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ORIGINAL ARTICLE

Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of the novel long-acting glucagon analogue HM15136 in overweight and obese patients with co-morbidities

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Abstract

Aim: To evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of the novel long-acting glucagon analogue HM15136 in overweight/obese patients with co-morbidities, with and without type 2 diabetes (T2D).

Materials and Methods: This was a phase 1, double-blind, randomized, placebo-controlled, two-part trial with a 12-week treatment period of once-weekly subcutaneous HM15136 (0.02/0.04/0.06 mg/kg). Part 1 included patients with dyslipidaemia and/or hypertension and no T2D. Part 2 included patients with dyslipidaemia and/or hypertension plus T2D.

Results: In part 1, 23/27 (85.2%) patients receiving HM15136 and all patients receiving placebo (9/9 [100%]) experienced a treatment-emergent adverse event (TEAE). Five of 27 (18.5%) patients receiving HM15136 developed anti-HM15136 antibodies. Dose-dependent increases in mean HM15136 serum concentration and fasting plasma glucose (FPG) were observed, as were dose-dependent weight reductions of 0.5%/2.3%/2.6% at doses of 0.02/0.04/0.06 mg/kg, respectively. In part 2, 8/12 (66.7%) patients receiving HM15136 and all patients receiving placebo (4/4 [100.0%]) reported a TEAE. Two (16.7%) patients developed anti-HM15136 antibodies. Dose-dependent increases in mean HM15136 serum concentration were observed. FPG of more than 200 mg/dL was reported in 4/9 (44.4%) and 2/3 (66.7%) patients receiving 0.02 and 0.06 mg/kg, respectively. The 0.06 mg/kg dose was not tolerated in part 2 because of hyperglycaemia. Patients receiving 0.02 mg/kg showed a 0.9% weight reduction. No serious TEAEs leading to discontinuation were reported in either study part.

Conclusions: This study of HM15136 provides a preliminary safety and tolerability profile with initial insights into its efficacy profile.

KEYWORDS
glucagon, hypoglycaemia, pharmacodynamics, pharmacokinetics

1 | INTRODUCTION

Glucagon has long been considered a candidate therapy for the treatment of hypoglycaemia because of its role in glucose homeostasis via glycogenolysis and gluconeogenesis.[1] Based on this role in glucose metabolism, glucagon has been proposed as a therapeutic agent for chronic hypoglycaemic diseases such as congenital hyperinsulinism[2] and postbariatric hypoglycaemia.[3] Recent studies have also shown that glucagon plays a central role in the regulation of lipid metabolism, energy expenditure and satiety regulation,[4] which implies that it may have a potential role in obesity management; this theory is supported by the fact that glucagon displays co-agonism with glucagon-like peptide-1 (GLP-1).[5] However, the long-term utilization of glucagon as a treatment option has been limited because of its poor solubility, limited stability at physiological pH and short duration of action.[6]

HM15136 is a novel long-acting glucagon analogue developed to address unmet needs in metabolic indications that might benefit from glucagon receptor agonism (e.g. hypoglycaemic disorders, obesity).[7,8] Compared with native glucagon, HM15136 has an extended half-life (0.2 vs. 36.0 hours), improved solubility (0.03 vs. ≥ 150 mg/mL) and 90% subcutaneous bioavailability, as shown in murine studies.[9] HM15136 was associated with reversal of acute hypoglycaemia and normalization of blood glucose in insulin-induced hypoglycaemic rodent models,[9] and significant body weight reduction over time in a dose-dependent manner in animals.[10] A first-in-human clinical study in healthy Korean adults (NCT04032782) confirmed that subcutaneous (s.c.) HM15136 has a prolonged half-life versus glucagon. Treatment-emergent adverse events (TEAEs) in that trial were mild, transient and resolved without sequelae, and safety and tolerability were shown at doses of 0.01-0.12 mg/kg, meriting further exploration of dose dependency.[8]

This initial clinical exploration was conducted in overweight and obese patients with co-morbidities (dyslipidaemia and/or hypertension) with and without type 2 diabetes (T2D), with the aim of evaluating the safety, tolerability, pharmacokinetics (PK) and dose dependence of multiple ascending doses of HM15136. Exploratory objectives included assessment of pharmacodynamics (PD).

