HM17321, a Novel UCN2 Analog, Improves Weight Loss Quality in combination with Amylin Analogs in DIO rats

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Poster
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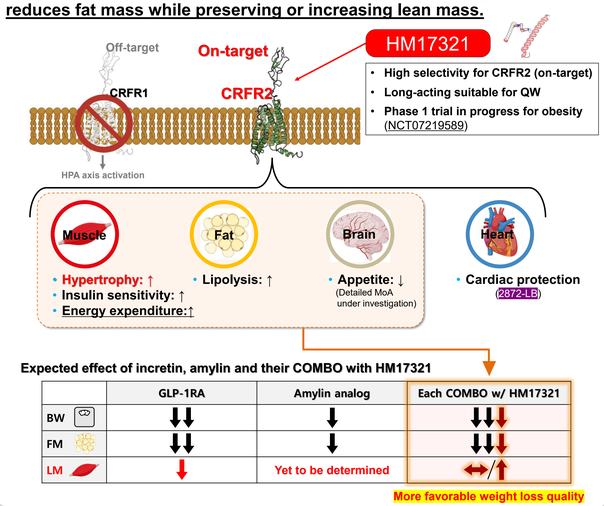
Abstract

Introduction & Objective: GLP-1 therapies have transformed the treatment landscape for obesity, yet significant unmet medical needs remain, including GI adverse events, variability in patient response, and notably lean mass (LM) loss. Amylin analogs are being developed to address these limitations, but their impact on LM remains unclear. Previously, HM17321 showed body weight (BW) loss while increasing functionally intact muscle mass, and improved weight loss quality (WLQ) in combination with incretin therapies. Here, we evaluated a novel combination potential of HM17321 and amylin analogs.
Methods: Combination efficacy of HM17321 and amylin analogs (cagrilintide, petrelintide, and eloralintide) was evaluated in DIO rats. At the end of treatment, body composition was assessed by time domain nuclear magnetic resonance.
Results: HM17321 monotherapy resulted in significant fat mass (FM) reduction and LM gain, confirming a favorable body recomposition. Each amylin analog showed significant BW loss, primarily through FM loss (-32.4% to -15.8% vs. day -1; $p < 0.001$ vs. DIO, vehicle). Combination treatment of HM17321 with amylin analogs promoted greater FM reduction (-56.5 % to -45.4 % vs. day -1; $p < 0.05 \sim 0.001$ vs. each mono) without additional food intake inhibition. Importantly, HM17321 combination markedly enhanced LM gain (17.9 % to 22.1 % vs. day -1; $p < 0.01 \sim 0.001$ vs. each mono) compared with each amylin monotherapy (9.2% to 12.9% / DIO, vehicle 6.6% vs. day -1), suggesting WLQ improvement. Similarly, all treatment groups improved blood glucose profile compared to DIO vehicle, and HM17321 combination showed a trend toward further improvement.
Conclusion: In DIO rats, combination treatment of HM17321 with amylin analogs enhanced FM reduction while promoting LM gain, leading to marked improvement in WLQ. These findings highlight the unique potential of HM17321 to improve body composition during weight loss and support its development both as a monotherapy and as a combination partner for amylin- or incretin-based therapies.

Background

HM17321, a novel long-acting CRFR2-selective UCN2 analog, selectively reduces fat mass while preserving or increasing lean mass.



Expected effect of incretin, amylin and their COMBO with HM17321

	GLP-1RA	Amylin analog	Each COMBO w/ HM17321
BW	↓↓	↓	↓↓↓
FM	↓↓	↓	↓↓↓
LM	↓	Yet to be determined	↔/↑

More favorable weight loss quality

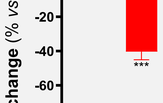
Methods

In vivo study design

Study 1. DIO mice, ♂ 20W *HFD for 14 weeks*
(C57BL/6 mice, n=6/group)

D0 → D28
Q2D drug treatment (HM17321, SEMA, TZP)
BW, FI monitoring
↓ Body composition measurement

Study 2. DIO rat, ♂ 11W *6-week-old, HFD for 5 weeks*
(SD rats, n=6/group)



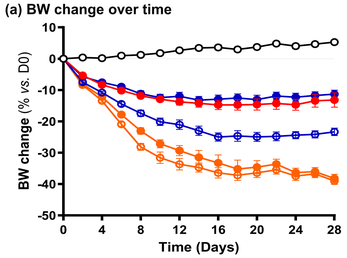
D0 → D28
Q3D drug treatment (HM17321, Amylin analogs)
BW, FI monitoring
↓ Body composition measurement

Cagrilintide
Petrelintide
Eloralintide
(*in-house synthesized*)

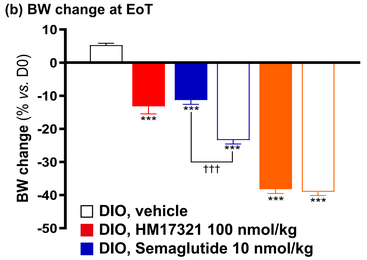
Study 1. Combination effects with commercial incretin drugs

Figure 1. Effects of HM17321 in combination with incretin-based drugs on body weight and body composition in DIO mice

(a) BW change over time



(b) BW change at EoT



*/†:***p<0.05~0.001, *vs.* Vehicle, by One-way ANOVA test.
†:†††p< 0.05~0.001, *vs.* each SEMA or TZP mono by an Welch's t-test.

