Safety, Tolerability, and Pharmacokinetics of HM15275, a Novel GLP-1, GIP, and Glucagon Triple Receptor Agonist: Results from a Phase 1 Study

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Abstract #1980-LB

Abstract

Introduction: HM15275 is a novel triple receptor agonist targeting GLP-1, GIP, and glucagon receptors, designed for balanced receptor activation, enhanced metabolic efficacy, and extended stability to enable once-weekly dosing. This first-in-human study evaluated the safety, pharmacokinetics (PK), and efficacy of HM15275 in adults.

Methods: This was a randomized, double-blind, placebo-controlled study. In the single ascending dose (SAD) part, healthy adults (BMI 20-27 kg/m²) received a single subcutaneous dose of HM15275 at 1, 2, or 4 mg. In the multiple ascending dose (MAD) part, obese adults (BMI 30–45 kg/m²) without diabetes received four weekly subcutaneous doses of HM15275: 1 mg (B1), 0.5 mg (B2), 0.5–2 mg (B3), 0.5–4 mg (B4), or 0.5–8 mg (B5).

Results: The SAD part included 24 healthy volunteers (66.7% male; age 42.2 ± 10.2 years; BMI 24.0 ± 2.0 kg/m²). The most common adverse events (AEs) in HM15275 recipients were mild to moderate gastrointestinal symptoms. No clinically significant changes in vital signs or laboratory parameters were observed.

The MAD part included 50 obese adults (62.0% male; age 46.9 ± 11.0 years; BMI 33.3 ± 2.9 kg/m²). The most common AEs included nausea, constipation, diarrhea, and emesis, which were mostly mild in severity. No serious AEs or discontinuations due to treatment-related AEs occurred in either part of the study.

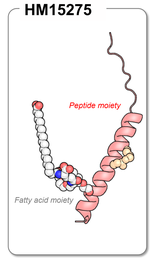
The PK profile after a single subcutaneous dose showed dose-proportional mean C_{max} (145.3–637.7 ng/mL) and mean AUC_{inf} (31,960-126,797 h·ng/mL). Median T_{max} was 12.0–30.0 hours, and the median elimination half-life was 148.7–157.2 hours, supporting weekly dosing.

Subjects receiving HM15275 exhibited reduction in body weight across all dose levels compared to placebo on Day 29. The highest-dose cohort (B5) showed the greatest reduction, with a mean placebo-adjusted weight loss of -4.81 ± 1.01 %. The greatest body weight loss observed after four doses was -10.64% from baseline.

Conclusion: HM15275 was well tolerated, with no serious AEs and a safety profile consistent with that of incretin-based therapies. Its PK characteristics support once-weekly dosing. Early weight loss findings suggest clinically meaningful efficacy, warranting further evaluation of HM15275 for the treatment of obesity and other cardiometabolic disorders.

Background: HM15275

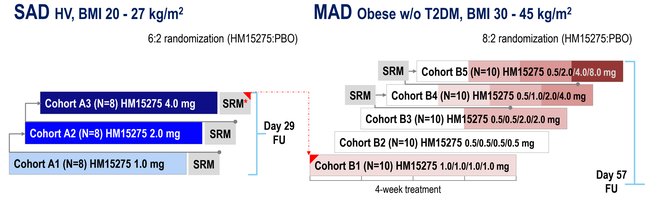
Rationally developed GLP-1/GIP/Glucagon triple co-agonist



- Activity balance of drug moiety optimized for both obesity and glycemic control
- Modality validated for obesity management and weekly dosing
- Potent weight loss was demonstrated in obese animal model
- Improved weight loss quality and CVRM benefits expected by proper implementation/utilization of glucagon

*More preclinical study results available at 755-P, 774-P**

Design of HM15275 Phase 1 Study



- **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

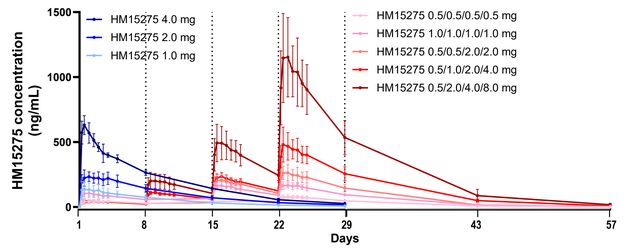
Demographics and Baseline Characteristics

