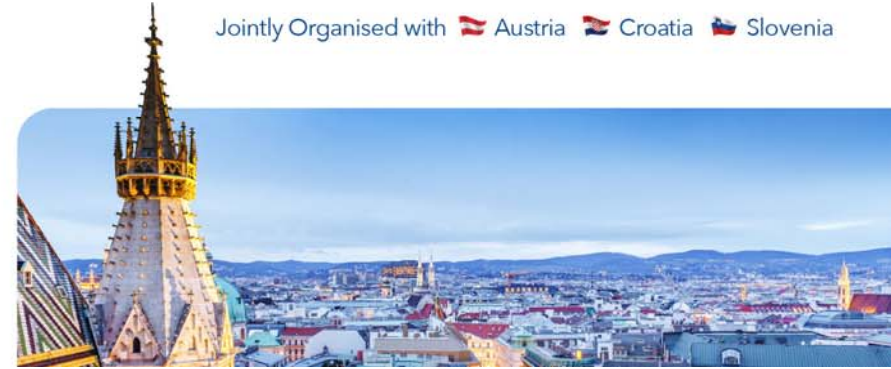




3-6 Sept 2022
VIENNA ESPEN
CONGRESS
ON CLINICAL NUTRITION & METABOLISM
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Pharmacological benefits of multifaceted mode of action for a novel combination of long-acting GLP-2 analog (HM15912) and **GLP-1RA** (efpeglenatide) in animal model of inflammatory bowel disease

Jaehyuk Choi, Jin Bong Lee, Eun Jin Park, Jung Kuk Kim, Sungmin Bae, Daejin Kim, Sang Hyun Lee, In Young Choi

 **Hanmi Pharm. Co., Ltd.**



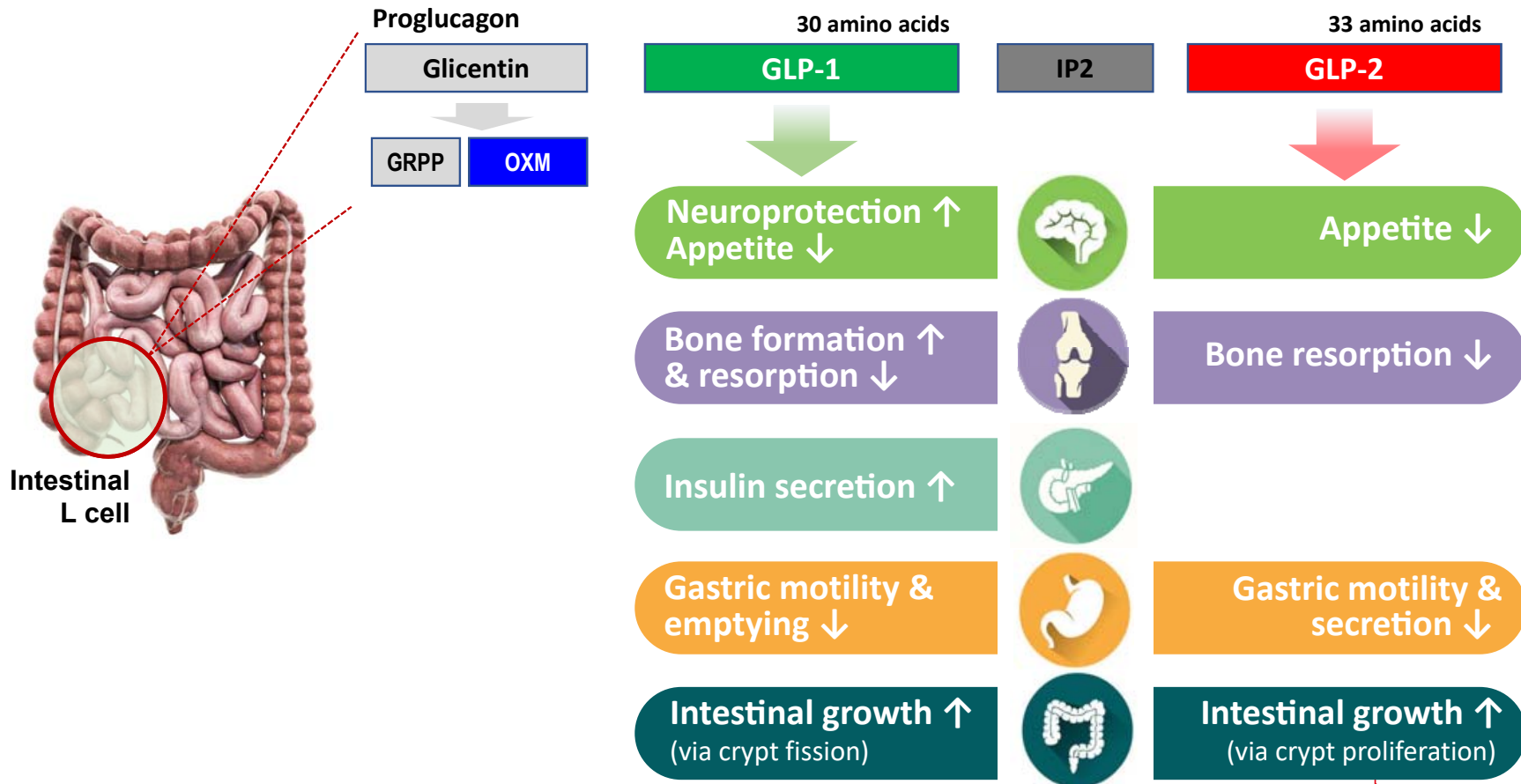
Disclosure for *Jaehyuk Choi*

In compliance with COI policy, ESPEN requires the following disclosures to the session audience:

