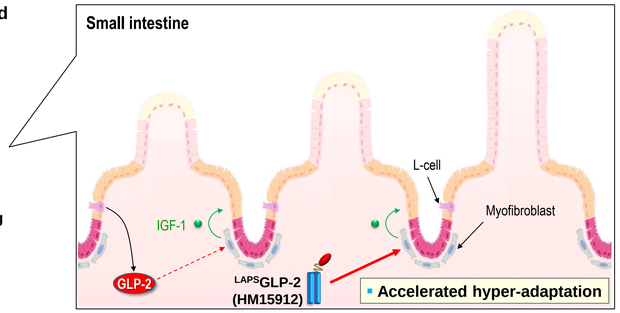
HM15912, a long-acting GLP-2 analog, provided significant morphological and functional improvement in small intestine compared to daily or weekly GLP-2 medications via substantially extended half-life and systemic exposure

HM15912 is conjugated with a human IgG4 Fc *via* flexible PEG linker, and has a same biological mode of action with human GLP-2 via IGF-1



[General profile]

- Rationally designed GLP-2 analog to have a more potent intestinotrophic action *vs* human GLP-2
- Extended half-life allows once-monthly dosing in human
- Ready-to-inject with soluble formation



This figure was modified from the following reference, *AJP-GI 307: G1147–G1168 (2014)*

LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

AIMS

- **Previously, HM15912 showed substantially extended half-life and systemic exposure compared to daily GLP-2 drug, teduglutide. Also, HM15912 significantly increased small intestine mass compared to teduglutide and weekly GLP-2 analog drugs, identical sequences with apraglutide or glepaglutide, even after extended dosing interval.**
- **To clearly investigate a beneficial effect of HM15912 over than teduglutide and weekly GLP-2 analogs, which are currently under clinical development, intestinotrophic effect after switching from daily or weekly GLP-2 analog drugs to HM15912 was evaluated.**

METHODS

Experimental scheme

Study #1 : Daily GLP-2 → HM15912 switching
(Teduglutide)

C57BL/6 mice
(n=6/group)

Typical treatment — 2 weeks
Switching — 2 weeks
4 weeks

Study #2 : Weekly GLP-2 analog drugs → HM15912 switching
*(Apraglutide or Glepaglutide)**

SD rats
(n=6/group)

Typical treatment — 2 weeks
Switching — 2 weeks
4 weeks

* In-house synthesized

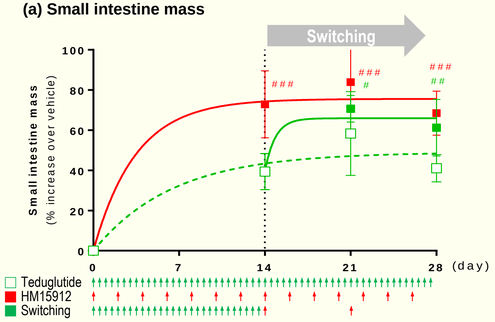
- In study #1, additional intestinotrophic efficacy after switching from teduglutide to HM15912 was investigated. C57BL/6 mice treated with twice daily administration (mimicking once daily in human) of teduglutide for 2 weeks (efficacy plateau) were switched to once-weekly administration (mimicking once monthly in human) of HM15912, or continued the typical treatment of teduglutide for the remaining 2 weeks.
- In study #2, additional intestinotrophic efficacy after switching from weekly GLP-2 analog drugs to HM15912 was investigated. GLP-2 analogs designed to have same sequences with glepaglutide and apraglutide were synthesized in-house. SD rats treated with every other day administration (mimicking once weekly in human) of weekly GLP-2 analogs for 2 weeks were switched to HM15912 or continued the typical treatment of them for the remaining 2 weeks.
- In both studies, small intestine wet mass was measured at week 2, 3 and 4, and blood D-xylose concentrations were measured to evaluate absorption capacity after oral challenge of D-xylose at the end of study.