Mean (SD)*	SAD HM15275 (mg) 1.0 (N=6)	SAD HM15275 (mg) 2.0 (N=6)	SAD HM15275 (mg) 4.0 (N=6)	SAD Pooled Placebo (N=6)	MAD HM15275 (mg) 0.5/0.5/0.5/0.5 (N=8)	MAD HM15275 (mg) 1.0/1.0/1.0/1.0 (N=8)	MAD HM15275 (mg) 0.5/0.5/2.0/2.0 (N=8)	MAD HM15275 (mg) 0.5/1.0/2.0/4.0 (N=8)	MAD HM15275 (mg) 0.5/2.0/4.0/8.0 (N=8)	MAD Pooled Placebo (N=10)
Age: year	40.3 (13.3)	41.5 (9.5)	42.8 (12.7)	44.0 (6.6)	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	3/3	2/4	2/4	1/5	2/6	3/5	3/5	2/6	3/5	6/4
Weight: kg	73.1 (10.1)	71.3 (12.5)	70.7 (7.5)	72.1 (4.3)	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	24.2 (1.8)	23.4 (2.6)	24.1 (2.0)	24.1 (2.1)	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	88.8 (3.3)	88.5 (7.2)	93.7 (6.6)	92.3 (2.3)	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	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	5 (62.5)	5 (62.5)	4 (50.0)	5 (62.5)	6 (75.0)	6 (60.0)
Not Hispanic or Latino	4 (66.7)	5 (83.3)	4 (66.7)	4 (66.7)	3 (37.5)	3 (37.5)	4 (50.0)	3 (37.5)	2 (25.0)	4 (40.0)
Not reported	0	0	0	1 (16.7)	0	0	0	0	0	0

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

PK Profile of HM15275

Plasma HM15275 concentration



Summary of PK parameters-SAD

Mean (SD)	HM15275 (mg) 1.0 (N=6)	HM15275 (mg) 2.0 (N=6)	HM15275 (mg) 4.0 (N=6)
C_{max} (ng/mL)	145.27 (61.57)	243.50 (39.09)	637.67 (75.19)
T_{max} (hr)	31.02 (24.71)	40.00 (25.92)	13.02 (5.90)
$t_{1/2}$ (hr)	141.11 (18.67)	158.53 (27.25)	151.91 (29.61)
$AUC_{0\text{-}last}$ (ng·h/mL)	28,322.21 (6,598.42)	61,506.81 (14,031.99)	100,307.93 (36,344.79)
$AUC_{0\text{-}inf}$ (ng·h/mL)	31,959.52 (7,558.40)	65,502.37 (16,374.39)	126,797.33 (9,475.50)

Summary of PK parameters-MAD

Mean (SD)	HM15275 (mg) 0.5/0.5/0.5/0.5 W1	0.5/0.5/0.5/0.5 W4	1.0/1.0/1.0/1.0 W1	1.0/1.0/1.0/1.0 W4	0.5/0.5/2.0/2.0 W1	0.5/0.5/2.0/2.0 W4	0.5/1.0/2.0/4.0 W1	0.5/1.0/2.0/4.0 W4	0.5/2.0/4.0/8.0 W1	0.5/2.0/4.0/8.0 W4
C_{max} (ng/mL)	47.74 (11.72)	82.25 (17.02)	108.76 (39.61)	175.33 (26.11)	44.91 (12.46)	273.00 (54.82)	42.08 (6.73)	509.43 (109.64)	47.74 (13.61)	1,205.0 (309.05)
T_{max} (hr)	37.50 (26.01)	37.50 (14.96)	25.50 (10.01)	30.00 (19.72)	45.00 (21.03)	22.00 (9.03)	52.54 (16.85)	29.16 (19.44)	22.5 (14.96)	24.00 (12.83)
$t_{1/2}$ (hr)	203.3 (101.36)	122.11 (15.96)	160.61 (40.65)	130.22 (13.24)	145.66 (32.38)	110.13 (7.9)	135.74 (12.55)	131.74 (13.61)	155.3 (76.25)	129.49 (18.61)
$AUC_{0\text{-}tau}$ (ng·h/mL)	6,385.48 (1,196.51)	11,103.18 (1,924.41)	13,070.62 (3,299.43)	22,416.26 (2,983.92)	6,404.02 (1,248.59)	34,684.95 (6,651.01)	5,759.21 (594.9)	61,232.32 (9,516.64)	5,708.99 (1,309.65)	140,081.87 (31,242.98)
$AUC_{0\text{-}last}$ (ng·h/mL)	6,126.24 (1,124.38)	16,642.99 (6,039.22)	12,564.31 (4,210.94)	34,763.88 (12,576.86)	5530.38 (1434.14)	57,999.37 (11,751.47)	5,458.89 (1,438.12)	107,660.97 (17,835.27)	5,705.23 (1,308.98)	23,9501.86 (57,585.29)