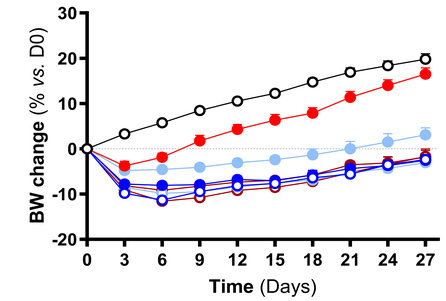
(c) Fat and lean mass change at EoT

- HM17321 showed similar BWL to SEMA with additive effects in combination, whereas HM17321+TZP combination showed comparable efficacy to TZP.
- Combination of HM17321 not only resulted in additional fat reduction, but also demonstrated lean mass preservation or improvement, suggesting a favorable body composition profile.

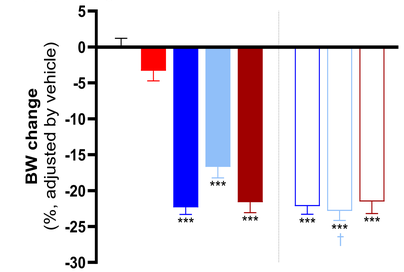
Study 2. Combination effects with amylin analogs

Figure 2. Effects of HM17321 in combination with amylin analogs on body weight and body composition in DIO rat

(a) BW change over time



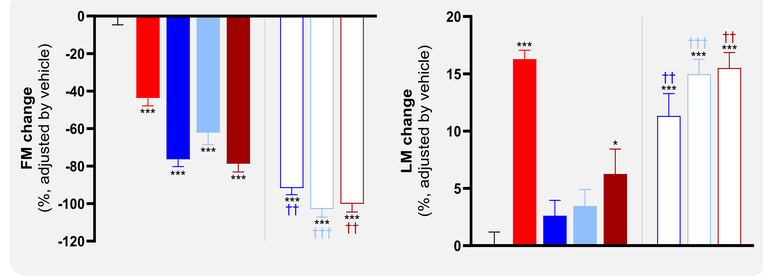
(b) BW change at EoT



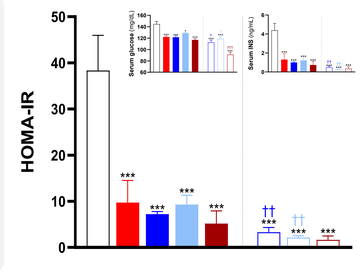
*/†:***p<0.05~0.001, *vs.* DIO, vehicle, by One-way ANOVA test.
†:†††p< 0.05~0.001, *vs.* each amylin analog by an Welch's t-test.

- Amylin analog-containing groups showed significant BWL vs. vehicle, and food intake was significantly reduced across all treatment groups.

(c) Fat and lean mass change at EoT



d) HOMA-IR



- HM17321 monotherapy did not induce significant BWL but was associated with favorable body recomposition characterized by reduced FM and increased LM.
- Amylin analog monotherapy reduced FM while preserving LM. In combination with HM17321, additional FM reduction and significant LM increase were observed, leading to markedly improved weight loss quality.
- Additionally, improved glycemic control was observed across all treatment groups, with further enhancement achieved by combination treatment with HM17321.

Concluding Remarks

- **HM17321, a novel CRFR2-selective agonist**, was designed to improve weight loss quality through fat mass (FM) reduction while preserving or increasing lean mass (LM), differentiating it from incretin-based therapies.
- Therapeutic potential of HM17321 as a monotherapy was demonstrated across multiple animal models with findings presented at ADA 2025 (843-P).
- DIO mouse and rat studies showed that **combination of HM17321 with either incretin- or amylin-analogs further enhanced FM reduction and LM preservation versus monotherapy**. All treatment groups showed improved glycemic control with greater improvements observed in the combination than monotherapy groups.
- **These findings support the potential of HM17321 to further improve weight loss potency and quality through combination with incretin- or amylin-based therapies.**
- Human relevance of HM17321 is being evaluated in a Phase 1 clinical study. (NCT07219589)
- Please also note additional posters presenting Hanmi's pipeline assets: HM17321 (1783-P, 1803-P, 2537-P, 2538-P, 2579-P and 2872-LB) and HM500197 (a peptide-based MSTN inhibitor; 3073-LB).