RESULTS

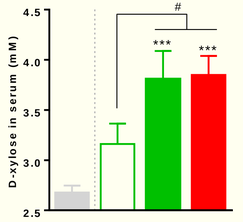
Beneficial effects after switching from daily GLP-2 analog to HM15912

Figure 1. Additional intestinotrophic efficacy after switching from teduglutide to HM15912 in C57BL/6 mice (Study #1)

(a) Small intestine mass



(b) D-xylose absorption at week 4



Vehicle
Teduglutide — 15.0 nmol/kg/BID **[E_{max}, EPAR]**
Teduglutide → HM1591 2 — 15.0 nmol/kg/BID → 58.1 nmol/kg/QW **[1.0 mg/kg/month HED]**
HM15912 — 16.6 nmol/kg/Q2D **[0.25 mg/kg/week HED]**

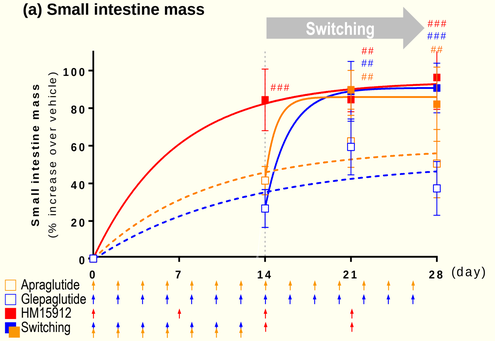
*p<0.05 *vs.* vehicle by One-way ANOVA
#p<0.05 *vs.* Teduglutide by One-way ANOVA

➢HM15912 treatment significantly increased small intestine mass compared to teduglutide treated group after 2 weeks. After 2 more weeks treatment, while showing the maintained small intestine increment in teduglutide treated group, small intestine mass was further increased after switching to HM15912. In consensus with small intestine mass increment, absorption capacity was also significantly increased after switching to once weekly administration of HM15912, which is mimicking once monthly administration in human.

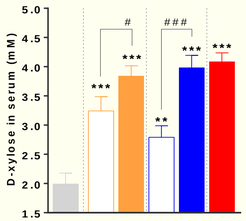
Beneficial effects after switching from weekly GLP-2 analog drugs to HM15912

Figure 2. Additional intestinotrophic efficacy after switching from apraglutide and glepaglutide to HM15912 in SD rats (Study #2)

(a) Small intestine mass



(b) D-xylose absorption at week 4



Vehicle
Apraglutide (Synthesized) — 63.7 nmol/kg/Q2D **[10 mg/week HED]**
Glepaglutide (Synthesized) — 55.6 nmol/kg/Q2D **[10 mg/week HED]**
Apraglutide (Synthesized) → HM15912 — 63.7 nmol/kg/Q2D → 57.9 nmol/kg/QW
Glepaglutide (Synthesized) → HM15912 — 55.6 nmol/kg/Q2D → 57.9 nmol/kg/QW
HM15912 — 57.9 nmol/kg/QW **[2 mg/kg/month HED]**

*p<0.05 *vs.* vehicle by One-way ANOVA
#p<0.05 *vs.* weekly GLP-2RA (synthesized) by One-way ANOVA

➢HM15912 treatment significantly increased small intestine mass compared to weekly GLP-2 analog drug treated groups after 2 weeks. After 2 more weeks treatment, while showing the slight increment in small intestine mass in weekly GLP-2 analogs, small intestine mass was further increased after switching to HM15912. In consensus with small intestine mass increment, absorption capacity was also significantly increased after switching to once weekly administration of HM15912, which is mimicking once monthly administration in human.

CONCLUSIONS

- **Significant improvement in intestinal morphology and function after switching from competitors to HM15912 with an extended administration interval mimicking once-a-month in human supports that HM15912 will provide benefits for less PN dependency and more convenient treatment option to SBS patients, who are still suffered from parenteral support with typical GLP-2 medication, such as teduglutide or weekly GLP-2 analog drugs in clinical development.**