Summary of Overall Treatment Emergent Adverse Events

Subject with any (n, %)	SAD HM15275 (mg) 1.0 (N=6)	SAD HM15275 (mg) 2.0 (N=6)	SAD HM15275 (mg) 4.0 (N=6)	SAD Pooled Placebo (N=6)	MAD HM15275 (mg) 0.5/0.5/0.5/0.5 (N=8)	MAD HM15275 (mg) 1.0/1.0/1.0/1.0 (N=8)	MAD HM15275 (mg) 0.5/0.5/2.0/2.0 (N=8)	MAD HM15275 (mg) 0.5/1.0/2.0/4.0 (N=8)	MAD HM15275 (mg) 0.5/2.0/4.0/8.0 (N=8)	MAD Pooled Placebo (N=10)
TEAE	6 (100.0)	5 (83.3)	6 (100.0)	6 (100.0)	7 (87.5)	7 (87.5)	7 (87.5)	6 (75.0)	8 (100.0)	10 (100.0)
TRAE	6 (100.0)	5 (83.3)	6 (100.0)	0	3 (37.5)	7 (87.5)	7 (87.5)	4 (50.0)	6 (75.0)	5 (50.0)
Maximum Severity										
Grade 1	6 (100.0)	5 (83.3)	3 (50.0)	0	2 (25.0)	5 (62.5)	6 (75.0)	1 (12.5)	5 (62.5)	3 (30.0)
Grade 2	0	0	2 (33.3)	0	1 (12.5)	2 (25.0)	1 (12.5)	3 (37.5)	1 (12.5)	2 (20.0)
Grade 3	0	0	1 (16.7)[a]	0	0	0	0	0	0	0
Serious TEAE	0	0	0	0	0	0	0	0	0	0
TEAE leading to study discontinuation	0	0	0	0	0	1 (12.5)[b]	1 (12.5)[c]	0	0	0
GI-TRAE	**5 (83.3)**	**5 (83.3)**	**6 (100.0)**	**0 (0.0)**	**3 (37.5)**	**7 (87.5)**	**5 (62.5)**	**4 (50.0)**	**6 (75.0)**	**4 (40.0)**
Abdominal discomfort	1 (16.7)	0	0	0	0	0	0	0	0	0
Abdominal distension	0	0	2 (33.3)	0	2 (25.0)	3 (37.5)	0	0	0	0
Abdominal pain	0	0	0	0	1 (12.5)	0	0	0 (0.0)	1 (12.5)	1 (10.0)
Constipation	0	2 (33.3)	3 (50.0)	0	3 (37.5)	0	0	2 (25.0)	1 (12.5)	3 (30.0)
Dyspepsia	1 (16.7)	0	1 (16.7)	0	0	1 (12.5)	2 (25.0)	0	0	0
Eructation	0	0	1 (16.7)	0	0	0	0	0	0	0
Gastroesophageal reflux disease	0	1 (16.7)	0	0	0	0	0	0	1 (12.5)	0
Diarrhea	0	0	0	0	1 (12.5)	0	0	4 (50.0)	1 (12.5)	0
Nausea	5 (83.3)	4 (66.7)	5 (83.3)	0	1 (12.5)	5 (62.5)	5 (62.5)	3 (37.5)	5 (62.5)	2 (20.0)
Vomiting	1 (16.7)	2 (33.3)	5 (83.3)	0	0	1 (12.5)	1 (12.5)	2 (25.0)	2 (25.0)	1 (10.0)

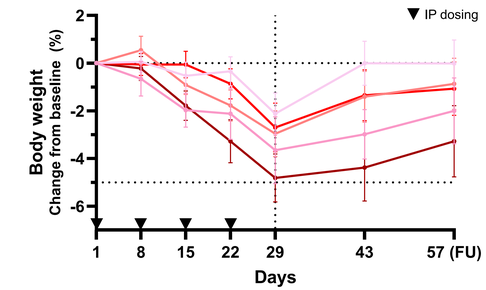
a. Nausea and Vomiting. In this study, severity grading for nausea/vomiting was assessed based on number of episode.[1] (Grade 1: 1-2 episodes / 24 hours, Grade 2: 3-5 episodes / 24 hours, Grade 3: > 6 episodes / 24 hours). This grading scale was to fully understand subject's GI-AEs, despite being more stringent than CTCAE grade.

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 by ECG, prior to the 3rd dosing.

Key Data from HM15275 MAD Study

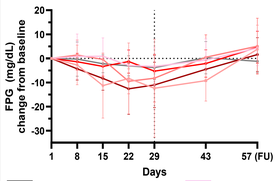
A. Body Weight (Placebo-adjusted)



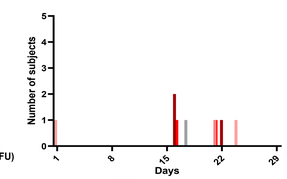
- Placebo-adjusted D29 % Change from baseline

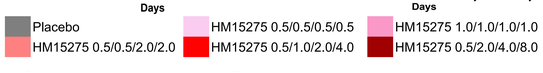
Dose (mg)	HM15275 0.5/0.5/0.5/0.5	HM15275 1.0/1.0/1.0/1.0	HM15275 0.5/0.5/2.0/2.0	HM15275 0.5/1.0/2.0/4.0	HM15275 0.5/2.0/4.0/8.0
Mean (SD)	-2.12 (0.87)	-3.65 (1.41)	-2.96 (0.96)	-2.70 (1.03)	-4.81 (1.01)

B. Fasting Plasma Glucose



C. Incidence of Vomiting





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

Concluding Remarks

- HM15275 was safe and well tolerated, consistent with 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 SAD PK profile demonstrates dose proportionality and supports a weekly dosing regimen.
- Weight loss observed over the short study duration suggests clinically meaningful effects and supports further investigation of HM15275.

References

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)

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