ASPEN 2021 Nutrition Science & Practice Conference

Intestinotrophic effect of a novel long-acting GLP-2 analog, HM15912, in animal model for short bowel syndrome and potential as monthly administration

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Hanmi

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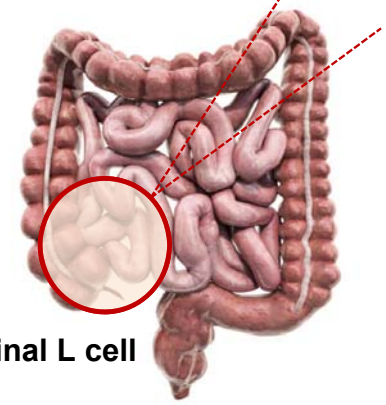
Disclosures

Employee of Hanmi Pharm. Co., Ltd.

What GLP-2 is



Intestinal L cell

Proglucagon

Glicentin

GRPP

OXM

GLP-1

IP2

33 amino acids

GLP-2

Various biological actions

↓ Food intake

↓ Bone resorption

↓ Gastric motility & secretion

↑ Energy absorption & mucosal morphology
- Intestinal growth
- Mucosal integrity

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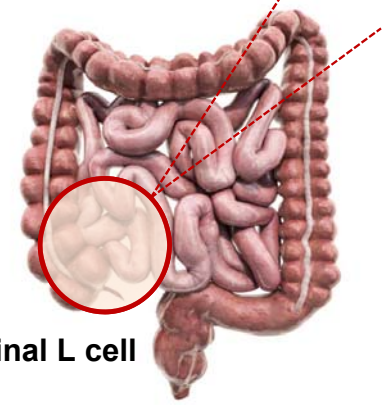

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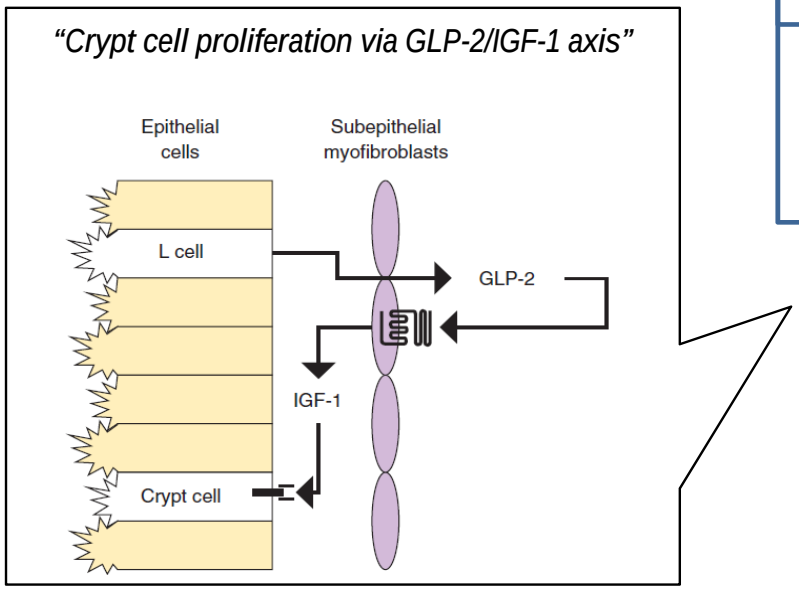

Various biological actions

- ↓ Food intake
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- ↑ Energy absorption & mucosal morphology
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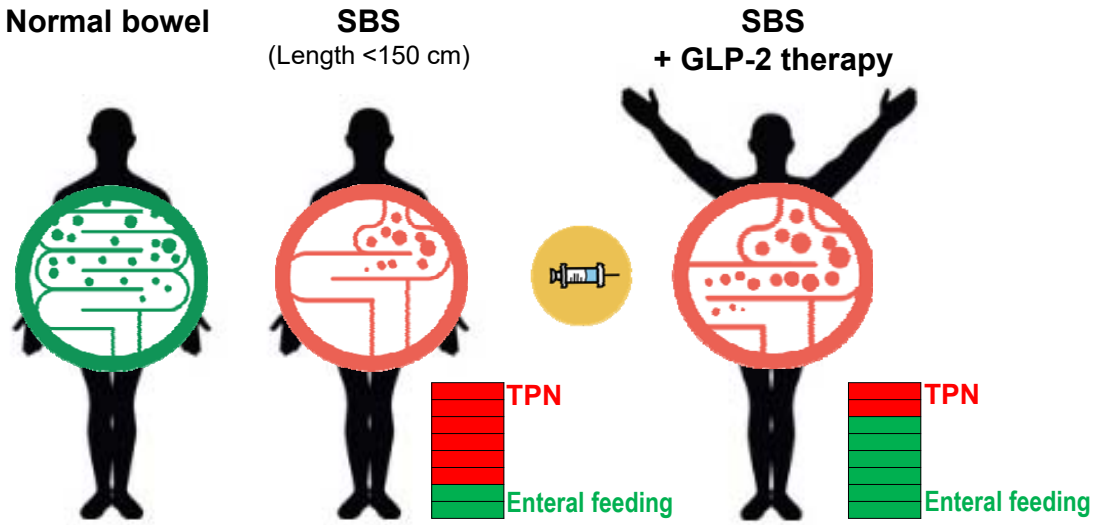
Treatment goal of Short bowel syndrome and benefits of GLP-2 therapy



