Efficacy and Safety of HM15275, a Novel Long-Acting Triple Agonist in Adults with Obesity

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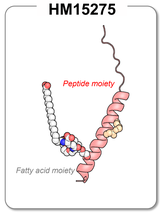
Poster P-218

Background



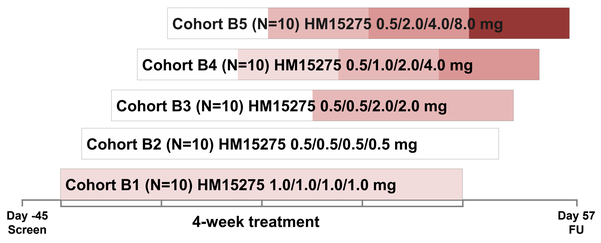
- Various multi-incretin agonists with different combinations and ratios are being developed; however, an optimal therapeutic strategy remains unclear.
- HM15275 is a novel long-acting GLP-1/GIP/GCG triple co-agonist, rationally designed with balanced activity optimized for weight reduction and glycemic control.

Methods

The first-in-human Phase 1 study (NCT06481098) of HM15275 was a randomized, double-blind, placebo-controlled study consisting of two parts: single ascending dose (SAD) and multiple ascending dose (MAD).

Here, we report results focusing on the MAD part of the study.

Study Design | Obese Subjects w/o T2DM, BMI 30 - 45 kg/m²



- **Primary Objective** To assess safety and tolerability of HM15275
- **Secondary Objective** To assess PK profile of HM15275
- **Exploratory Objective** To assess PD properties of HM15275

Demographics and Baseline Characteristics

Mean (SD)*	HM15275 (mg) 0.5/0.5/0.5/0.5 (N=8)	1.0/1.0/1.0/1.0 (N=8)	0.5/0.5/2.0/2.0 (N=8)	0.5/1.0/2.0/4.0 (N=8)	0.5/2.0/4.0/8.0 (N=8)	Pooled Placebo (N=10)
Age: year	47.4 (11.9)	44.5 (13.6)	49.1 (10.5)	44.9 (13.5)	46.0 (10.7)	49.1 (8.1)
Gender, F/M	2/6	3/5	3/5	2/6	3/5	6/4
Weight: kg	95.0 (5.9)	97.1 (11.8)	99.7 (19.0)	102.7 (10.5)	89.8 (10.4)	93.6 (17.3)
BMI: kg/m²	32.6 (1.6)	33.0 (2.3)	33.5 (3.2)	35.1 (4.3)	31.9 (1.7)	33.7 (3.1)
FPG: mg/dL	92.3 (9.3)	97.9 (11.6)	98.8 (6.1)	95.4 (5.0)	101.1 (12.6)	100.1 (8.0)
Ethnicity: n (%)						
Hispanic or Latino	5 (62.5)	5 (62.5)	4 (50.0)	5 (62.5)	6 (75.0)	6 (60.0)
Not Hispanic or Latino	3 (37.5)	3 (37.5)	4 (50.0)	3 (37.5)	2 (25.0)	4 (40.0)

* Gender data presented as number of subjects. Ethnicity data presented as n (%).

Summary of Overall Treatment Emergent Adverse Events

Subject with any (n, %)	HM15275 (mg) 0.5/0.5/0.5/0.5 (N=8)	1.0/1.0/1.0/1.0 (N=8)	0.5/0.5/2.0/2.0 (N=8)	0.5/1.0/2.0/4.0 (N=8)	0.5/2.0/4.0/8.0 (N=8)	Pooled Placebo (N=10)
TEAE	7 (87.5)	7 (87.5)	7 (87.5)	6 (75.0)	8 (100.0)	10 (100.0)
TRAE	3 (37.5)	7 (87.5)	7 (87.5)	4 (50.0)	6 (75.0)	5 (50.0)
Maximum Severity [a]						
Grade 1	2 (25.0)	5 (62.5)	6 (75.0)	1 (12.5)	5 (62.5)	3 (30.0)
Grade 2	1 (12.5)	2 (25.0)	1 (12.5)	3 (37.5)	1 (12.5)	2 (20.0)
Grade 3	0	0	0	0	0	0
Serious TEAE	0	0	0	0	0	0
TEAE leading to study discontinuation	0	1 (12.5)[b]	1 (12.5)[c]	0	0	0
GI-TRAE	**3 (37.5)**	**7 (87.5)**	**5 (62.5)**	**4 (50.0)**	**6 (75.0)**	**4 (40.0)**
Abdominal distension	2 (25.0)	3 (37.5)	0	0	0	0
Abdominal pain	1 (12.5)	0	0	0 (0.0)	1 (12.5)	1 (10.0)
Constipation	3 (37.5)	0	0	2 (25.0)	1 (12.5)	3 (30.0)
Dyspepsia	0	1 (12.5)	2 (25.0)	0	0	0
Gastroesophageal reflux disease	0	0	0	0	1 (12.5)	0
Diarrhea	1 (12.5)	0	0	4 (50.0)	1 (12.5)	0
Nausea	1 (12.5)	5 (62.5)	5 (62.5)	3 (37.5)	5 (62.5)	2 (20.0)
Vomiting	0	1 (12.5)	1 (12.5)	2 (25.0)	2 (25.0)	1 (10.0)