2 | MATERIALS AND METHODS

2.1 | Study design

This phase 1, double-blind, randomized, placebo-controlled, multiple-ascending dose study was conducted in two sequential parts, each with a 12-week treatment period (Figure S1). The study took place from 30 August 2019 to 9 December 2020. Postscreening, the study comprised two in-house periods, 16 outpatient day visits and three follow-up visits. The study design for sequential dosing is shown in Figure S1.

2.2 | Study participants

Patients aged 18-65 years with stable weight (change < 5%) in the 3 months prior to study start and accompanying weight co-morbidities (i.e. body mass index [BMI] ≥ 30 kg/m^2 [obese] or ≥ 27 kg/m^2 [overweight], according to United States Food and Drug Administration [FDA] guidance)[11] were eligible to participate. In part 1, eligible patients had dyslipidaemia and/or hypertension, no diagnosis of T2D (defined by fasting plasma glucose [FPG] < 5.6 mmol/L [< 100 mg/dL]) and HbA1c less than 5.7%. In part 2, eligible patients had dyslipidaemia and/or hypertension, a diagnosis of T2D (treated orally with metformin) and HbA1c of 9% or less in the previous 3 months.

Individuals were excluded if they had: a history of prior gastrointestinal (GI) surgical treatment for obesity; receipt of medication known to modify GI motility within 2 weeks prior to screening; uncontrolled hypertension (blood pressure [BP] > 160 [systolic]/ ≥ 100 [diastolic] mmHg); uncontrolled dyslipidaemia (fasting triglycerides > 500 mg/dL and/or fasting low-density lipoprotein [LDL] cholesterol > 200 mg/dL); history/current diagnosis of heart disease; infection with coronavirus disease 2019 (COVID-19) within 30 days prior to participation; prior treatment with a GLP-1 receptor agonist (GLP-1 RA), sodium-glucose co-transporter-2 inhibitor, insulin or dipeptidyl peptidase-4 inhibitors within 3 months prior to screening. As the study took place during the COVID-19 pandemic, protocol modifications were made as per FDA guidance for clinical trial conduct during this time (e.g. inpatient assessment visits could be moved to an outpatient setting, and timing of visits adjusted to accommodate limited site access, where appropriate). Protocol deviations in visit scheduling because of the COVID-19 pandemic are shown in Table S1. As per protocol, patients could discontinue study participation at any time.

Patients were to be randomized to s.c. HM15136 or placebo in a ratio of 3:1 (part 1), 3:1 (part 2, 0.02 mg/kg dose) and 1:1 (part 2, 0.06 mg/kg) once weekly for 12 weeks. Part 1 cohort dose escalations and progression to part 2 occurred following independent Data Monitoring Committee review of safety data. Written informed consent was obtained from eligible patients prior to any study-related procedure. The study was conducted in full accordance with the Declaration of Helsinki (ClinicalTrials.gov: NCT04167553).

2.3 | Safety, tolerability and immunogenicity

Safety and tolerability were assessed by monitoring TEAEs, clinical laboratory variables (haematology, clinical chemistry, coagulation and urinalysis), physical examination findings, vital signs, 24-hour ambulatory blood pressure measurement (ABPM) and 12-lead electrocardiogram monitoring, and injection-site reactions at regular intervals throughout the study. For safety reasons, participants in part 1 were to be withdrawn from the study if they had an FPG of 180 mg/dL or higher, and participants in part 2 were to be withdrawn if they had an FPG of 270 mg/dL or higher. Immunogenicity testing for antidrug

antibodies and neutralizing antibodies followed a multi-tiered testing approach (Appendix S1).

2.4 | Pharmacokinetics and pharmacodynamics

PK analyses included concentration–time and area under the curve (AUC) data, terminal elimination rate, apparent clearance and volume of distribution. Exploratory PD included the assessment of body weight, FPG (following a ≥ 10-hour overnight fast), lipid profiles, estimated glomerular filtration rate (eGFR), HbA1c and liver and visceral fat (as per magnetic resonance imaging-estimated proton density fat fraction).