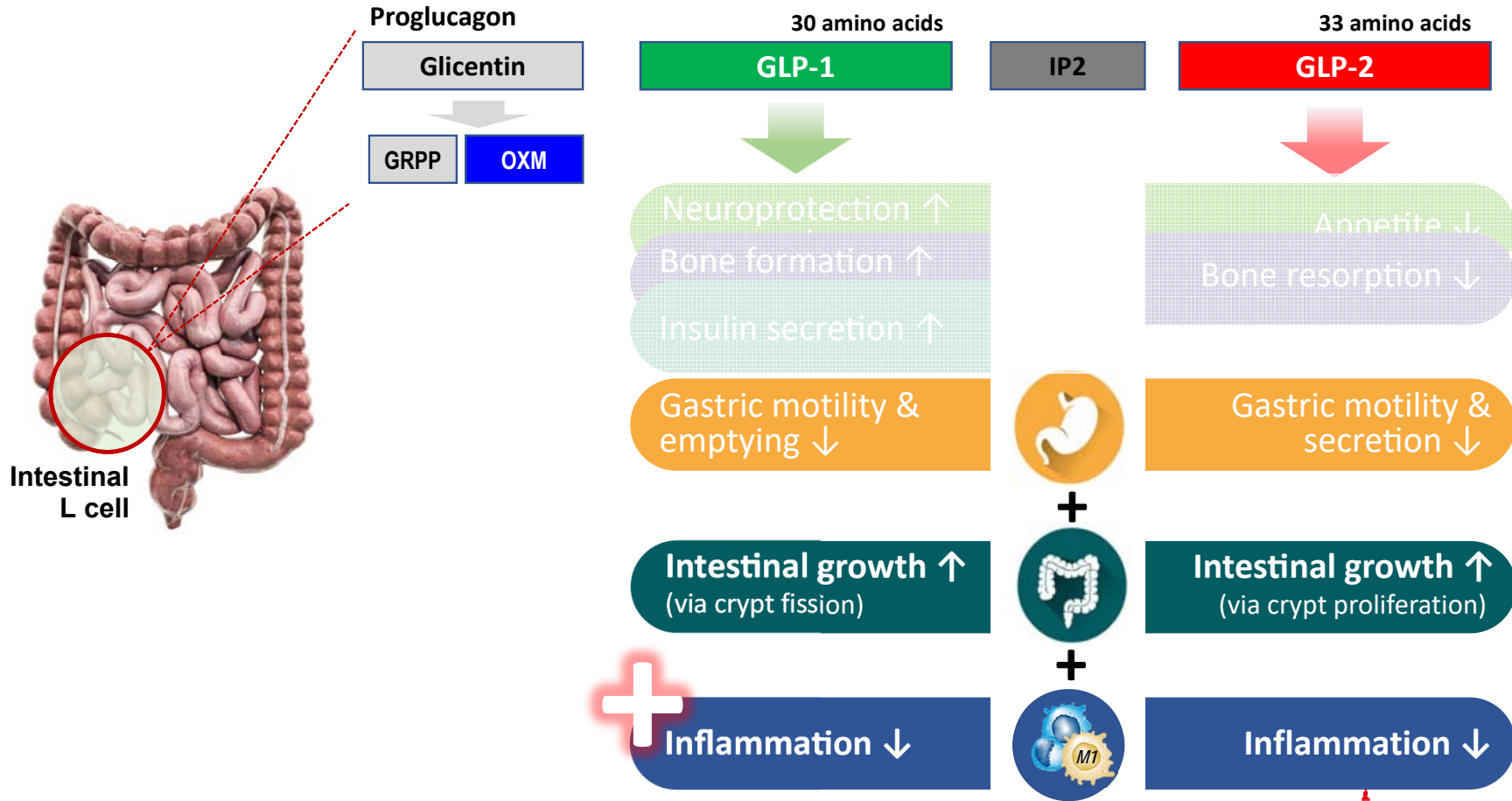
Shareholder	No relevant conflicts of interest to declare.
Grant / Research Support	No relevant conflicts of interest to declare.
Consultant	No relevant conflicts of interest to declare.
Employee	Employee of Hanmi Pharm. Co., Ltd.
Paid Instructor	No relevant conflicts of interest to declare.
Speaker Bureau	No relevant conflicts of interest to declare.
Other	No relevant conflicts of interest to declare.



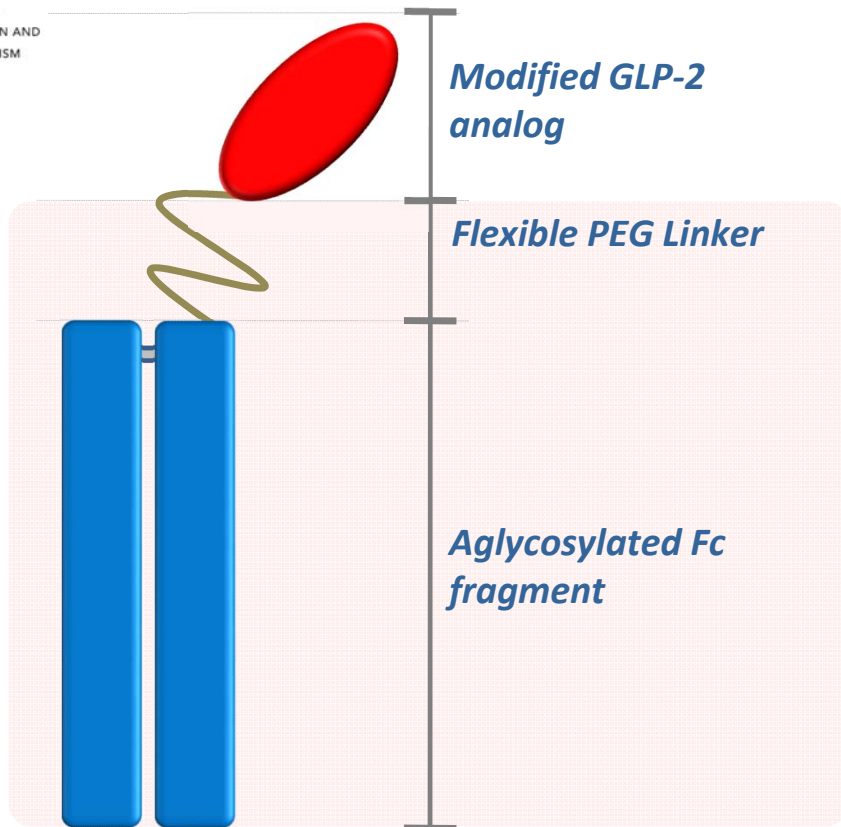
What GLP-2 and GLP-1 are?



