# A Novel CRFR2 Selective UCN2 Analog, HM17321, Facilitates Weight Loss and Improves Body Composition across Animal Models of Obesity

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Poster
843-P

## Abstract

**Introduction and Objective**: Incretin drugs effectively promote weight loss, but also cause inevitable lean mass loss, compromising weight loss quality (WLQ). Urocortin-2 (UCN2) shows potential for enhancing lipolysis and muscle hypertrophy, offering a strategy to improve WLQ. To achieve these outcomes, a novel corticotropin-releasing factor receptor-2 (CRFR2) selective UCN2 analog, HM17321, was developed. The present study evaluates the potential effects of HM17321 on body weight (BW) and body composition.

**Methods**: In DIO mice and rats, BW, body composition, muscle tissue and blood parameters were analyzed after chronic treatment of HM17321. Semaglutide (Sema) was included as a comparative control. Monkeys were utilized for potential human translation.

**Results**: In DIO mice, HM17321 treatment significantly reduced BW in a dose-dependent manner. Although BW loss was slightly less pronounced, HM17321 showed a greater fat mass loss compared to Sema. Importantly, unlike Sema, HM17321 significantly increased lean mass and reduced lipid content in muscle tissue, indicating both quantitative and qualitative muscle improvement effect. In addition, HM17321 significantly reduced serum BG, total cholesterol, and ALT. As to the mode of action for this WLQ improvement, HM17321 showed a greater fat mass reduction along with a significant muscle hypertrophic effect compared to pair-fed control, suggesting HM17321's direct actions on adipose tissue catabolism and skeletal muscle anabolism. The favorable body recomposition was reproduced in DIO rats. Most strikingly, HM17321 treatment was associated with fat mass loss-driven BW loss in monkeys.

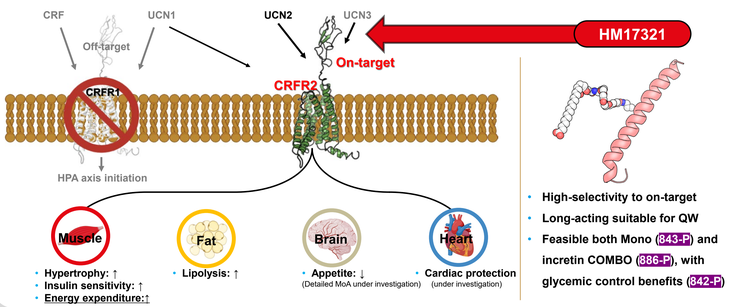
**Conclusion**: HM17321 demonstrates robust fat mass reduction and lean mass increasing effect across animal models including monkeys. These findings underscore the potential of HM17321 for high quality weight management, supporting its continued development as a differentiated anti-obesity drug.

## Background

**Breaking the Trade-Off: Burn Fat, Build Muscle — The Future of Obesity Drugs?**

**HM17321, a novel long-acting CRFR2 selective and biased UCN2 analog, is optimally designed to selectively reduce fat while simultaneously increasing muscle mass during weight loss, maximizing WLQ and metabolic improvement.**

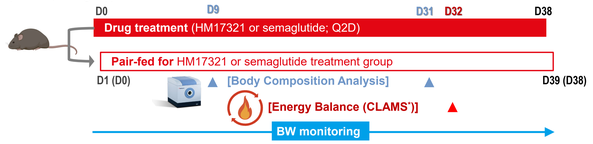
### CRF2 Receptor expression & Expected Effects of UCN2 Analog



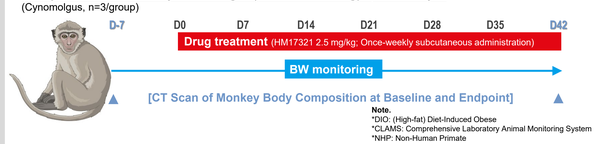

## Methods

***In vivo* study**

**Study 1. DIO* mice, ♂ 19W** *6-week-old, HFD for 13 weeks*
(C57BL/6, n=12/group)




**Study 2. NHP* PoC study, overweight (mean BW: 5.5kg) ♀ 14 ~ 16 yrs**
(Cynomolgus, n=3/group)




Note.
*DIO: (High-fat) Diet-Induced Obese
*CLAMS: Comprehensive Laboratory Animal Monitoring System
*NHP: Non-Human Primate

- To evaluate the effect of HM17321 (*vs.* Sema) on high-quality weight loss (exclusively derived from fat mass), HM17321 (or Sema) was administered for 5 weeks (D38). **Body composition** was assessed using the minispec LF90II (Bruker), and **energy expenditure was analyzed through CLAMS for energy balance**. Following sacrifice, muscle weight was measured and muscle triglycerides (TG) were assessed to evaluate muscle quality. To validate **human translation**, a PoC study was conducted on overweight female Cynomolgus monkeys, analyzing body weight and body composition through CT scan **[*In vivo* study].**

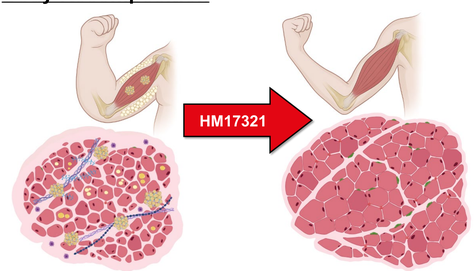
***In vitro* study**

**Study 1. Primary Human White Preadipocytes (HWP)**
obtained from visceral adipose tissue (omentum) of an 85-year-old Caucasian male (PromoCell)