Patients on IV nutrition

Suffer from malnutrition, liver failure, sepsis
Especially, 50% of pediatric patients died ≤ age 3

GLP-2 receptor agonist is ideal therapy

↓ PN dependency, ↑ patient's quality of life, But …

Treatment burden in the patients who need long-term administration

More effective drug desired for further PN reduction

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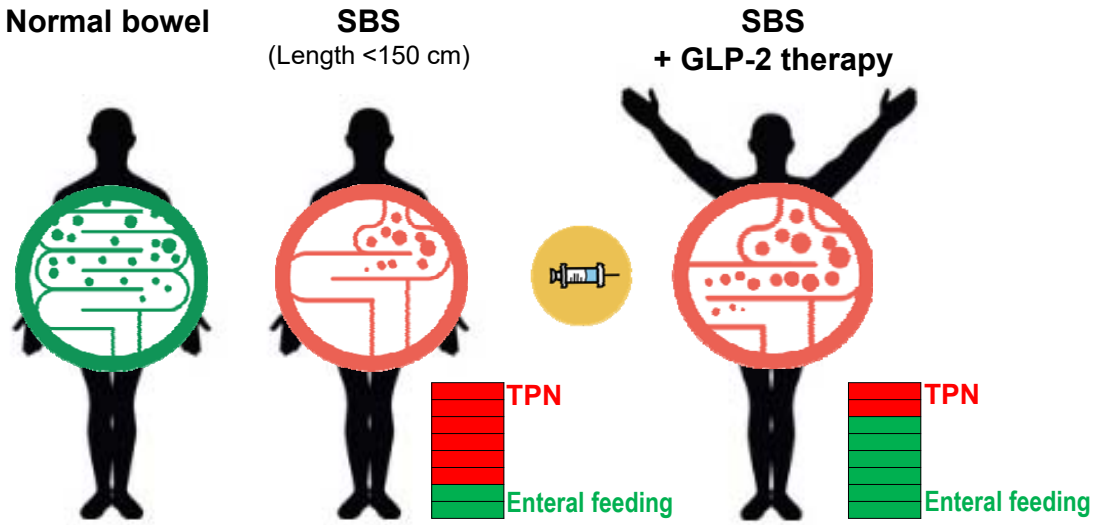

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What is a medical requirement for the next generation for hormonal therapies?

Daily → Weekly + Ready to use → **Monthly HM15912** + Ready to use + Better efficacy

- ***"Less injection stress"*** *(30 inj. → Single inj. per month)*
- ***"Convenient SC administration"*** *(Read-to-inject)*
- ***"Accelerated adaptation"*** *(Rapid small bowel action)*
- ***"Increase in PN wean-off rate"*** *(Potent intestintrophic effect)*