What GLP-2 and GLP-1 are?



What a long-acting GLP-2 analog is?



LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

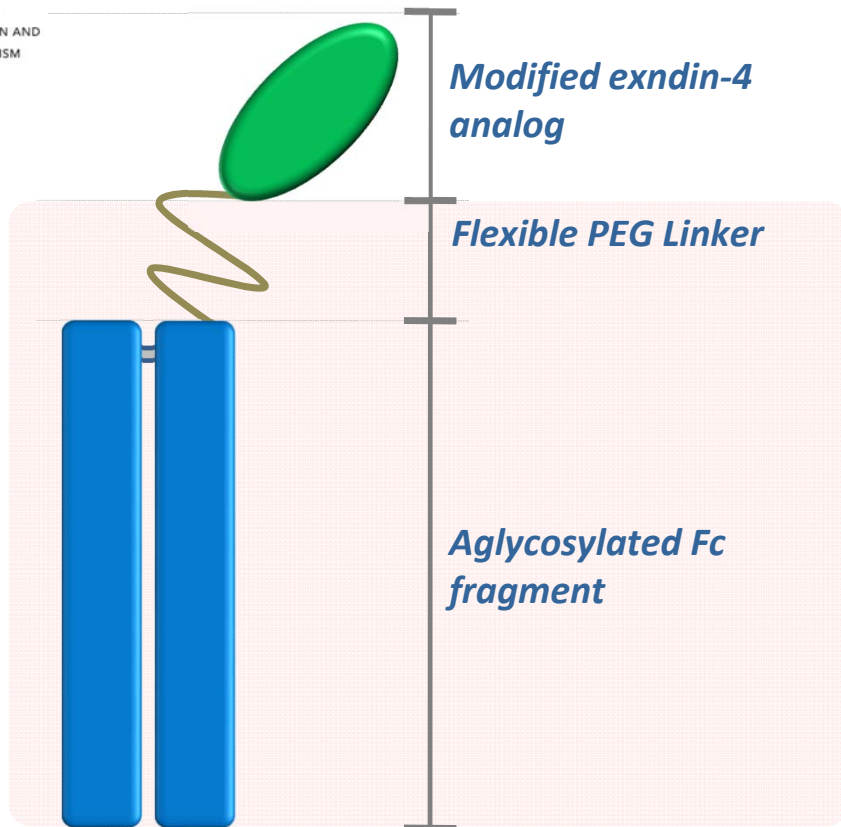
Hanmi's GLP-2 analog (HM15912) is conjugated with a human IgG Fc fragment *via* flexible linker

[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 formulation
- FIH study is completed and Ph2 IND (US) approved
- Fast track, RPD (US) and ODD (FDA, EMA, MFDS) granted



What a long-acting GLP-1 receptor agonist is?



LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

Hanmi's GLP-1RA (efpeglenatide) is conjugated with a human IgG Fc fragment *via* flexible linker





[General profile]

- Rationally designed exendin-4 analog for less desensitization of GLP-1 receptor
- Extended half-life allows up to once-monthly dosing
- Better gastrointestinal tolerability
- Comparable glucose lowering and weight loss to semaglutide
- Currently under Ph3 development



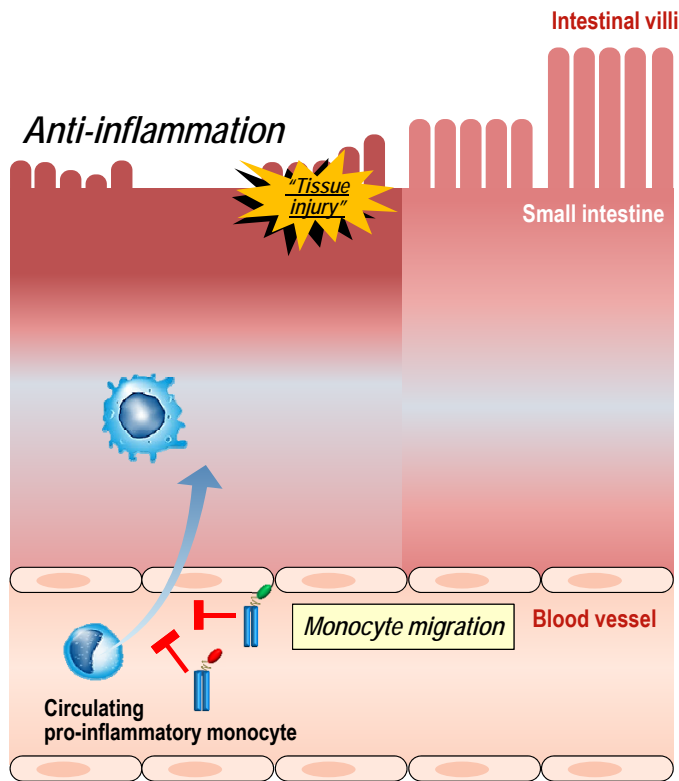
Hypothesis & study methods

HM15912 and efpeglenatide may have a COMBO potential for inflammatory bowel disease (IBD) by distinct or somewhat overlapped intestinotrophic and anti-inflammatory mode of actions