2.5 | Statistical analysis

No formal sample size calculation was performed. Descriptive statistics were used to summarize baseline characteristics, safety and tolerability, immunogenicity, PK and PD outcomes. AUC variables, $AUC_{0\text{-}t}$ at steady state and maximum concentration (C_{max}), were log-transformed as per geometric statistics using the linear rule for AUC absorption phase and the logarithmic rule for elimination phase. Dose proportionality was assessed by log-transformed PK variables, $AUC_{0\text{-}t}$ at steady state and C_{max}, and a linear regression approach was used for log-transformed dose levels. Determination of dose proportionality of AUC_{tau} and C_{max} was based on the 90% confidence interval (CI) of the ratio of dose-normalized geometric least squares (LS) means falling within the prespecified limits of 0.8-1.25. A mixed-model repeated-measures analysis was performed for changes from baseline in PD variables. LS mean (95% CI) differences between each treatment group and placebo were calculated for weight, liver and visceral fat volume and FPG. Post hoc linear regression analyses were also carried out to examine the possibility of a correlation between time-matched FPG and eGFR.

Statistical analyses were performed using SAS version 9.4. PK variables were derived using standard non-compartmental methods (WinNonlin v. 5.2) and PD variables were derived with SAS version 9.4.

3 | RESULTS

3.1 | Patient disposition and characteristics (parts 1 and 2)

In part 1, 30/37 (81.1%) randomized patients completed the study; study completers were treated with either HM15136 (administered s.c. once weekly at doses of 0.02 mg/kg [$n = 8$], 0.04 mg/kg [$n = 9$] and 0.06 mg/kg [$n = 6$]), or placebo ($n = 7$; Table S2). One patient (randomized to 0.04 mg/kg) withdrew consent prior to receiving treatment. Six patients (16.2%) discontinued study participation after receiving treatment because of personal reasons not related to health ($n = 3$), lost to follow-up ($n = 2$), or for reasons related to the COVID-19 pandemic ($n = 1$). In part 2, 11/16 (68.8%) randomized patients with T2D completed the study; study completers were treated with s.c. HM15136 once weekly at doses of 0.02 mg/kg ($n = 6$) or 0.06 mg/kg ($n = 1$), or received placebo ($n = 4$; Table S2). In part 2, five patients (31.3%) discontinued the study after receiving treatment, either because of personal reasons ($n = 1$) or based on the physician's decision ($n = 4$). Of these latter four patients ($n = 2$ [0.02 mg/kg]; $n = 2$ [0.06 mg/kg]), three had hyperglycaemic FPG levels of 270 mg/dL or higher and were withdrawn from the study as per the protocol. The fourth patient had hyperglycaemic FPG of 200 mg/dL or higher after their first dose (0.06 mg/kg), and could not continue the study because of COVID-19 travel restrictions. Demographic and baseline characteristics were generally well balanced between groups (Table 1).

3.2 | Safety, tolerability and immunogenicity in part 1

In part 1, TEAEs of any kind were reported by 23/27 (85.2%) patients who received HM15136 (any dose) and 9/9 (100%) who received placebo; the majority of TEAEs were mild in terms of severity. The most commonly reported classes of TEAE across all groups were: infections and infestations; general disorders and administration-site conditions; GI disorders; and skin and s.c. tissue disorders (Table 2A). No serious TEAEs leading to discontinuation were reported in part 1. One patient receiving HM15136 0.06 mg/kg experienced a mild TEAE (diarrhoea) and a severe TEAE (peritonsillar abscess) that were considered unrelated to the study drug; ongoing peritonsillar abscess complications led the patient to discontinue treatment and the abscess eventually resolved.

Five of the 27 patients treated with HM15136 (18.5%) developed anti-HM15136 antibodies during the study (Table 3A; Table S3A); in one patient, a neutralizing effect was observed on HM15136 (but not on endogenous glucagon) towards the end of the treatment period. There were no clinically significant TEAEs or PK/PD findings at the time of anti-HM15136 antibody observation. No patients who received placebo had anti-HM15136 antibodies, and no patients in any treatment group showed treatment-emergent anti-PEG antibodies during the study.

