A double-blind, placebo-controlled single ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of HM15136, a novel long-acting glucagon analogue, in healthy subjects

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ABSTRACT

HM15136 is a novel long-acting glucagon analogue with an extended half-life. In vivo efficacy studies of HM15136 in animal models showed its therapeutic potential in congenital hyperinsulinism, hypoglycaemia post-bariatric surgery, and obesity. We performed a randomized, double-blind, placebo-controlled first-in-human trial to assess the safety, pharmacokinetics, and pharmacodynamics of a single subcutaneous dose of HM15136 in healthy adults. Fifty-six subjects randomly received HM15136 or its matching placebo in a ratio of 6:2 in 7 cohorts (10, 20, 30, 50, 80, 100, and 120 μg/kg). All adverse events were transient and mild in severity. Neither serious adverse event nor discontinuation due to adverse event occurred during the study. The most frequent Treatment Emergent Adverse Event was nausea (7.2%, only in the 100 and 120 μg/kg groups). Injection site erythema, which was barely noticeable and spontaneously subsided without sequelae, was reported in 2 out of 42 subjects who received HM15136. HM15136 was slowly, but steadily absorbed with the peak serum concentration reaching 34.2-65.2 hours after dose. The terminal half-life ranged from 69.8 to 85.6 hours, which was significantly greater than that of glucagon (< 1 hour). HM15136, particularly at doses >50 μg/kg, increased mean serum glucose from baseline by up to 27.7 mg/dL, which was maintained until 17 days after dose. In conclusion, a single subcutaneous dose of HM15136 at 10-120 μg/kg was safe and well-tolerated. The long half-life of HM15136, coupled with increase in serum glucose for ~2 weeks, may warrant a weekly or longer dosing regimen.

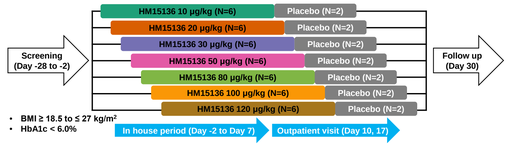
BACKGROUND

HM15136 is a glucagon analogue, conjugated with a human IgG Fc fragment *via* a flexible PEG linker

[General Profile of HM15136]

- **Although glucagon is considered as one of the most potent therapeutic options, its utilization is limited due to poor solubility, limited stability at physiological pH and short duration of action.**
- **To overcome these limitations, HM15136, a novel long-acting glucagon analogue with an extended half-life, is being developed.**
- **Stable and highly soluble weekly glucagon analog**
- **Sufficient PK profile for once a week administration**
- ***In vivo* efficacy studies of HM15136 in animal models showed its therapeutic potential in congenital hyperinsulinism, hypoglycaemia post-bariatric surgery, and obesity.**

STUDY DESIGN



- **Primary objective:** To assess safety and tolerability of HM15136 after single subcutaneous (sc) doses
- **Secondary objective:** To assess pharmacokinetic profile of HM15136 after single sc doses
- **Exploratory objective:** To assess pharmacodynamics properties of HM15136 after single sc doses

RESULTS

- **Demographics and baseline characteristics**

	HM15136 dose (μg/kg)							
	10 (N=6)	20 (N=6)	30 (N=6)	50 (N=6)	80 (N=6)	100 (N=6)	120 (N=6)	Placebo (N=14)
Male sex	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	14 (100.0)
Age (years)	31.7 ± 5.8	35.2 ± 6.5	31.2 ± 5.3	27.8 ± 2.7	32.3 ± 6.3	32.2 ± 12.4	26.2 ± 7.9	31.4 ± 6.9
Weight (kg)	67.4 ± 7.1	65.7 ± 7.2	69.7 ± 7.5	75.2 ± 7.9	71.1 ± 9.0	69.3 ± 11.1	63.7 ± 6.4	70.7 ± 6.3
Height (cm)	172.4 ± 4.5	173.0 ± 4.0	172.2 ± 3.0	174.0 ± 3.7	172.6 ± 7.2	172.6 ± 6.8	172.0 ± 6.4	174.3 ± 5.6
BMI (kg/m²)	22.6 ± 1.9	21.9 ± 2.5	23.5 ± 2.3	24.8 ± 1.6	23.8 ± 1.7	23.2 ± 3.0	21.6 ± 3.1	23.3 ± 2.0
HbA1c (%)	5.2 ± 0.3	5.2 ± 0.3	5.3 ± 0.3	5.2 ± 0.2	5.3 ± 0.2	5.2 ± 0.4	5.2 ± 0.3	5.2 ± 0.3

* Mean ± standard deviation was presented except for male sex, where number of subjects (percentage of subjects) was presented.

- **Safety and tolerability**

a. All adverse events were mild in severity and transient. Neither serious adverse event nor discontinuation due to adverse event occurred during the study. The most frequent Treatment Emergent Adverse Event was nausea (7.2%, only in the 100 and 120 μg/kg groups).