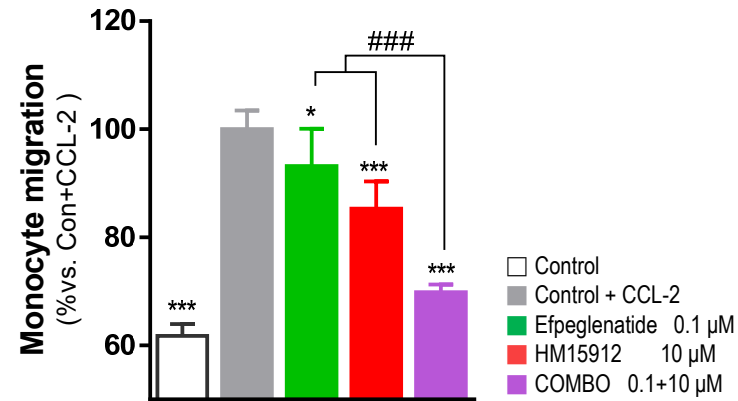
Purpose		Species / Strain	Induction method	Note
1. <i>In vitro</i> mechanistic study	Human monocyte migration, differentiation, and activation	 Human monocyte (THP-1)	Migration by CCL-2 Differentiation by PMA M1 macrophage polarization by LPS	-
2. <i>In vivo</i> mechanistic study	Small bowel trophic effect	 C57BL/6 mice	Normal	
3. Therapeutic potential	Anti-inflammation on small intestine	 Sprague dawley rat	Indomethacin-induced IBD model	
4. Therapeutic potential	Survival rate	 Sprague dawley rat	Indomethacin-induced IBD model	



Mechanism of HM15912/efpeglenatide COMBO



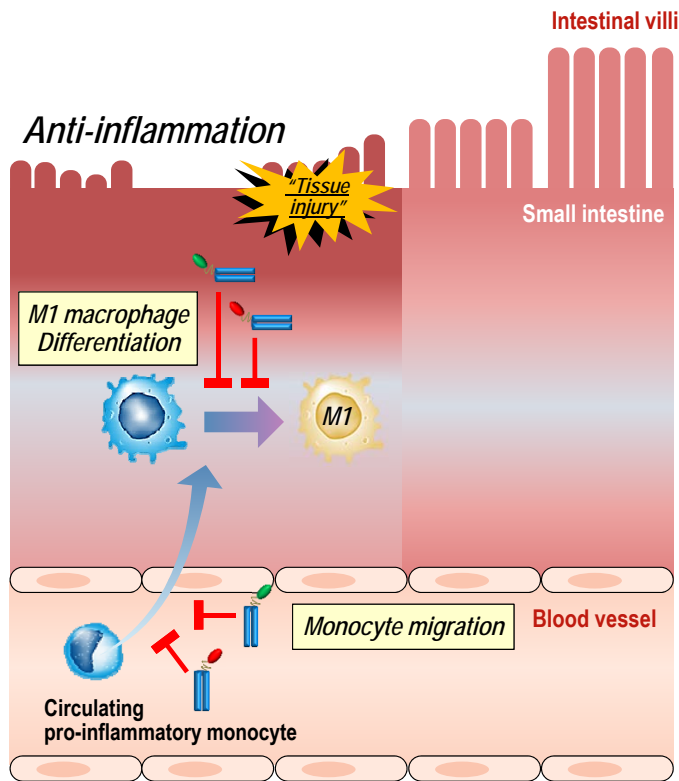
(1) Inhibition of monocyte migration (THP-1, CCL-2 50 ng/mL)



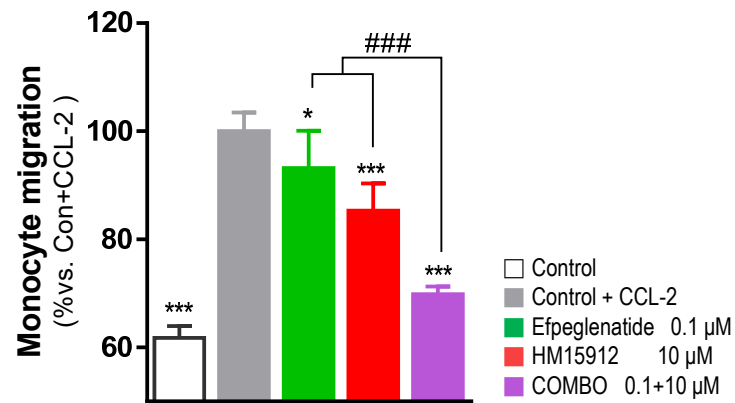
* Significantly differ. vs. stimulated vehicle by one-way ANOVA, # Significantly differ. vs. COMBO by one-way ANOVA



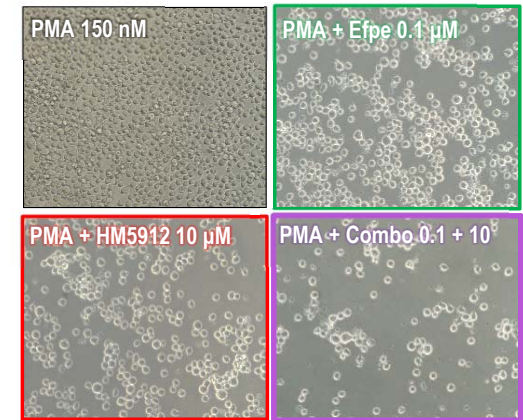
Mechanism of HM15912/efpeglenatide COMBO



(1) Inhibition of monocyte migration (THP-1, CCL-2 50 ng/mL)



