HM500197, a De Novo-Designed Long-Acting Peptide Myostatin Inhibitor, Improves Skeletal Muscle Mass and Body Composition in Diet-Induced Obese Mice

Jaehyuk Choi, Jinyoung Kim, Jae young Kim, Won young Jang, Jieun Lee, Jeong A Kim, Sungmin Bae, Sang Hyun Lee, In Young Choi
R&D Devision, Hanmi Pharm. Co., Ltd., Gyeonggi-do, Republic of Korea

Hanmi

Poster
3073-LB

Abstract

Introduction and Objective: Myostatin (MSTN)/activin signaling is a key negative regulator of muscle homeostasis, and inhibition of this pathway has been explored to enhance muscle mass and function in muscle wasting diseases, leading to development of various antibody-based therapeutics. Recently, incretin-based therapies have demonstrated substantial weight reduction but are frequently accompanied by lean mass loss, highlighting MSTN/activin inhibition as a promising strategy to preserve skeletal muscle during weight loss. However, the antibody-based modality and multi-ligand inhibitory profile of existing agents may limit their suitability for combination with incretin therapies. Here, we report the development of HM500197, a long-acting MSTN-selective peptide generated through *de novo* design, and evaluate its ability to preserve skeletal muscle during incretin-induced weight loss in DIO mice.

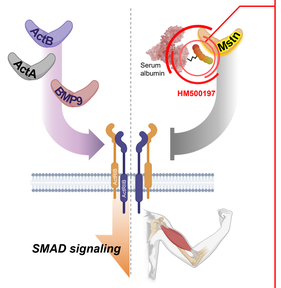
Methods: *In vitro* inhibitory activity against MSTN, activins, and BMP9 was evaluated in A204 cells. DIO mice were treated for 4 weeks to compare the efficacy of HM500197 with Bima and assess its effects in combination with incretin therapy. Body weight and composition were measured, and skeletal muscle mass was quantitatively assessed.

Results: HM500197 demonstrated MSTN inhibitory activity comparable to Bima while showing markedly reduced activity against Activin A (<0.01%), Activin B (<0.01%), and BMP9 (0.02%). In DIO mice, HM500197 dose-dependently increased lean mass by up to 6.7% from baseline (vs. 11.0% with Bima) and reduced fat mass by up to 17.0% (vs. 21.0% with Bima). Although the lean mass gain was lower than that achieved with Bima, HM500197 increased skeletal muscle mass comparable to Bima without increases in liver or heart weight, supporting its skeletal muscle–selective activity. Furthermore, in combination with incretin therapies, HM500197 effectively preserved lean mass over a 4-week treatment period.

Conclusion: HM500197 significantly increased skeletal muscle mass relative to Bima and prevented lean mass loss during caloric restriction-induced weight reduction, supporting its potential to improve the quality of weight loss and to serve as an optimal combination partner for incretin therapies.

Background

HM500197 is a novel long-acting, MSTN-selective peptide binder conjugated with a fatty acid moiety, designed for muscle enhancement.



Key features

- **AI-designed *de novo* peptide conjugated with fatty acid chain**
- **Selectively binds to MSTN, minimizing off-target interactions** (e.g., Activins, BMP9)
- **Skeletal muscle-selective effect on muscle mass and quality without increasing appetite**
- **Extended half-life enabling once-weekly subcutaneous dosing and well-suited for co-formulation with incretin-based therapies**

Methods

a) *In vitro* activity profiles (HM500197 *vs* bimagrumab)

A204 cells stably expressing SMAD-dependent ($CAGA_{12}$) luciferase reporter were treated with ligands and inhibitors, followed by measurement of luciferase activity.

b) Dose-dependent efficacy in diet-induced obese mice

DIO mice (C57BL/6, 17 weeks HFD, n=6/group)

0 — 28 (day)

HM500197 (Q2D, SC)

Bimagrumab (QW, SC)

[Body composition measurement]

c) Combination efficacy with incretin-therapy in diet-induced obese mice

DIO mice (C57BL/6, 15 weeks HFD, n=6/group)

0 — 28 (day)

HM500197 (Q2D, SC)

Tirzepatide; Acylated GLP/GIP (Q2D, SC)

HM500197 + Tirzepatide (Q2D, SC)

[Body composition measurement]

Myostatin-Selective Action of HM500197

Figure 1. *In vitro* characteristics of HM500197

a) Selectivity of HM500197 to MSTN *vs* bimagrumab

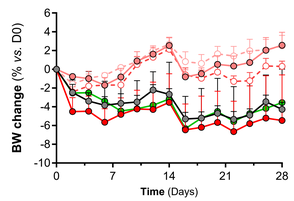
Materials	% Relative activity (*vs* IC_{50} of Bimagrumab)			
	Myostatin	Activin A	Activin B	BMP9
Bimagrumab	100%	100%	100%	100%
HM500197	**106.8%**	**< 0.01%**	**< 0.01%**	**0.02%**

➢According to *in vitro* characteristics, HM500197 selectively inhibits MSTN without affecting activins or BMP9, potentially enabling an improved safety profile by minimizing off-target-mediated adverse effects compared to non-selective inhibitors.