**Study 2. Primary Human Skeletal Muscle Cells (HSkMC).**
obtained from two sources: (1) PromoCell: 65-year-old Caucasian female, striated gluteus maximus; (2) ATCC: Caucasian female neonate, thigh muscle

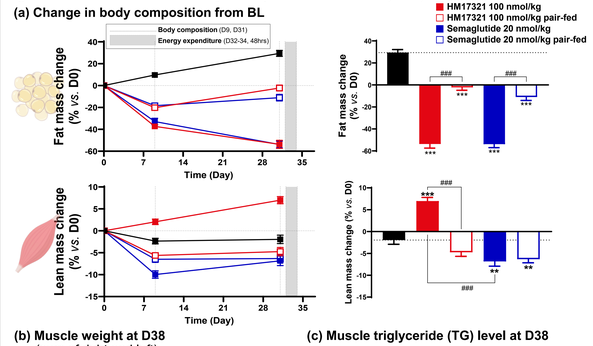
- To support human translation and investigate the **direct MoAs of HM17321 on fat mass reduction and muscle hypertrophy observed *in vivo***, experiments were conducted using primary human white preadipocytes and skeletal muscle cells **[*In vitro* study].**

### Body Recomposition




## Body Recomposition in DIO Mice

**Figure 1. Effect of HM17321 on Body recomposition in DIO mice (n=12)**

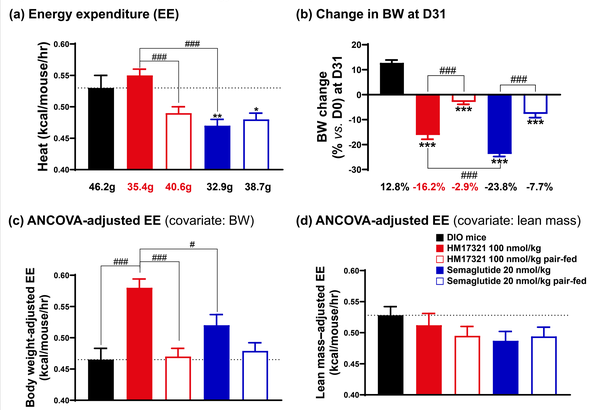



*~***$p$<0.05~0.001 *vs.* DIO vehicle by One-way ANOVA test, ##~###$p$<0.01~0.001 by an unpaired t-test

➢ In DIO mice, HM17321 enhanced weight loss quality (WLQ) by reducing fat and promoting lean mass gain, unlike Sema which leads to lean loss.

## Metabolic Enhancement Independent of BW in DIO Mice

**Figure 2. Effect of HM17321 on energy expenditure in DIO mice (n=12)**

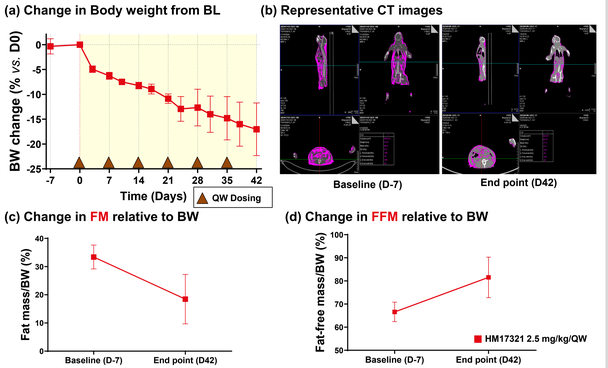



*~***$p$<0.05~0.001 *vs.* DIO vehicle by One-way ANOVA test, #~###$p$<0.05~0.001 by an unpaired t-test

➢ The increase in EE observed with HM17321 treatment appears to result from greater lean mass, rather than being driven by direct metabolic activation; however, EE remained significantly elevated when adjusted for BW, indicating that mice treated with HM17321 expended more energy at the same BW.

## Weight Loss and Body Recomposition in Overweight NHP

**Figure 3. Effect of HM17321 on Body recomposition in overweight female monkeys (n=3)**




➢ In a 6-week PoC study in overweight monkeys, HM17321 achieved sustained body weight loss of up to ~17%. Body recomposition confirmed at D42 further supports its translational potential to humans.

## Direct Lipid Lowering and Muscle Hypertrophic Effects

**Figure 4. Effect of HM17321 on adipocytes and skeletal muscle cells**




***$p$<0.001 *vs.* DM vehicle by One-way ANOVA test, #$p$<0.05 by an unpaired t-test

###$p$<0.001 by an unpaired t-test

➢ HM17321 promoted lipolysis in differentiated human visceral adipocytes by reducing lipid droplets and TG levels and also enhanced myogenic differentiation in human skeletal muscle cells by decreasing intramuscular lipid and increasing MyoD expression.

## Concluding Remarks

- HM17321 demonstrated robust, **high-quality weight loss** in DIO mice by selectively reducing fat mass and increasing lean mass, with elevated energy expenditure even after body weight adjustment.
- In a 6-week PoC study in monkeys, HM17321 induced sustained body weight loss of up to ~17%, accompanied by **favorable body recomposition**.
- *In vitro* MoA studies using human cells confirmed that HM17321 promotes lipolysis in adipocytes and enhances differentiation in skeletal muscle cells.
- Collectively, these findings highlight the potential of HM17321 as a metabolically driven anti-obesity therapy that delivers durable and high-qualfity weight loss.

* **Please note additional posters presenting Hanmi's incretin pipeline, a GLP-1/GIP/Glucagon triple agonist, HM15275 (755-P, 774-P: Preclinical; 1980-LB: Phase 1 clinical) and its COMBO w/ HM17321 (Poster, 886-P).**

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