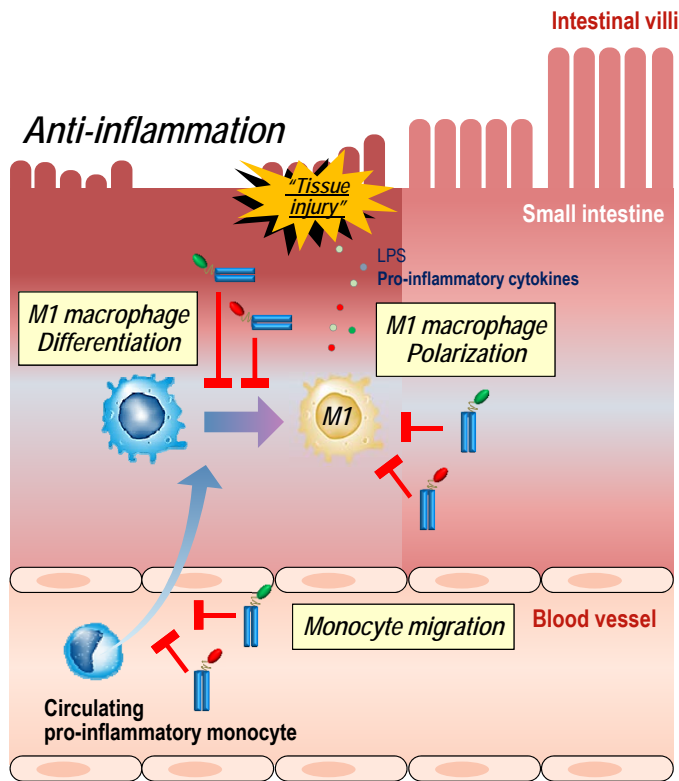
(2) Inhibition of monocyte to M ϕ differentiation (THP-1, PMA 150nM)



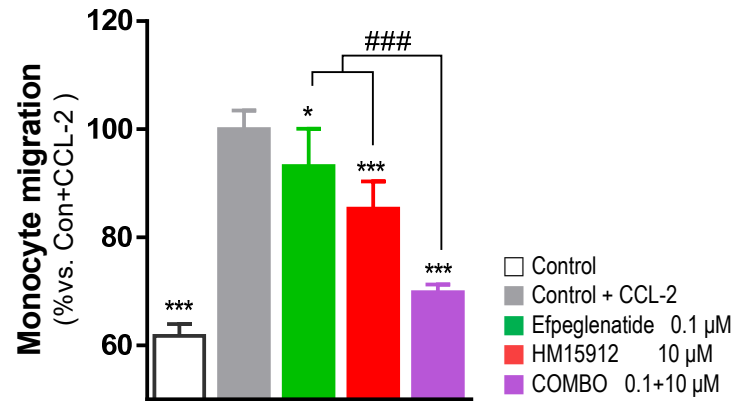
* Significantly differ. vs. stimulated vehicle by one-way ANOVA, # Significantly differ. vs. COMBO by one-way ANOVA



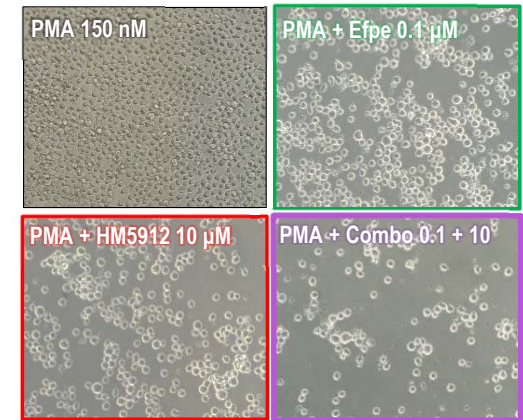
Mechanism of HM15912/efpeglenatide COMBO



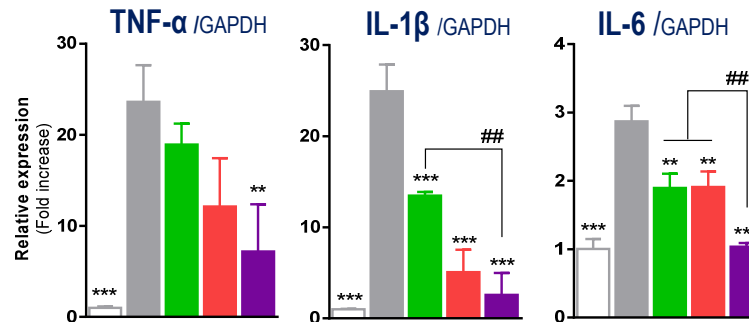
(1) Inhibition of monocyte migration (THP-1, CCL-2 50 ng/mL)



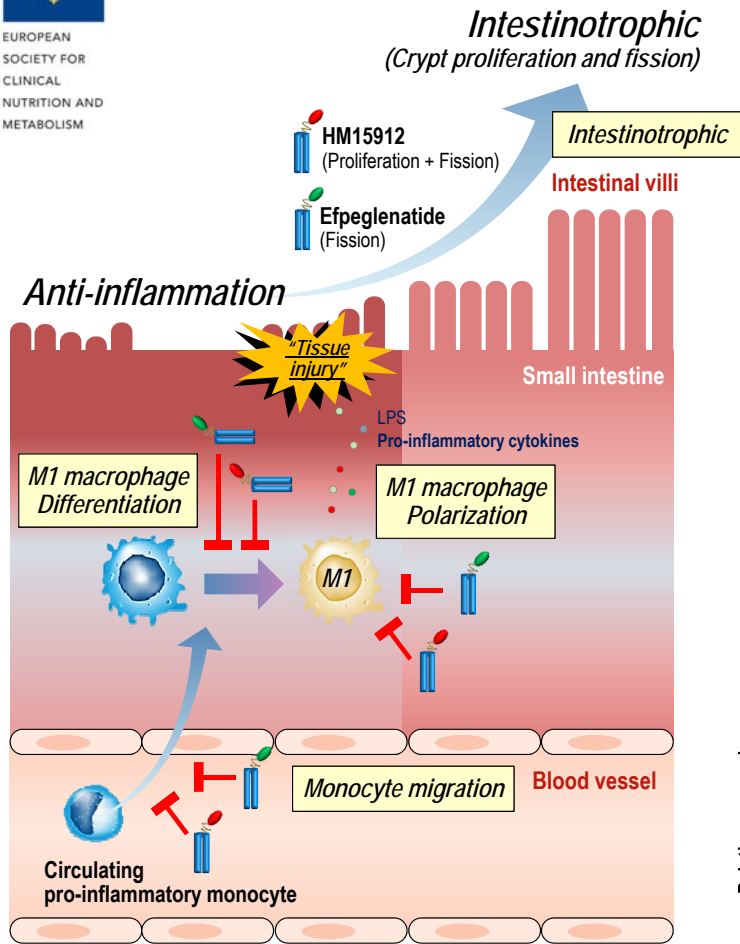
(2) Inhibition of monocyte to MØ differentiation (THP-1, PMA 150nM)