a. The severity grading for nausea/vomiting was assessed based on number of episodes.[1] (Grade 1: 1-2 episodes in 24 hours, Grade 2: 3-5 episodes in 24 hours, Grade 3: > 6 episodes in 24 hours). This grading scale was to fully understand subject's GI-AEs, despite being more stringent than CTCAE grading.
b. Subject discontinued due to gout flare (G2, not related). Subject had a medical history of gout flare.
c. Subject discontinued due to atrial fibrillation (G2, not related). Subject was asymptomatic and AE found on ECG, prior to the 3rd dosing.

Summary of Immunogenicity

- Of the 40 HM15275-treated participants, three (3) participants were confirmed ADA-positive; One (1) in 0.5/1.0/2.0/4.0 mg, two (2) in 0.5/2.0/4.0/8.0 mg group.
- Only one HM15275-treated subject (0.5/2.0/4.0/8.0 mg group) had positive titer results.
- None of the confirmed ADA-positive samples exhibited cross-reactivity with endogenous GLP-1, GIP, or glucagon.
- No relevant adverse events were reported.

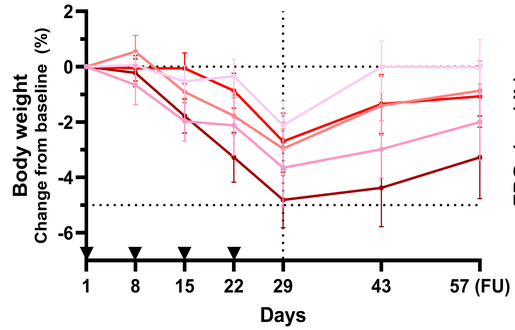
Summary of Changes in Lipid Parameters

Mean (SD)	HM15275 (mg) 0.5/0.5/0.5/0.5 (N=8)	1.0/1.0/1.0/1.0 (N=8)	0.5/0.5/2.0/2.0 (N=8)	0.5/1.0/2.0/4.0 (N=8)	0.5/2.0/4.0/8.0 (N=8)	Pooled Placebo (N=10)
N at Day 29	7	5	6	3[a]	8	9
% Change from baseline at D29						
Total cholesterol (mg/dL)	-0.6 (21.85)	-20.4 (9.98)	-21.1 (11.03)	-13.6 (3.25)	-28.3 (9.75)	-12.0 (7.85)
LDL-C (mg/dL)	1.3 (28.82)	-23.4 (15.29)	-22.8 (16.52)	-11.4 (8.84)	-32.6 (13.17)	-13.7 (10.58)
HDL-C (mg/dL)	7.1 (21.40)	-10.5 (10.50)	-6.1 (12.31)	-24.3 (5.38)	-18.9 (10.10)	-4.3 (13.78)
VLDL-C (mg/dL)	-21.8 (25.36)	-16.4 (15.47)	-23.3 (30.05)	-5.7 (25.76)	-22.7 (16.60)	-5.7 (26.00)
Triglycerides (mg/dL)	-24.0 (27.80)	-19.5 (15.35)	-25.9 (28.32)	-10.0 (33.48)	-28.8 (19.99)	-9.9 (25.98)
Free fatty acids (mEq/L)	61.67 (72.77)	33.67 (66.46)	31.48 (45.05)	72.22 (25.46)	90.63 (87.45)	23.70 (55.51)