HM500197 Improves Muscle Quality Comparable to Bimagrumab

Figure 2. Changes in body weight and composition

a) Body weight profile over time



b) Changes in body composition at day 28

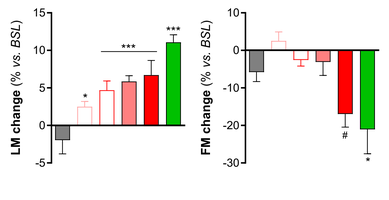
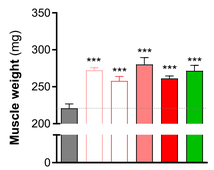
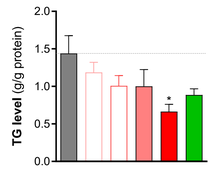


Figure 3. Improvements in skeletal muscle mass, strength, and metabolic function

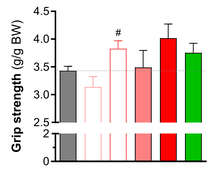
a) Quadriceps weight



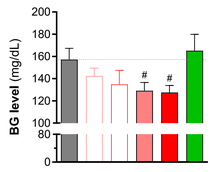
b) Quadriceps TG level



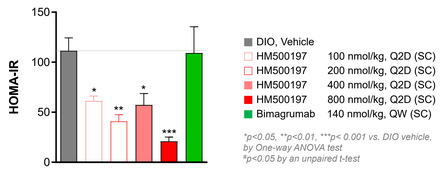
c) Grip strength



d) Non-fasting blood glucose



e) HOMA-IR

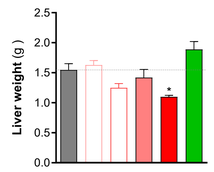


**p<0.05, **p<0.01, ***p< 0.001 vs. DIO vehicle, by One-way ANOVA test*
#p<0.05 by an unpaired t-test

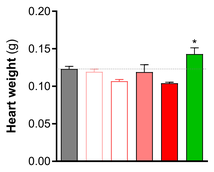
➢In DIO mice, HM500197 significantly increased lean mass, primarily driven by skeletal muscle expansion, suggesting a more skeletal muscle-focused effect than bimagrumab. In addition, improved glycemic control further supports the pharmacological advantages of selective MSTN inhibition.

Figure 4. Changes in non-target tissue weights

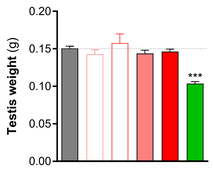
a) Liver



b) Heart



c) Testis

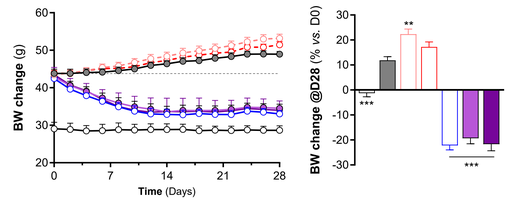


➢Unlike bimagrumab, HM500197 did not induce hazardous changes in non-target organ weights, including the liver, heart and testis, supporting its MSTN-selective pharmacological profile.

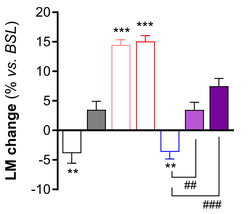
HM500197 Preserves LM During Incretin-Induced Weight Loss

Figure 5. Changes in body weight and composition

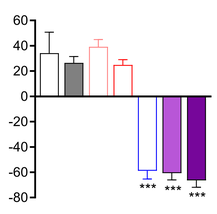
a) Body weight change



b) Lean mass change at day 28



c) Fat mass change at day 28



Normal, Vehicle
DIO, Vehicle
HM500197, 200 nmol/kg, Q2D
HM500197, 800 nmol/kg, Q2D
Tirzepatide, 10 nmol/kg, Q2D
HM500197, 200 nmol/kg + TZP, 10 nmol/kg
HM500197, 800 nmol/kg + TZP, 10 nmol/kg

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

➢HM500197 significantly preserved tirzepatide-induced lean mass reduction without affecting overall body weight. Although fat mass was not significantly changed by co-treatment with HM500197, a decreasing trend was observed.

Concluding Remarks

- HM500197, a *de novo* peptide-based long-acting MSTN inhibitor, demonstrated selective *in vitro* inhibition of MSTN, suggesting the potential to minimize off-target adverse effects.
- In DIO mice, HM500197 showed comparable skeletal muscle enhancement to bimagrumab, while demonstrating improved metabolic function, including glycemic control, and a favorable safety profile.
- Efficient preservation of muscle mass during caloric restriction-induced weight loss supports its potential as a combination partner for incretin therapies.
- As a small peptide-based therapeutic, HM500197 may also offer advantages over antibody-based agents for co-formulation with existing incretin therapies.
- Please also note Hanmi's additional presentations on our pipeline: HM17321, a UCN2 analog (1783-P, 1803-P, 2537-P, 2538-P, 2579-P, 2872-LB, 3078-LB)

References

1. Jastreboff AM, Aronne LJ, *et al. N Engl J Med.* **2022**;387(3):205-216
2. Bechenati D MD, Castaneda R, *et al.*, **2025** ADA, poster number 1757-P
3. Heymsfield SB, Aronne LJ, *et al., Nat Med.* **2026**;32(3):869-882.