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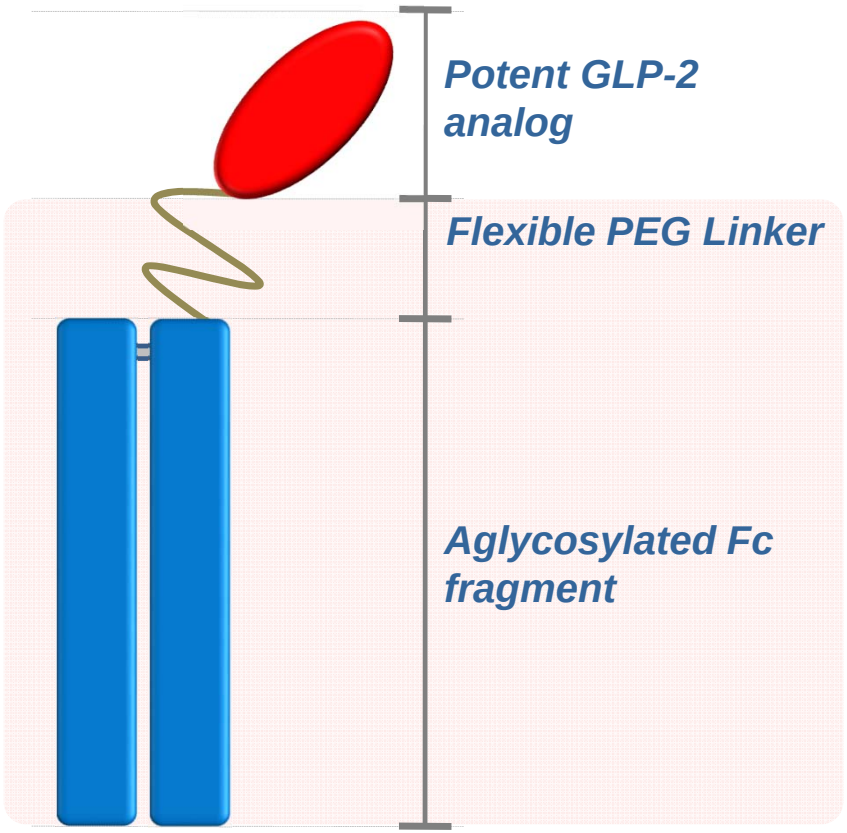
What a long-acting GLP-2 analog is



LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

Hanmi's GLP-2 analog (HM15912) is conjugated with a human IgG4 Fc fragment *via* flexible linker

[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**
- **Ready-to-inject with soluble formation**
- **Significant intestinotrophic efficacy in animal models**

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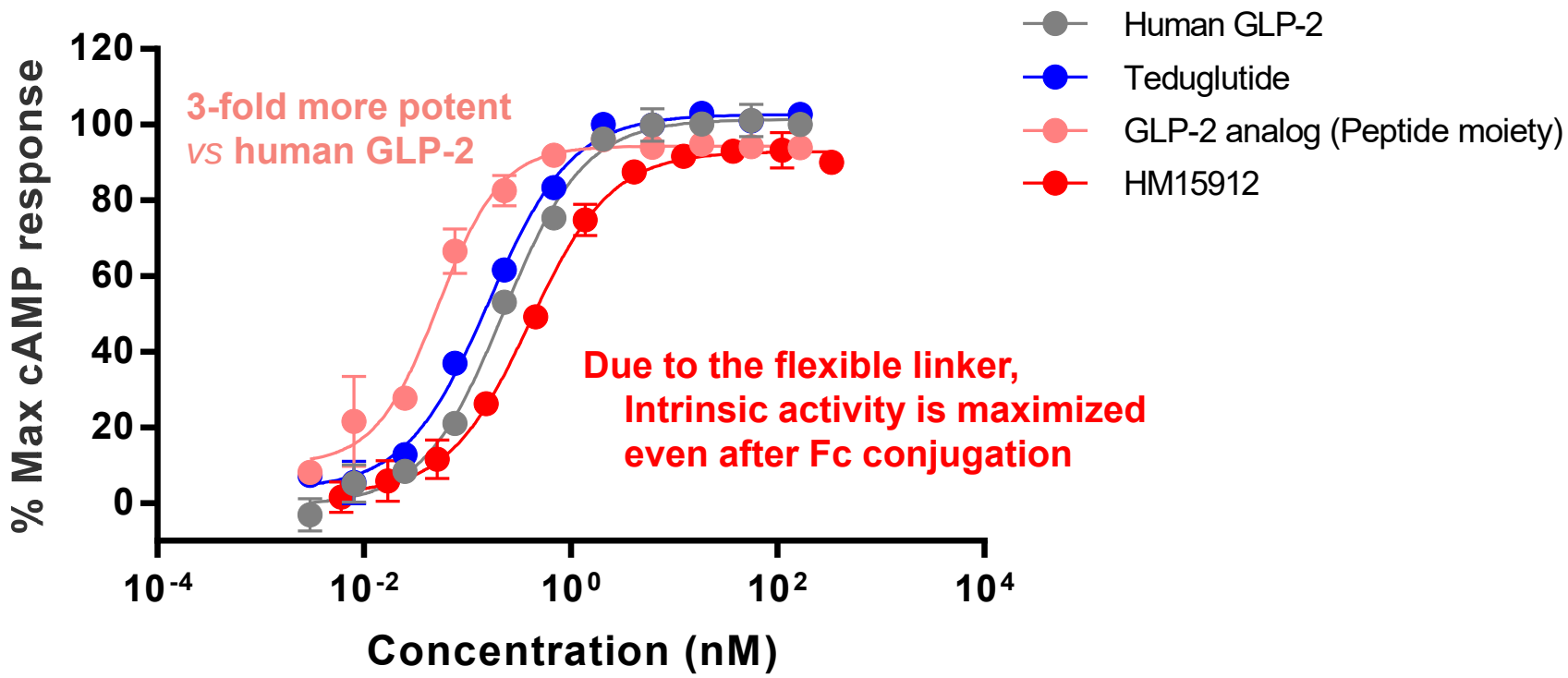
Potent intrinsic activity and high sequence homology with human GLP-2