Type of TEAEs, n (%)	HM15136 dose (μg/kg)							
	10 (N=6)	20 (N=6)	30 (N=6)	50 (N=6)	80 (N=6)	100 (N=6)	120 (N=6)	Placebo (N=14)
Any TEAE	1 (16.7)	3 (50.0)	4 (66.7)	1 (16.7)	3 (50.0)	3 (50.0)	5 (83.3)	3 (21.4)
Maximum Severity of TEAE								
Mild	1 (16.7)	3 (50.0)	4 (66.7)	1 (16.7)	3 (50.0)	3 (50.0)	5 (83.3)	3 (21.4)
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Any TEAE related to IMP	0	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	4 (66.7)	1 (7.1)
Maximum Severity of TEAE related to IMP								
Mild	0	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	4 (66.7)	1 (7.1)
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Any TEAE resulting in death	0	0	0	0	0	0	0	0
Any TEAE leading to withdrawal	0	0	0	0	0	0	0	0
Any serious TEAE	0	0	0	0	0	0	0	0

b. Injection site erythema, which was barely noticeable and spontaneously subsided without sequelae, was reported in 2 out of 42 subjects who received HM15136.

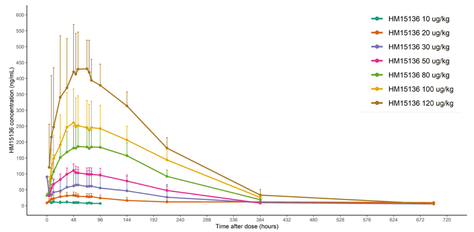
c. Overall, no anti-drug antibodies and anti-polyethylene glycol antibodies were detected in the study. There were no subjects had confirmed antibodies, so neutralizing antibodies were not analyzed.

Time point	Tier	Category, n (%)	HM15136 dose (μg/kg)							
			10 (N=6)	20 (N=6)	30 (N=6)	50 (N=6)	80 (N=6)	100 (N=6)	120 (N=6)	Placebo (N=14)
Baseline	Screen	Negative	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	13 (92.9)
		Positive	0	0	0	0	0	0	0	1 (7.1)
	Confirm	N/A	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	13 (92.9)
		Negative	0	0	0	1 (16.7)	0	0	0	1 (7.1)
Day 17	Screen	Negative	5 (83.3)	6 (100.0)	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	13 (92.9)
		Positive	1 (16.7)	0	1 (16.7)	0	0	0	0	1 (7.1)
	Confirm	N/A	5 (83.3)	6 (100.0)	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	13 (92.9)
		Negative	1 (16.7)	0	1 (16.7)	0	0	0	0	1 (7.1)
Day 30	Screen	Negative	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)	14 (100.0)
		Positive	1 (16.7)	0	0	0	0	0	0	0
	Confirm	N/A	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)	14 (100.0)
		Negative	1 (16.7)	0	0	0	0	0	0	0

* Number of subjects (percentage of subjects)

- **Pharmacokinetics**

a. Mean serum HM15136 concentration versus time



* Error bars denoted standard deviation.

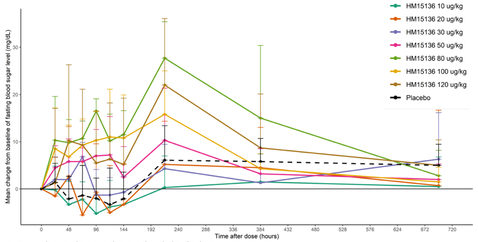
b. Summary PK parameters of HM15136

	HM15136 dose (μg/kg)						
	10 (N=4)	20 (N=6)	30 (N=6)	50 (N=6)	80 (N=6)	100 (N=6)	120 (N=6)
C_{max} (ng/mL)	9.9 ± 4.6	33.1 ± 9.8	66.9 ± 48.5	110.5 ± 20.8	199.2 ± 61.7	273.7 ± 93.9	469.5 ± 134.8
T_{max} (hr)	46.0 [12.1-56.0]	48.0 [36.0-56.0]	56.0 [35.6-80.0]	48.0 [48.0-48.0]	68.0 [48.0-80.0]	48.0 [36.0-96.0]	60.0 [24.0-80.0]
AUC_{0-t} (hr*ng/mL)	668.1 ± 399.2	5,068.4 ± 4,308.2	11,926.2 ± 12,860.7	19,575.9 ± 5,196.2	38,429.5 ± 11,281.1	53,516.0 ± 11,828.7	83,623.1 ± 11,367.1
AUC_{inf} (hr*ng/mL)	1,472.2 ± 159.6	6,499.6 ± 5,398.4	13,084.3 ± 12,749.7	22,146.8 ± 4,095.3	42,217.2 ± 11,155.6	56,625.9 ± 10,607.4	87,613.8 ± 10,135.5
$t_{1/2}$ (hr)	77.1 ± 41.0	101.1 ± 77.1	84.3 ± 26.2	84.0 ± 21.4	79.2 ± 24.6	79.7 ± 19.0	81.5 ± 16.5

* Mean ± standard deviation was presented except for T_{max}, where median [minimum-maximum] was presented.

- **Pharmacodynamics**

a. Mean change from baseline of fasting blood sugar level versus time



* Error bars denoted standard deviation.

CONCLUSIONS

A single subcutaneous dose of HM15136 at 10-120 μg/kg was safe and well-tolerated.

The long half-life of HM15136, coupled with increase in serum glucose, may warrant a weekly or longer dosing regimen.

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Hanmi Pharm. Co., Ltd.