Changes in clinical laboratory evaluations, vital signs and physical examination findings were minor and did not differ between treatment groups. Mean changes from baseline to day 80 in diurnal diastolic ABPM ranged from −2.4 to −6.8 mmHg across groups, while the corresponding values for systolic ABPM ranged from −2.1 to −4.9 mmHg across groups.

3.3 | PK and PD in part 1

In the PK population ($n = 25$ patients who received HM15136), mean serum concentrations (Figure S2A), mean AUC over the dosing

TABLE 1 Patient baseline demographics and characteristics in A, Part 1, and B, Part 2 of the study (safety population)

	(A) Part 1				
	HM15136			Placebo	Total
Characteristics	0.02 mg/kg ($n = 9$)	0.04 mg/kg ($n = 9$)	0.06 mg/kg ($n = 9$)	($n = 9$)	($N = 36$)
Sex, male, *n* (%)	7 (77.8)	3 (33.3)	4 (44.4)	4 (44.4)	18 (50.0)
Age (y)	33.6 (7.8)	33.3 (7.5)	42.6 (10.8)	40.6 (10.7)	37.5 (9.8)
Ethnicity, *n* (%)					
Hispanic or Latino	5 (55.6)	6 (66.7)	3 (33.3)	3 (33.3)	17 (47.2)
Not Hispanic or Latino	4 (44.4)	3 (33.3)	6 (66.7)	6 (66.7)	19 (52.8)
Race, *n* (%)					
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.8)
Black or African American	1 (11.1)	2 (22.2)	2 (22.2)	1 (11.1)	6 (16.7)
White	8 (88.9)	7 (77.8)	6 (66.7)	6 (66.7)	27 (75.0)
Multiple	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.8)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.8)
BMI (kg/m^2)	32.5 (3.3)	34.4 (2.9)	32.1 (4.2)	36.5 (5.0)	33.9 (4.2)
Weight (kg)	99.3 (16.1)	95.1 (19.5)	93.9 (13.7)	104.6 (15.3)	98.2 (16.1)
Liver fat via MRI-PDFF (%)	13.0 (13.3)	5.2 (4.8)	5.9 (4.1)	9.1 (6.8)	8.3 (8.4)
Visceral fat via MRI (L)	1.9 (0.7)	1.6 (0.6)	1.6 (0.7)	1.9 (0.8)	1.7 (0.7)
HbA1c (%)	5.3 (0.3)	5.3 (0.3)	5.3 (0.3)	5.2 (0.3)	5.3 (0.3)
Insulin (μIU/mL)	17.3 (13.7)	15.8 (8.8)	13.8 (5.2)	13.7 (6.1)	15.1 (8.8)
FPG (mg/dL)	93.1 (5.5)	93.0 (6.2)	92.6 (3.9)	90.6 (6.2)	92.3 (5.4)
Total cholesterol (mg/dL)	180.7 (22.0)	164.7 (25.9)	195.8 (35.5)	204.9 (43.9)	186.5 (35.1)
HDL (mg/dL)	42.2 (8.9)	45.6 (12.1)	47.4 (14.5)	49.6 (11.3)	46.2 (11.7)
LDL (mg/dL)	111.4 (17.8)	95.7 (22.6)	119.1 (30.3)	133.7 (38.0)	115.0 (30.4)

