Efficacy of the novel UCN2 analogue HM17321 in weight loss without muscle wasting in obese non-human primates and its applications with incretins in obese mice

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Abstract #819

Abstract

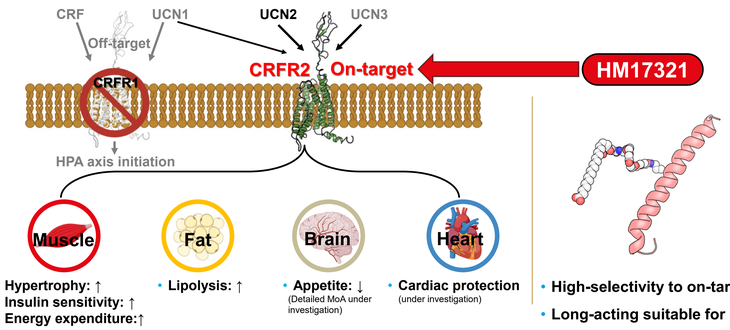
Background and aims: Incretin-based drugs have shown strong efficacy in obesity management, but their limitation of reducing lean mass has become evident. To address this, HM17321, a CRFR2-selective and biased UCN2 agonist, is being developed and has shown fat-specific weight loss in rodent studies. Current studies focus on confirming fat reduction without lean mass loss in middle-aged obese monkeys and exploring its potential both as monotherapy and in combination with incretin-based drugs in DIO mice.

Results: HM17321 significantly reduced body weight and fat mass in obese monkeys while preserving lean mass. Following 13 weeks of treatment, animals exhibited a marked body weight reduction of over 25%, with fat mass reduced by more than 70%, while lean mass not only remained preserved but also showed a trend toward increase. In DIO mice, when HM17321 was added to incretins, it showed further decrease in body weight and fat mass, even after the efficacy of incretins had plateaued. By the end of the study, the addition of HM17321 resulted in a greater reduction in both parameters compared to each monotherapy, with differences of 12.8 ~19.8%-point and 23.9~49.2%-point, respectively. In contrast, switching from incretins resulted in either additional fat loss or maintenance of the fat reduction by incretins, while dramatically increasing lean mass (11.0~13.3%-point increased from before switching).

Conclusion: The fat reducing efficacy of HM17321 without muscle wasting was confirmed in non-human obese primates, highlighting its potential as a monotherapy for obesity treatment with human relevance. Along with its human relevance, applications for the best quality in weight loss through various dosing regimens were also confirmed. These findings suggest that HM17321 could be a promising therapeutic option for treating obesity.

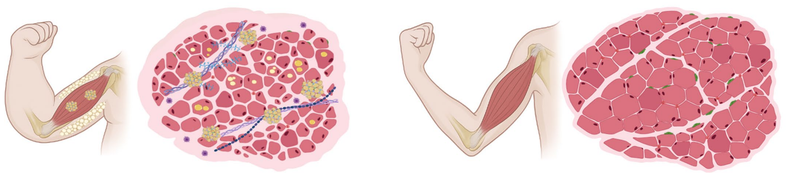
Background

CRF2 Receptor expression & Expected Effects of UCN2 Analog



- Hypertrophy: ↑
- Insulin sensitivity: ↑
- Energy expenditure:↑
- Lipolysis: ↑
- Appetite: ↓ (Detailed MoA under investigation)
- Cardiac protection (under investigation)
- High-selectivity to on-target
- Long-acting suitable for QW

Body Recomposition



Pathophysiological Changes in Muscle under Obesity

Interstitial space ( ): ↑
- MΦ infiltration: ↑
- Mt function: ↓
- Capillary density: ↓
- Satellite cell number: ↓
- ECM deposition: ↑
- Intramuscular fat: ↑
- Intermuscular fat: ↑
- → pseudo-hypertrophy

HM17321

- Muscle fiber CSA*: ↑
- Inter- /Intramuscular fat: ↓
- MΦ infiltration: ↓
- Mt function: ↑
- Capillary density: ↑
- Satellite cell number: ↑
- ECM deposition: ↓