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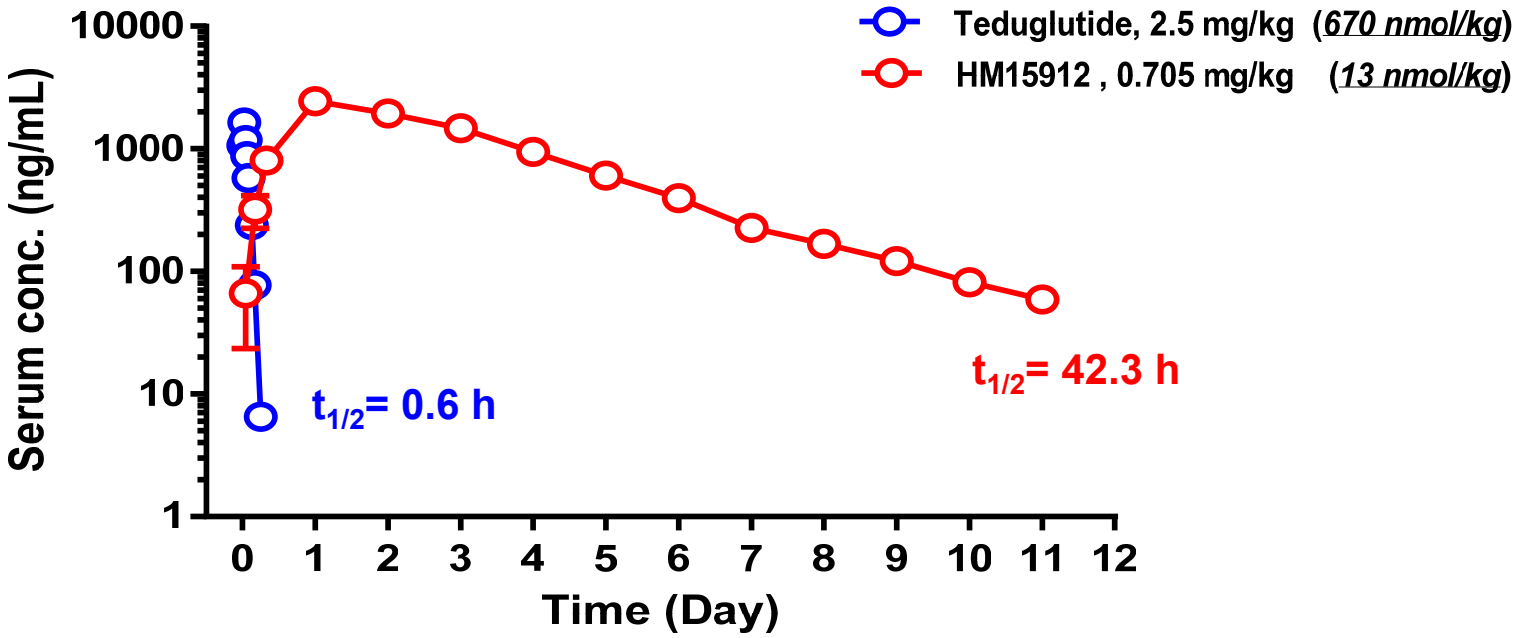
Pharmacokinetics in rodent



Materials	Dose-normalized AUC (ng*hr/mL per μg/kg)
Teduglutide	1.0
HM15912	283.3

Hypothesis & study methods

HM15912, long-acting GLP-2 analog, is desired to have therapeutic potential for short bowel syndrome with significant efficacy

Purpose		Species / Strain	Induction method	Presentation No.
1. Therapeutic potential	**Efficacy in pathophysiological condition of SBS**	 Sprague dawley rat	80% jejunoileal resection	-
2. Monthly potential	**Various dosing interval**	 C57BL/6 mice	Normal	
3. Best-in-class efficacy	Switching from **Weekly GLP-2 drugs**	 Sprague dawley rat	Normal	**#P95** (Poster)
	Switching from **Daily GLP-2 drug**	 C57BL/6 mice	Normal	

#P116: A First-in-Human, Double-blinded, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of HM15912 in Healthy Korean Subjects