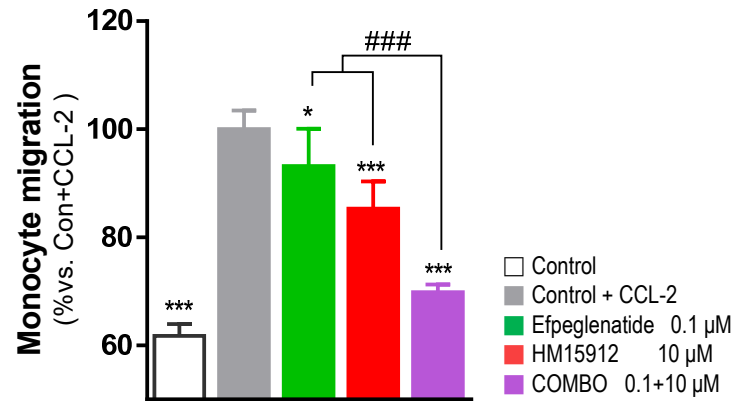
(3) Inhibition of M1 macrophage polarization (THP-1, LPS 1 μg/mL)



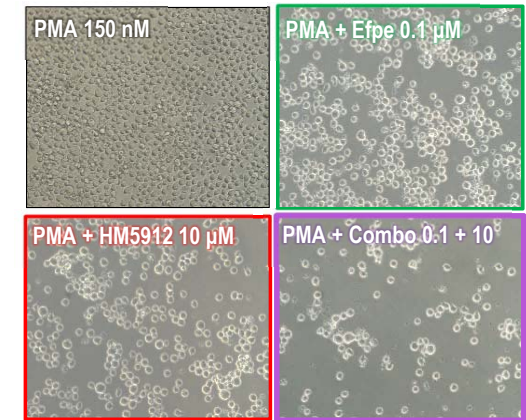
Mechanism of HM15912/efpeglenatide COMBO



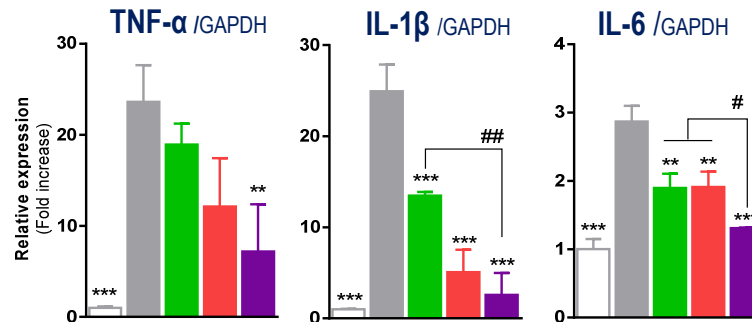
(1) **Inhibition of monocyte migration**
(THP-1, CCL-2 50 ng/mL)



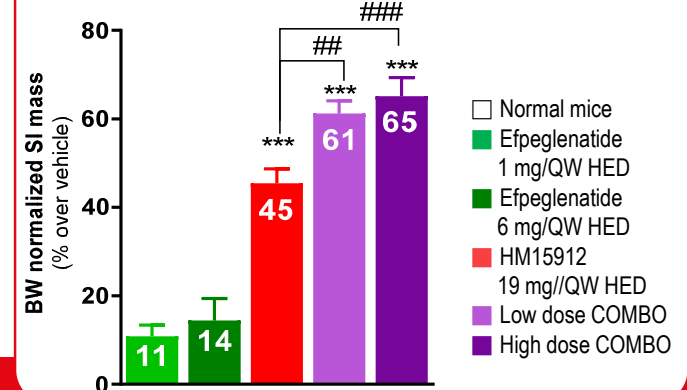
(2) **Inhibition of monocyte to MØ differentiation**
(THP-1, PMA 150nM)



(3) **Inhibition of M1 macrophage polarization**
(THP-1, LPS 1 µg/mL)



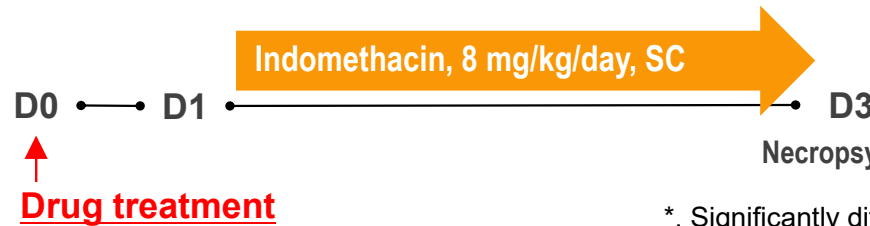
(4) **Intestintrophic effect (small intestine mass)**
(C57BL/6 mice, n=6/group)



*P<0.05, **P<0.01, ***P<0.001 vs. vehicle, #P<0.05, ##P<0.01 vs. HM15912 by one-way ANOVA
###P<0.001 vs. Efpe by unpaired t-test