	(B) Part 2			
	HM15136		Placebo	Total
Characteristics	0.02 mg/kg ($n = 9$)	0.06 mg/kg ($n = 3$)	($n = 4$)	($N = 16$)
Sex, male, *n* (%)	6 (66.7)	1 (33.3)	0 (0.0)	7 (43.8)
Age (y)	49.7 (5.6)	53.0 (3.0)	57.0 (2.5)	52.1 (5.4)
Ethnicity, *n* (%)				
Hispanic or Latino	7 (77.8)	3 (100.0)	3 (75.0)	13 (81.3)
Not Hispanic or Latino	2 (22.2)	0 (0.0)	1 (25.0)	3 (18.8)
Race, *n* (%)				
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	1 (11.1)	0 (0.0)	0 (0.0)	1 (6.3)
White	8 (88.9)	3 (100.0)	4 (100.0)	15 (93.8)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BMI (kg/m^2)	33.3 (5.3)	32.4 (4.4)	33.6 (2.8)	33.2 (4.4)
Weight (kg)	92.4 (22.6)	89.6 (7.8)	80.9 (7.2)	89.0 (17.7)
Liver fat via MRI-PDFF (%)	15.1 (8.9)	6.4 (2.6)	12.8 (3.7)	12.7 (7.4)
Visceral fat via MRI (L)	1.7 (0.6)	1.6 (0.3)	2.0 (0.3)	1.7 (0.5)
HbA1c (%)	7.5 (0.7)	6.7 (1.0)	6.6 (0.3)	7.1 (0.8)
Insulin (μIU/mL)	16.6 (15.1)	17.5 (6.4)	15.2 (5.5)	16.4 (11.6)
FPG (mg/dL)	139.1 (34.3)	125.7 (26.0)	134.0 (28.8)	135.3 (30.2)
Total cholesterol (mg/dL)	156.2 (24.7)	212.0 (41.0)	179.5 (54.2)	172.5 (40.2)

TABLE 1 (Continued)

	(B) Part 2			
	HM15136		Placebo	Total
Characteristics	0.02 mg/kg ($n = 9$)	0.06 mg/kg ($n = 3$)	($n = 4$)	($N = 16$)
HDL (mg/dL)	40.6 (7. 7)	45.3 (18.8)	55.0 (15.2)	45.1 (12.8)
LDL (mg/dL)	81.3 (28.2)	126.0 (41.9)	101.8 (38.9)	94.8 (35.7)

Note: Data are presented as mean (SD), unless otherwise stated.
Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; IU, international units; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; SD, standard deviation.

interval, C_{max} and C_{trough} increased with ascending HM15136 dose, while mean time to C_{max} decreased as the HM15136 dose increased (data not shown). AUC_{tau} and C_{max} did not fall within the prespecified limits of 0.8-1.25 for dose proportionality. The geometric mean (SE) terminal half-life for HM15136 ranged from 82.7 (3.5) to 167.4 (not applicable) hours.

In the PD population ($n = 36$, including 27 patients who received HM15136 and nine who received placebo), mean FPG levels increased from baseline during HM15136 treatment in a dose-related manner (Figure 1A, Table 4A). FPG in the diabetic range (≥126 mg/dL)[12] was reported in 10/27 patients who received HM15136, including one, four and five patients on 0.02, 0.04 and 0.06 mg/kg doses, respectively. In these patients, FPG returned to baseline 3 weeks after HM15136 discontinuation. Placebo-treated patients exhibited stable FPG levels over time (Figure 1A) and none experienced FPG in the diabetic range.

eGFR mean change from baseline values generally increased among patients receiving HM15136 0.04 and 0.06 mg/kg, compared with a slight decrease among patients receiving HM15136 0.02 mg/kg or placebo (Figure S3A). Linear regression analyses indicated a weak correlation between eGFR and time-matched FPG levels ($R^2 = 0.0318$ for observed FPG values and $R^2 = 0.0930$ for change from baseline FPG data; Figure S4).

At day 85, patients receiving HM15136 showed small weight losses (0.5%, 2.3% and 2.6% in the 0.02, 0.04 and 0.06 mg/kg groups, respectively), while patients receiving placebo showed a small weight gain (2.1%; Table 4A). Minimal changes from baseline were observed in liver and visceral fat (Table 4A), as well as cholesterol (high-density lipoprotein and LDL), triglycerides and HbA1c (Table S4A).