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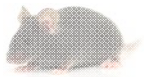
	Switching from Daily GLP-2 drug	 C57BL/6 mice	Normal	

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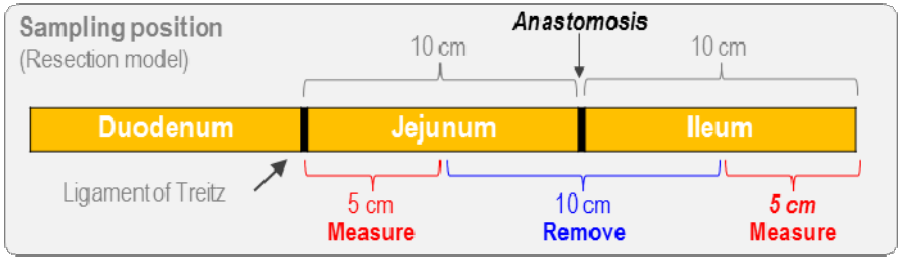
Intestinotrophic efficacy in SBS model rats

Experimental design

SBS rat
(n=9, 80% intestinal resection)

Operation

-1 — **0** **Drug treatment** **2 weeks** **13** **Necropsy**



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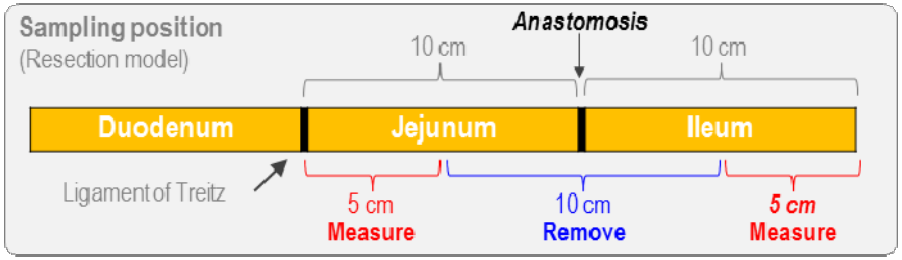
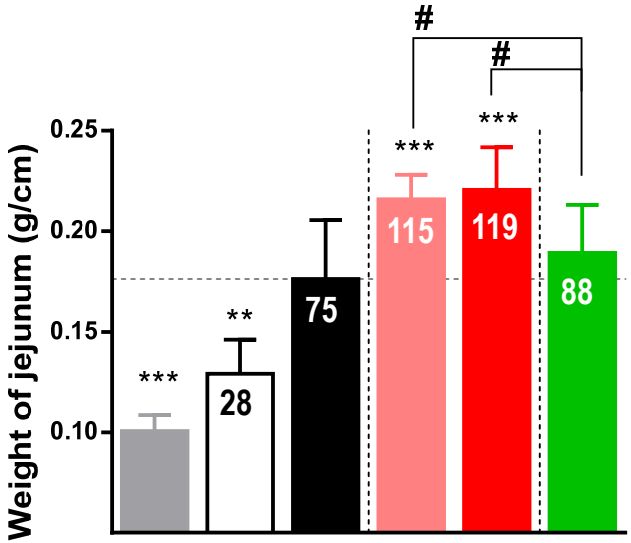


Weight of Jejunum (*Physical improvement*)



- Non-operation
- Sham-operation
- 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]**

*, Significantly differ. vs. Non-operation by one way ANOVA test
#, Significantly differ. vs. teduglutide by one way ANOVA test

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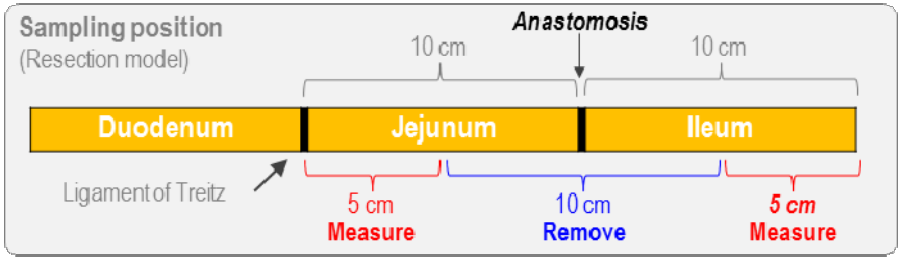