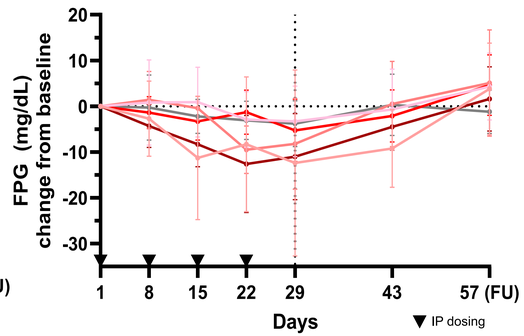
a. Reduced number of samples were available due to an unexpected temperature excursion during shipment.

Key Pharmacodynamics

A. Body Weight (Placebo-adjusted)



B. Fasting Plasma Glucose



- **Placebo-adjusted Day 29 Percent Change from Baseline**

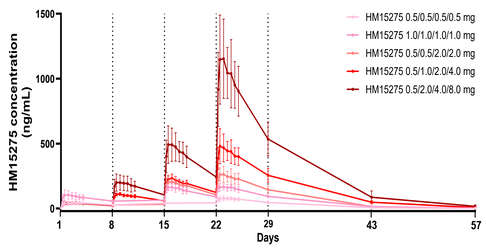
Dose (mg)	HM15275 0.5/0.5/0.5/0.5	HM15275 1.0/1.0/1.0/1.0	HM15275 0.5/0.5/2.0/2.0	HM15275 0.5/1.0/2.0/4.0	HM15275 0.5/2.0/4.0/8.0
Mean (SD)	-2.12 (0.87)	-3.65 (1.41)	-2.96 (0.96)	-2.70 (1.03)	-4.81 (1.01)

Placebo
HM15275 0.5/0.5/0.5/0.5
HM15275 1.0/1.0/1.0/1.0
HM15275 0.5/0.5/2.0/2.0
HM15275 0.5/1.0/2.0/4.0
HM15275 0.5/2.0/4.0/8.0

* Presented data are mean with standard deviation (SD).

Pharmacokinetics

Plasma HM15275 concentration



Summary of PK parameters (Week 4)

Mean (SD)	HM15275 (mg) 0.5/0.5/0.5/0.5 (N=8)	1.0/1.0/1.0/1.0 (N=8)	0.5/0.5/2.0/2.0 (N=8)	0.5/1.0/2.0/4.0 (N=8)	0.5/2.0/4.0/8.0 (N=8)
C_{max} (ng/mL)	82.25 (17.02)	175.33 (26.10)	273.00 (54.82)	509.43 (109.64)	1,205.00 (309.05)
T_{max} (h)	37.50 (14.96)	30.00 (19.72)	22.00 (9.03)	29.16 (19.44)	24.00 (12.83)
$t_{1/2}$ (h)	122.11 (15.96)	130.22 (13.24)	110.13 (7.90)	131.74 (13.61)	129.49 (18.61)
$AUC_{0\text{-}tau}$ (h·ng/mL)	11,103.18 (1,924.41)	22,416.26 (2,983.92)	34,684.95 (6,651.01)	61,232.32 (9,516.64)	140,081.87 (31,242.98)
$AUC_{0\text{-}last}$ (h·ng/mL)	16,642.99 (6,039.22)	34,763.88 (12,576.86)	57,999.37 (11,751.47)	107,660.97 (17,835.27)	239,501.86 (57,585.29)

Concluding Remarks

- HM15275 was safe and well-tolerated, consistent with the safety profile of incretin-based therapies. The favorable safety and tolerability observed, despite the rapid 4-week titration, support the potential for higher dose exposure in future clinical studies.
- The MAD demonstrated approximately dose-dependent PK profiles with a half-life supporting a weekly dosing regimen.
- Weight loss observed over the short study duration suggests clinically meaningful effects and supports further investigation of HM15275.
- Phase 2 study for treatment of **obesity** will be initiated in **4Q 2025**. (NCT07205900)
- Phase 2 study for treatment of **T2DM** is planned for **1Q 2026**.
- **Hanmi's posters in ObesityWeek® 2025**
  - HM17321: Muscle preservation and blood glycemic control (P-105)
    AI-based discovery (P-320), Blood & muscle proteomics for muscle preservation (P-571)

1. U.S. Food and Drug Administration. *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (2007)