# Body Composition and Functional Outcomes of HM17321, a CRFR2-Selective UCN2 Analog, Alone and in Combination with Myostatin/Activin Inhibition in DIO Mice

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Poster
2537-P

## Abstract

**Introduction & Objective**: The current paradigm in obesity management is shifting from maximizing weight loss to improving weight loss quality (WLQ). Clinical studies combining incretin therapies with myostatin/activin pathway inhibition, such as bimagrumab (Bima), suggested benefits for WLQ. HM17321 is a CRFR2-selective UCN2 analog developed to promote fat-selective body weight loss (BWL) with favorable metabolic effects. This study evaluated either HM17321 alone or in combination with Bima in male and female DIO mice.

**Methods**: Male and female DIO mice were treated for 4 weeks with HM17321 alone or with Bima. Body weight and body composition were assessed, and skeletal muscle function was evaluated using wire hang and grip strength tests.

**Results**: HM17321 (100 nmol/kg) induced significant BWL in both male and female DIO mice (-17.5%, -12.7% *vs.* day 0), whereas Bima (20 mg/kg) alone showed minimal or opposite effects (-1.1%, +3.1%). The combination treatment (COMBO) achieved greater BWL (-22.6%, -24.8%). HM17321 reduced fat mass with modest lean mass gains in both sexes (-41.1%/+3.2% and -34.0%/+3.5% *vs.* baseline), whereas Bima primarily increased lean mass with marginal fat mass reduction (-15.7%/+12.9% and -15.6%/+18.6%). COMBO showed the most pronounced improvement in body composition, with substantial fat mass reduction and lean mass gain (-67.9%/+19.2% and -69.3%/+25.0%) compared with either monotherapy. Improvements in muscle function were confirmed following HM17321 treatment; however, no functional benefit was observed in the Bima monotherapy or COMBO groups despite pronounced muscle mass accrual in both sexes.

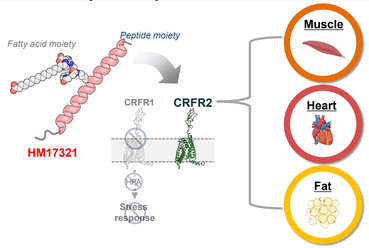
**Conclusion**: HM17321 induced fat-selective BWL with functional lean mass gain in both sexes, supporting its potential as a novel foundational WLQ therapy. These findings provide proof-of-concept for additional benefits of incorporating myostatin/activin pathway inhibition for body weight and body composition, warranting longer-term evaluation.

## Background

**Lose Weight. Gain Muscle. Too Good to Be True?**

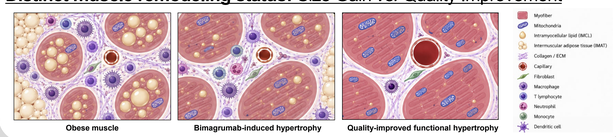
**HM17321, a novel long-acting CRFR2 selective UCN2 analog, is optimally designed to selectively reduce fat while simultaneously increasing muscle mass during weight loss and maximizing WLQ and metabolic improvement.**

### CRF2 Receptor expression & Effects of UCN2 Analog



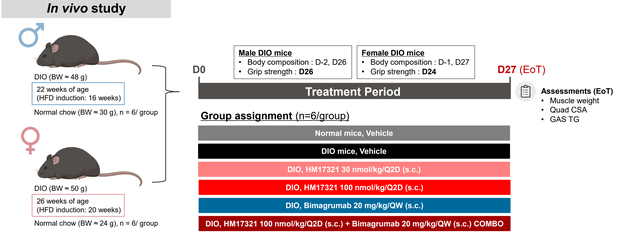

- Muscle hypertrophy
- Insulin sensitivity improvement
- Improved cardiovascular function
- Cardiac protection
- Fat mass reduction
- Insulin sensitivity improvement

**Distinct muscle remodeling status:** Size Gain *vs.* Quality Improvement




## Methods

***In vivo* study**




- To evaluate the effects of HM17321, bimagrumab, and combination treatment on **body composition and muscle function**, male and female DIO mice were treated for 27 days. Body composition was monitored during treatment, and grip strength was assessed prior to endpoint analysis. At study completion, muscle weight, quadriceps cross-sectional area (CSA), and gastrocnemius triglyceride (GAS TG) levels were evaluated.