*CSA: Cross-sectional area

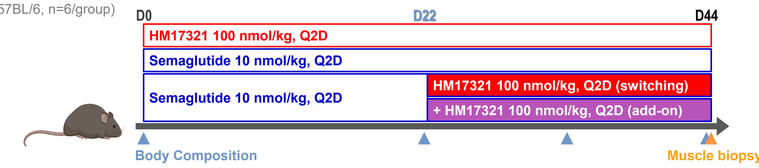
Study 1. Efficacy in Obese monkeys *(conducted by Primed)*

Obese monkey study (mean BW: 18.0kg) ♂ 10 ~ 18 yrs
(Rhesus, n=6-7/group)

- In a non-human primate study, obese monkeys aged 10–18 years (initial BMI: 49.3 kg/m²) received subcutaneous injections of vehicle or HM17321 once weekly for 13 weeks. Body weight was measured weekly, and fat/lean composition was assessed every 4 weeks by DEXA scan. Blood pressure, heart rate, and blood chemistry were evaluated at 4-week intervals.

Study 2. Combination strategies with incretin in DIO mice

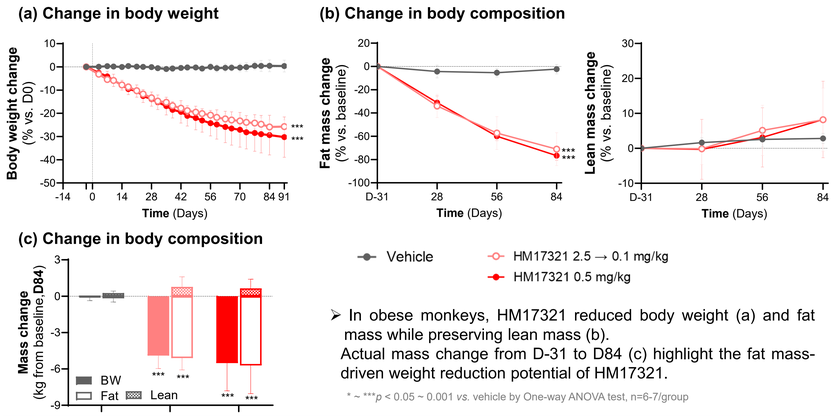
DIO mice, ♂ *22-week-old, HFD for 16 weeks*
(C57BL/6, n=6/group)



- In rodent studies, high fat diet-induced obesity (DIO) mice were subcutaneously treated with vehicle, HM17321 and semaglutide for 22 days, followed by either switching from or adding HM17321 to semaglutide. Body composition was assessed before and after treatment change. At the end, skeletal muscles were collected and stained to quantify hypertrophy across muscle fiber types.

Fat driven weight loss efficacy in obese monkey

Figure 1. Effect of HM17321 on Body recomposition in obese monkeys

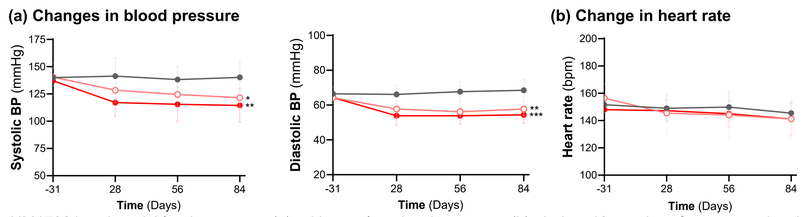


➢ In obese monkeys, HM17321 reduced body weight (a) and fat mass while preserving lean mass (b).
Actual mass change from D-31 to D84 (c) highlight the fat mass-driven weight reduction potential of HM17321.

* ~ ***p < 0.05 ~ 0.001 *vs.* vehicle by One-way ANOVA test, n=6-7/group

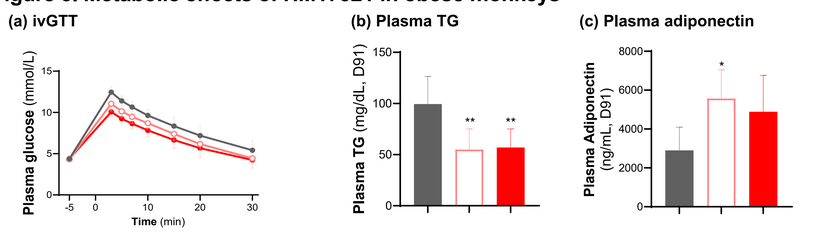
Cardio-metabolic benefits in obese monkey

Figure 2. Efficacy in blood pressure lowering without tachycardia in obese monkeys



➢ HM17321 reduced blood pressure (a) without elevating heart rate (b) during 13 weeks of treatment in obese monkeys.