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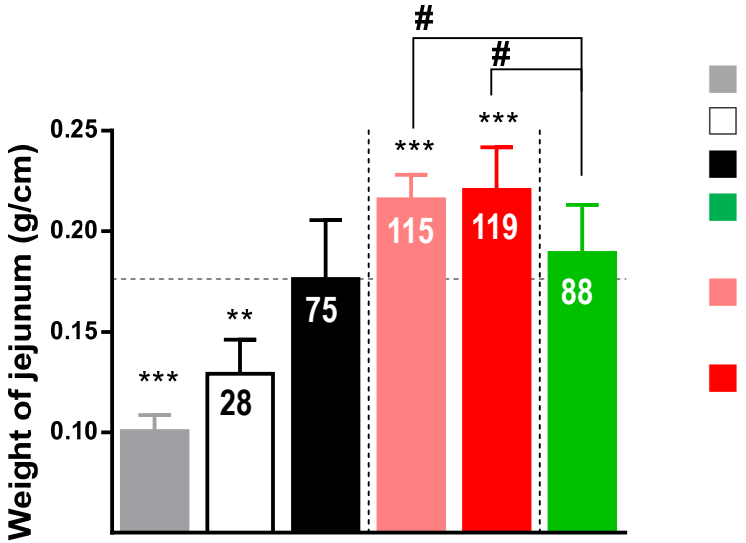

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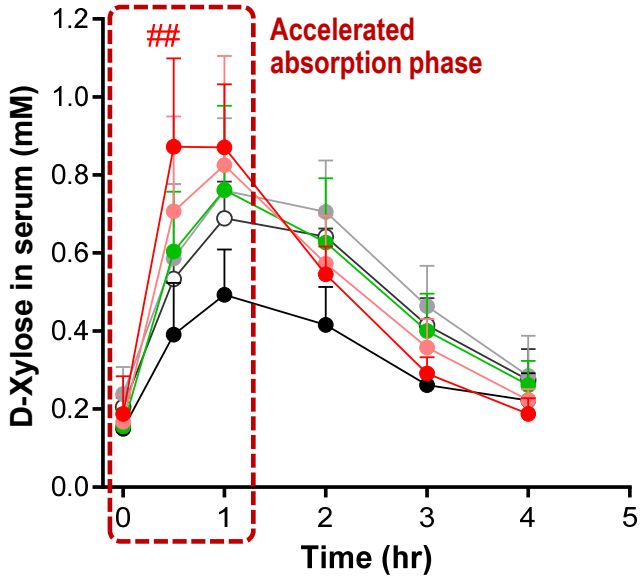
D-Xylose absorption (*Functional improvement*)



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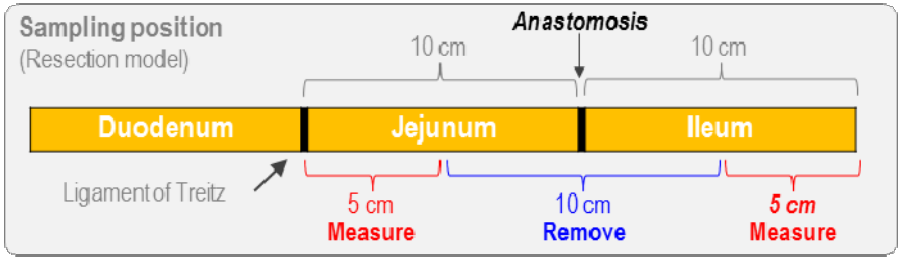