Intestinal growth & anti-inflammatory effect in indomethacin-induced IBD rat

Experimental design

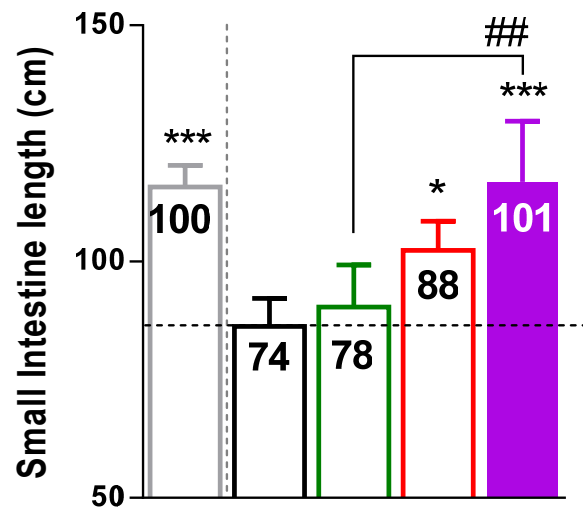


Small intestine histology

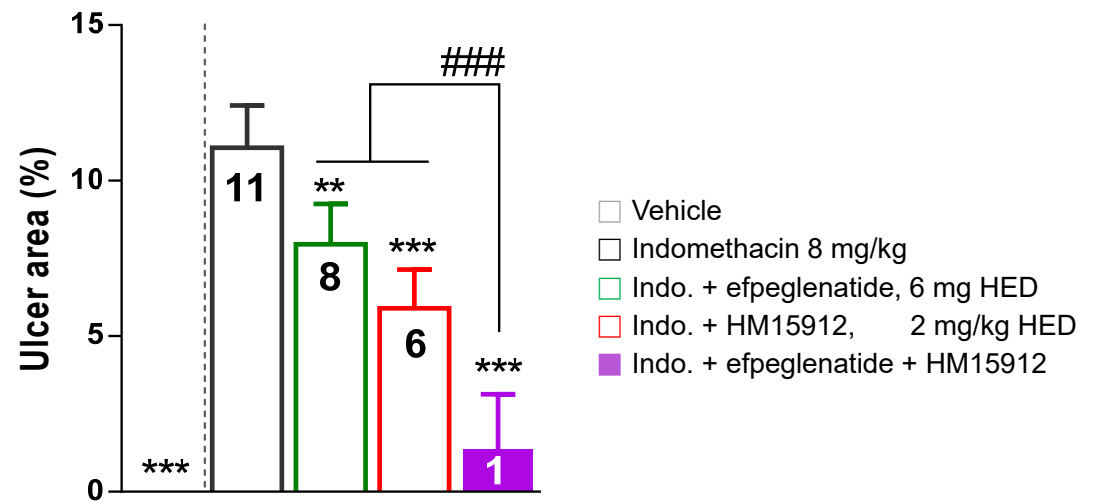
- Small intestine length
- Ulcer area (Evans blue)
- Inflammation score (H&E)

*, Significantly different vs. indomethacin 8 mg by one-way ANOVA
 #, Significantly different vs. HM11260C or HM15912 by unpaired T-test

Small intestine length



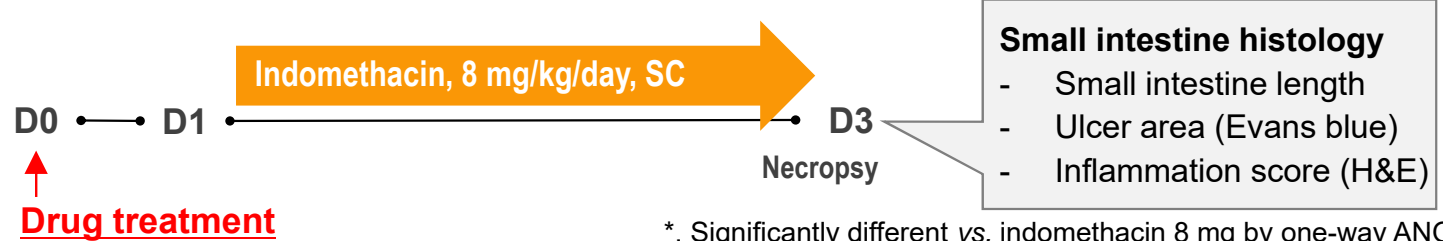
Ulcer area in small intestine



- Vehicle
- Indomethacin 8 mg/kg
- Indo. + efpeglenatide, 6 mg HED
- Indo. + HM15912, 2 mg/kg HED
- Indo. + efpeglenatide + HM15912

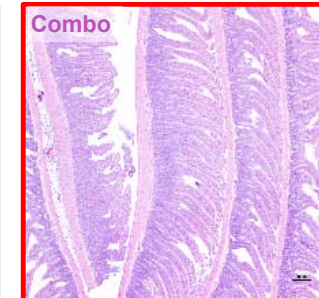
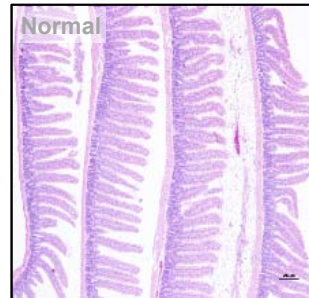
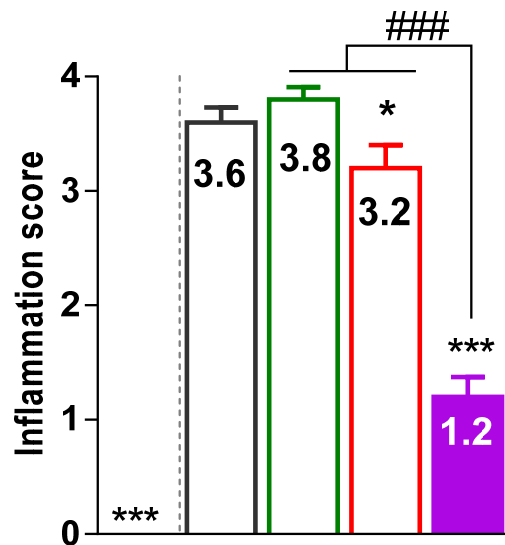
Intestinal growth & anti-inflammatory effect in indomethacin-induced IBD rat

Experimental design



*, Significantly different vs. indomethacin 8 mg by one-way ANOVA
#, Significantly different vs. HM11260C or HM15912 by unpaired T-test