***In vitro* study**

- To evaluate the **direct effects of HM17321 on muscle quality**, *in vitro* studies were performed using oleic acid (OA)-treated primary human skeletal muscle cells derived from female striated muscle of the gluteus maximus (PromoCell).

## Effect of HM17321 and Combination Treatment on Weight Loss Quality

**Figure 1. Effect of HM17321 alone and in combination with bimagrumab on body weight in DIO mice**

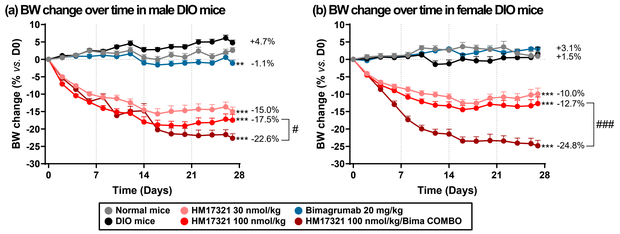
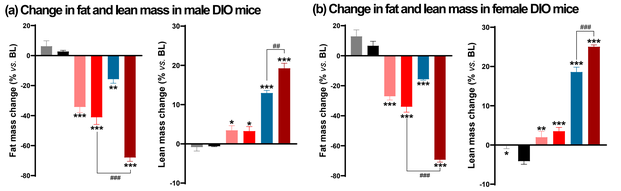
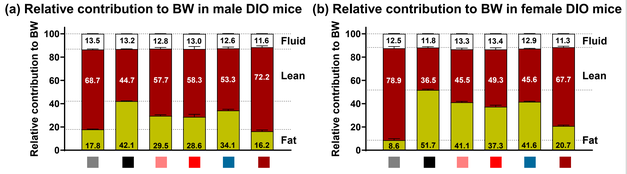



**Figure 2. Effect of HM17321 alone and in combination with bimagrumab on body composition in DIO mice**




*,**,***p< 0.05~0.001 *vs.* DIO vehicle control by one-way ANOVA test, #,###p< 0.05~0.001 *vs.* by one-tailed unpaired t-test

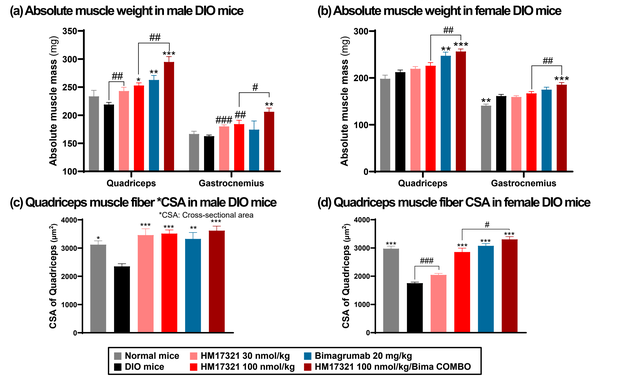
**Figure 3. Effect of HM17321 alone and in combination with bimagrumab on body recomposition in DIO mice**



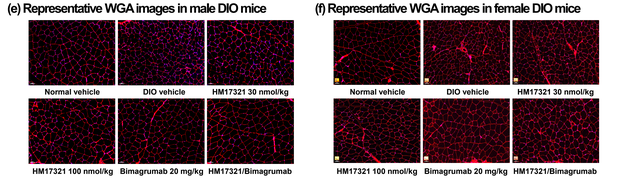

➢HM17321 improved weight loss quality through favorable body recomposition, while combination with bimagrumab further enhanced reductions in fat mass and gains in lean mass beyond monotherapy.

## Effect of HM17321 and Combination Treatment on Muscle Growth

**Figure 4. Effect of HM17321 and combination treatment on skeletal muscle growth and morphology in DIO mice**



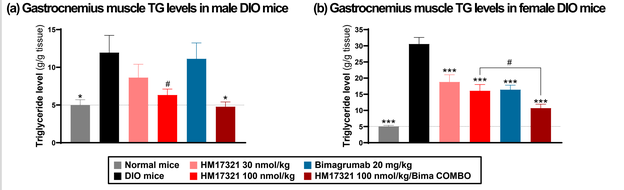

*,**,***p< 0.05~0.001 *vs.* DIO vehicle control by one-way ANOVA test, #,###p< 0.01~0.001 *vs.* by one-tailed unpaired t-test




➢HM17321 increased skeletal muscle mass and muscle fiber hypertrophy in DIO mice, while combination with bimagrumab further enhanced these effects, suggesting additional benefits on muscle growth and quality beyond monotherapy.