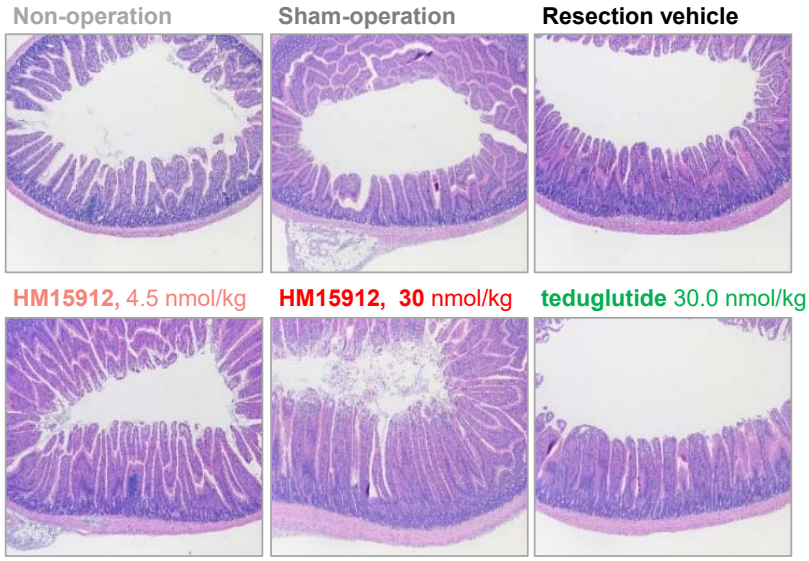

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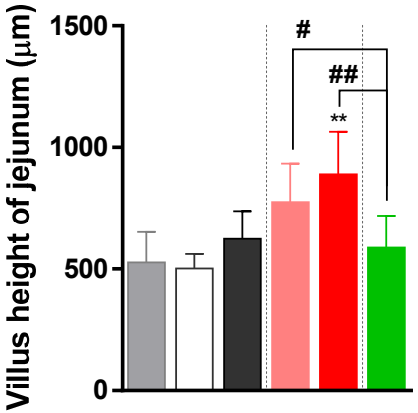
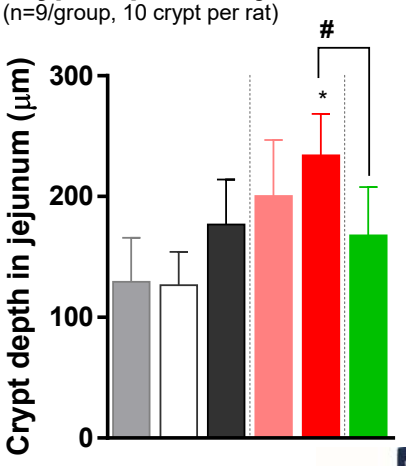
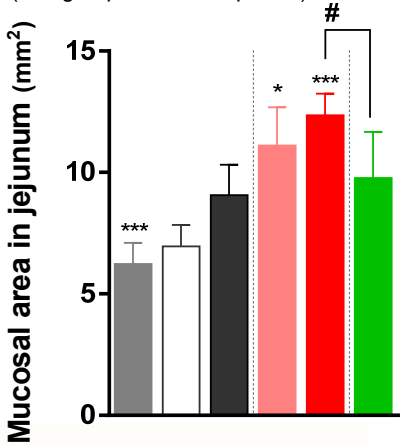
Villus height in Jejunum
(n=9/group, 10 villi per rat)



Crypt depth in Jejunum
(n=9/group, 10 crypt per rat)



Mucosal area in Jejunum
(n=9/group, 2 sections per rat)



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Intestinotrophic efficacy in the various dosing intervals

Experimental design

C57BL/6 mice
(8 weeks old, n=5)

Drug treatment (Weekly, Bi-weekly, Monthly)

2 weeks

Body weight
Small intestine mass
D-xylose absorption

Teduglutide	0.2xHED, QD	**[E_{max}, EPAR]**
Apraglutide (Synthesized)	~10 mg/week	HED
Glepaglutide (Synthesized)	~10 mg/week	HED
HM15912 (weekly)	0.2~1.5 mg/kg/week	HED
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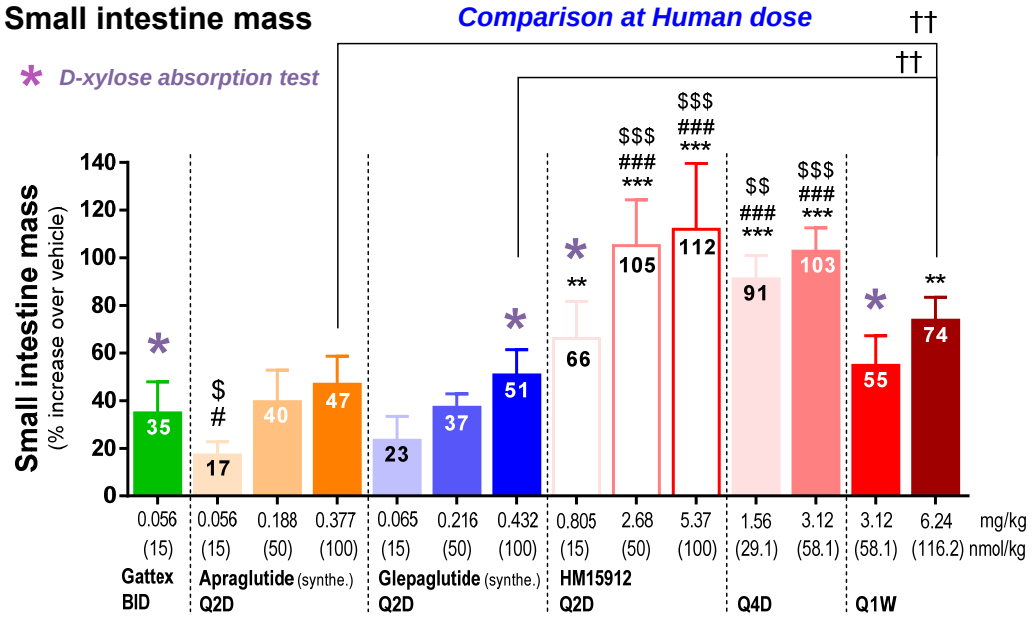