Inflammation score



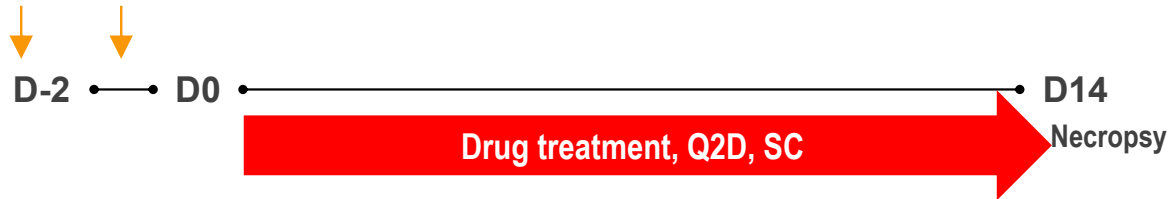
- Vehicle
- Indomethacin 8 mg/kg
- Indo. + efpeglenatide, 6 mg HED
- Indo. + HM15912, 2 mg/kg HED
- Indo. + efpeglenatide + HM15912

Survival rate in indomethacin-induced IBD rat

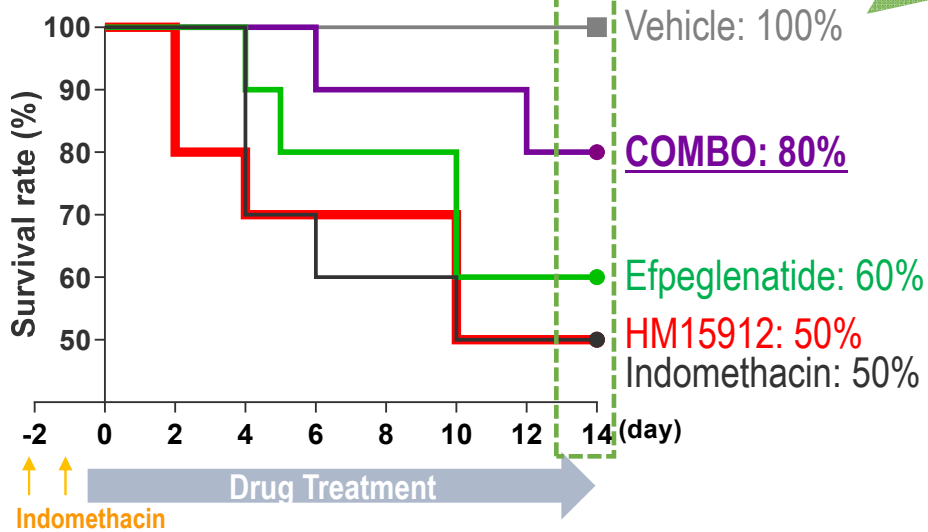
Experimental design



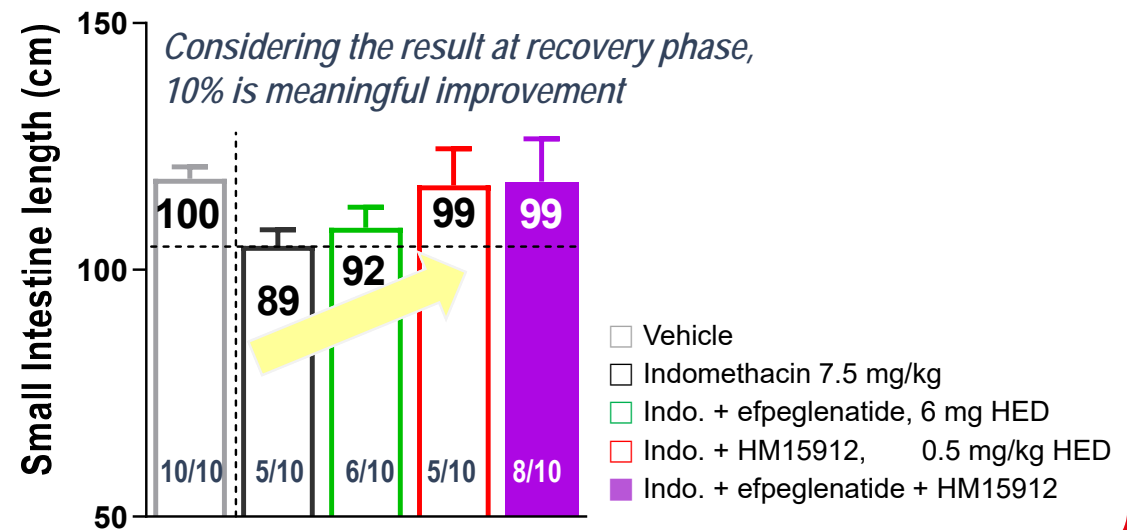
Indomethacin 7.5 mg/kg, SC



Survival rate



Small Intestine Length



Executive summary

- **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 the gastrointestinal tract such as intestinal growth, anti-inflammation, and inhibition of gut motility.**
- **Based on these pleiotropic mechanisms of GLP-2 and GLP-1 receptor agonists (RA), 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 additional / synergistic effect on inflammatory bowel disease.**
- **HM15912 and efpeglenatide directly and significantly inhibited the migration, differentiation, and M1 macrophage polarization of human monocyte, respectively, and were further inhibited when they were co-treated. And, small intestine (SI) mass was also significantly increased by the combo in normal mice.**
- **In indomethacin-induced IBD rats, significantly reduced SI length by indomethacin was completely recovered up to normal condition, and ulcer area and inflammation score were also significantly alleviated by the combination of HM15912 and efpeglenatide.**
- **2 weeks treatment of the COMBO significantly prevented from mortality compared to indomethacin vehicle**

Along with intestinal hypertrophic effect, direct anti-inflammatory effect of HM15912 efficiently mitigated intestinal inflammation. Furthermore, its combination with efpeglenatide elicited additional benefits on anti-inflammatory and intestinotrophic effects, speculating that their COMBO may be novel treatment option for IBD



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Thank you