## Effects of HM17321 on Muscle Lipid Metabolism and Quality

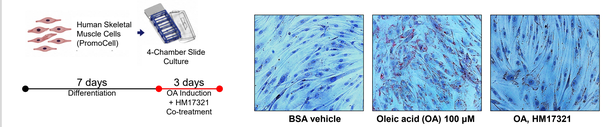
**Figure 5. Effect of HM17321 and combination treatment on intramuscular lipid accumulation in DIO mice**




*,**,***p< 0.05~0.001 *vs.* DIO vehicle control by one-way ANOVA test, #p< 0.05 *vs.* by one-tailed unpaired t-test

**Figure 6. Effect of HM17321 on intramyocellular lipid accumulation in OA-treated human skeletal muscle cells**

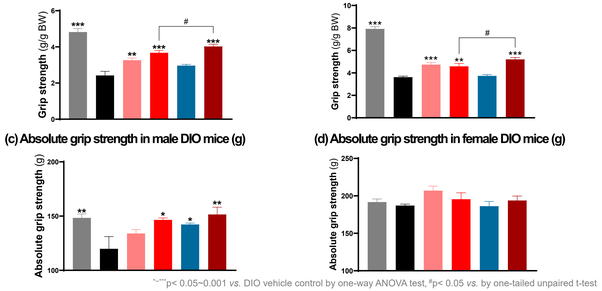
(a) Representative Oil Red O staining images of OA-treated human skeletal muscle cells following HM17321 treatment




➢HM17321 reduced lipid accumulation in skeletal muscle and preserved myotube integrity, supporting improved muscle quality through optimization of the muscle metabolic environment.

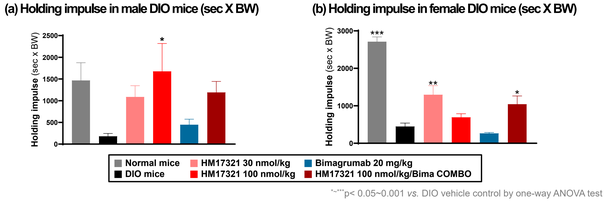
## Effect of HM17321 and Combination Treatment on Muscle Function

**Figure 7. Effect of HM17321 and combination treatment on grip strength in DIO mice**




*,**,***p< 0.05~0.001 *vs.* DIO vehicle control by one-way ANOVA test, #p< 0.05 *vs.* by one-tailed unpaired t-test

**Figure 8. Effect of HM17321 and combination treatment on wire hang in DIO mice**




*,**,***p< 0.05~0.001 *vs.* DIO vehicle control by one-way ANOVA test

➢HM17321 improved muscle function in DIO mice, as demonstrated by enhanced grip strength and endurance. Combination with bimagrumab further improved grip strength, although additional benefits on endurance were not evident within this study period.

## Concluding Remarks

- HM17321 promoted favorable body recomposition through fat mass reduction and muscle augmentation in both male and female DIO mice, with enhanced efficacy in combination with bimagrumab.
- Unlike bimagrumab, HM17321-associated gains in lean mass were accompanied by functional improvement, suggesting that muscle quality and systemic metabolic remodeling may contribute more to physical performance than muscle mass alone.
- Together, these findings support a differentiated profile of HM17321 beyond body composition changes, linking improved weight loss quality to functional benefits.
- Combination with bimagrumab further enhanced muscle hypertrophy and body recomposition, suggesting synergistic effects between bimagrumab-driven anabolic signaling and HM17321-mediated metabolic improvement.
- HM17321 is currently in a **Phase 1 clinical trial in the U.S.**
- Please also note additional presentations from our pipeline

  **: Therapeutic potential of HM17321 Sarcopenia (1783-P), Osteoarthritis & Osteoporosis (1803-P), CVRM (2538-P), Muscle Proteomics (2579-P), Heart Failure (2872-LB), and Incretin/Amylin Combination Therapy (3078-LB)**

  **: Discovery of HM500197, peptide-based MSTN inhibitor (3073-LB)**

American Diabetes Association (ADA), June 5-8, 2026

Hanmi Pharm. Co., Ltd.