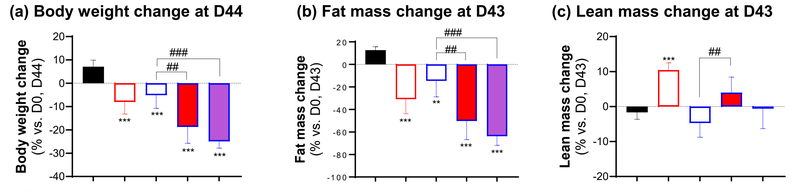
Figure 3. Metabolic effects of HM17321 in obese monkeys



➢ At the end of treatment (D91), HM17321 lowered glucose excursion during ivGTT (a) and reduced plasma triglyceride (TG)(b) as well as adiponectin (c). Changes in blood pressure, triglyceride and adiponectin were evident from day 28.

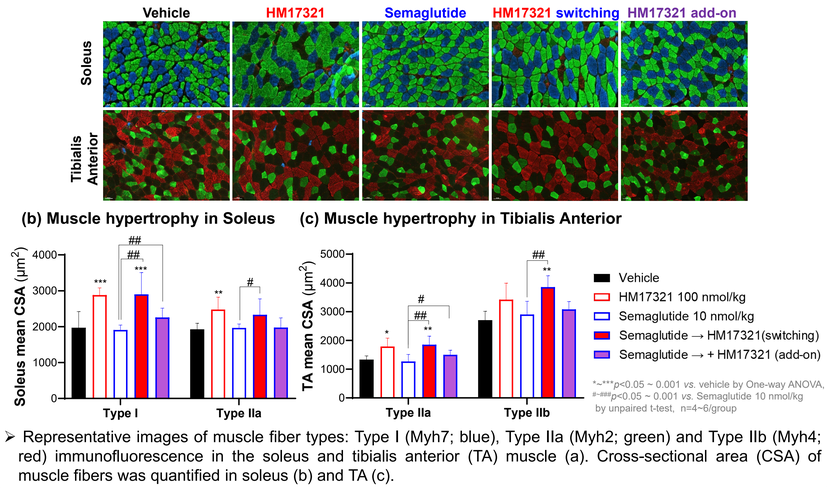
Synergistic benefits with incretins in DIO mice

Figure 4. Switching or add-on effects of HM17321 on body composition



➢ Effects of HM17321 on body composition following switch or add-on to semaglutide. HM17321 induced additional body weight loss (a), reduced fat mass (b), and restored lean mass (c).

Figure 5. Switching or add-on effects of HM17321 on muscle hypertrophy



*~***p<0.05 ~ 0.001 *vs.* vehicle by One-way ANOVA, #~###p<0.05 ~ 0.001 *vs.* Semaglutide 10 nmol/kg by unpaired t-test, n=4~6/group

➢ Representative images of muscle fiber types: Type I (Myh7; blue), Type IIa (Myh2; green) and Type IIb (Myh4; red) immunofluorescence in the soleus and tibialis anterior (TA) muscle (a). Cross-sectional area (CSA) of muscle fibers was quantified in soleus (b) and TA (c).

Concluding Remarks

- HM17321 demonstrated a novel weight-loss quality profile by reducing fat mass while preserving lean mass, and its efficacy was confirmed in non-human primates, underscoring strong clinical translatability as a stand-alone obesity therapy.
- Beyond monotherapy, additional therapeutic benefits were observed when combined with incretin agents, supporting the versatility of HM17321 in obesity management.
- Collectively, these findings highlight HM17321 as a promising next-generation treatment option with broad application potential in obesity therapy.
- Please also note Hanmi's additional presentations on our obesity pipeline:
  HM15275, a GLP-1/GIP/Glucagon triple agonist (P-765) / Oral GLP-1 RA (LBA-47) / HM17321, a UCN2 analog (P-730, P-669, P-226)