*, Significantly differ. vs. Teduglutide by one way ANOVA test
†, Significantly differ. by unpaired T-test

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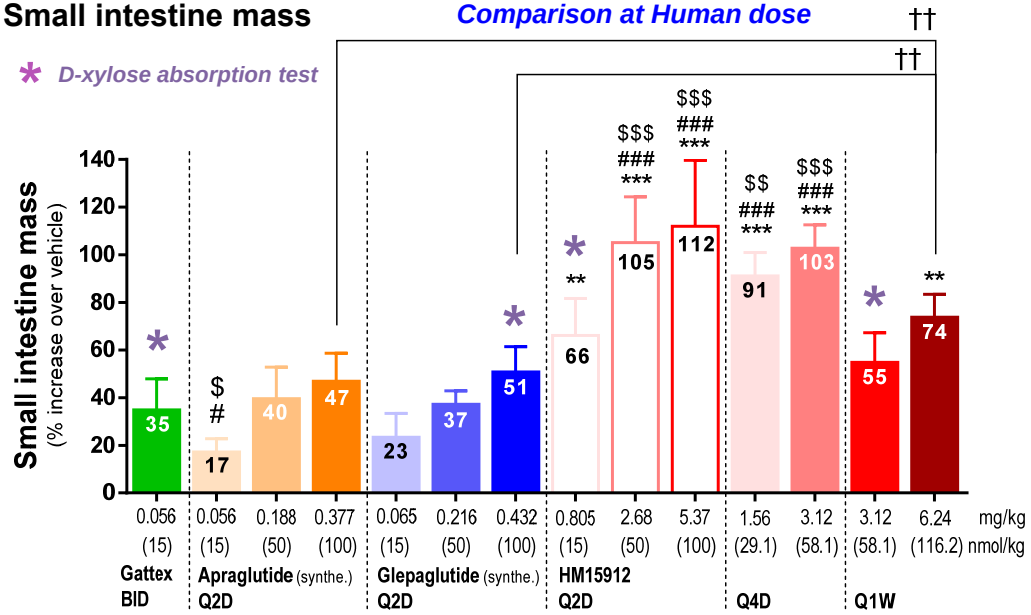
Small intestine mass — *Comparison at Human dose*



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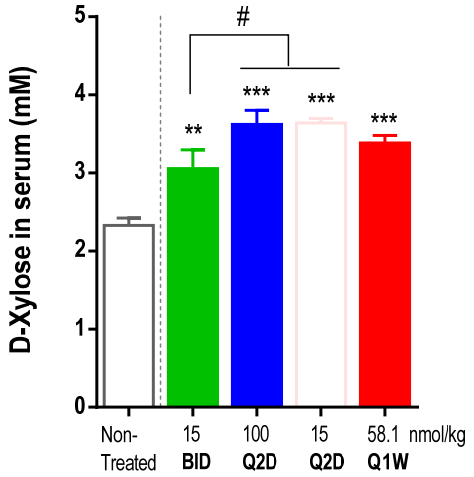
D-xylose absorption



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Executive summary

- **Maximize remnant intestinal absorptive capacity and wean off PN, has become the focus and breakthrough point of SBS treatment. For this, teduglutide was firstly approved based on its intestinotrophic effect**
- **The only approved GLP-2 drug may have a limited efficacy due to insufficient exposure during treatment period**
- **HM15912 is rationally designed to have potent intrinsic activity via minimal sequence modification, and substantially extended half-life and systemic exposure compared to daily GLP-2 drug, tedugltudie.**
- **In 80% jejuno-ileal resection rats, HM15912 led to the greater efficacy than teduglutide**
- **In mice, HM15912 led to the greater efficacy than weekly GLP-2 drugs, currently under clinical development, even after human monthly mimic dosing regimen**

- HM15912 will provide a more convenient dosing regimen (once monthly, ready-to-use) **possibly with the significant intestinotrophic efficacy to the patients suffered from intestinal failure caused by short bowel syndrome**

- ODD granted in US and EU, RPD in US, and P2 clinical study is on-going in SBS patients (US)

Please note poster presentation reporting more information about HM15912:

#P95 Beneficial effects of a long-acting GLP-2 analog, HM15912, after switching from daily or weekly GLP-2 analog drugs in animal model

#P116 A First-in-Human, Double-blinded, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of HM15912 in Healthy Korean Subjects

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