3.4 | Safety, tolerability and immunogenicity in part 2

In part 2, TEAEs of any kind were reported by 8/12 (66.7%) patients who received HM15136 and 4/4 (100%) who received placebo. The most commonly reported classes of TEAE across all groups were GI disorders; skin and s.c. tissue disorders; metabolism and nutrition disorders; and general disorders and administration-site conditions (Table 2B). No serious TEAEs leading to discontinuation were reported. Two of the three (66.7%) patients receiving the 0.06 mg/kg dose did not tolerate treatment as they developed hyperglycaemia (a moderate TEAE) and discontinued study participation because they met the protocol stopping criteria of an FPG of 270 mg/dL or higher. TEAEs that were considered related to HM15136 were reported by 4/12 patients (33.3%), which led to study discontinuation in one (8.3%) patient.

Two of the 12 patients (16.7%) who received HM15136 developed anti-HM15136 antibodies. No neutralizing effect was observed on HM15136 or endogenous glucagon (Table 3B; Table S3B) and no patients showed treatment-emergent anti-PEG antibodies.

As in part 1, changes in clinical laboratory evaluations, vital signs or findings on physical examination were minor and did not differ between treatment groups. Mean changes from baseline to day 80 in diurnal diastolic ABPM ranged from −1.4 to 2.3 mmHg across groups, while the corresponding values for systolic ABPM ranged from −2.8 to 3.4 mmHg across groups.

3.5 | PK and PD in part 2

In the PK population ($n = 8$ patients who received HM15136), mean serum concentration of HM15136 increased when the dose was increased from 0.02 to 0.06 mg/kg (Figure S2B). Because of the small sample size, additional PK findings were limited and are not detailed here.

In the PD population ($n = 16$, including 12 patients who received HM15136 and four who received placebo), individual FPG levels of more than 200 mg/dL were seen in six patients who received HM15136: 4/9 receiving 0.02 mg/kg and 2/3 receiving 0.06 mg/kg. In these patients, FPG returned to baseline 3 weeks after HM15136 discontinuation. No placebo-treated patients experienced FPG levels of more than 200 mg/dL (Figure 1B, Table 4B).

eGFR mean change from baseline showed an increase among patients receiving HM15136 0.06 mg/kg and a decrease among patients receiving HM15136 0.02 mg/kg or placebo (Figure S3B). Linear regression analyses indicated no correlation between eGFR and time-matched FPG levels ($R^2 = 0.0312$ for observed values and $R^2 = 0.0176$ for change from baseline data; Figure S4).

Minimal change in weight from baseline to day 85 was observed in any treatment arm (range: −0.9% to 0.3%). Minimal changes from baseline were observed in liver and visceral fat (Table 4B) and in other exploratory PD variables (Table S4B).

TABLE 2 Summary of adverse drug reactions in A, Part 1, and B, Part 2 of the study (safety population)

	(A) Part 1 ($N = 36$)				
	HM15136				Pooled placebo
System organ class, *n* (%)	0.02 mg/kg ($n = 9$)	0.04 mg/kg ($n = 9$)	0.06 mg/kg ($n = 9$)	Pooled HM15136 ($n = 27$)	($n = 9$)
Any treatment-emergent adverse event	8 (88.9)	7 (77.8)	8 (88.9)	23 (85.2)	9 (100.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.7)	0 (0.0)
Gastrointestinal disorders	1 (11.1)	4 (44.4)	3 (33.3)	8 (29.6)	0 (0.0)
General disorders and administration-site conditions	3 (33.3)	3 (33.3)	3 (33.3)	9 (33.3)	5 (55.6)
Infections and infestations	1 (11.1)	5 (55.6)	8 (88.9)	14 (51.9)	5 (55.6)
Injury, poisoning and procedural complications	0 (0.0)	1 (11.1)	1 (11.1)	2 (7.4)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
Metabolism and nutrition disorders	1 (11.1)	3 (33.3)	0 (0.0)	4 (14.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (11.1)	1 (11.1)	2 (22.2)	4 (14.8)	0 (0.0)
Nervous system disorders	1 (11.1)	0 (0.0)	2 (22.2)	3 (11.1)	3 (33.3)
Renal and urinary disorders	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (33.3)	1 (11.1)	0 (0.0)	4 (14.8)	2 (22.2)
Skin and subcutaneous tissue disorders	1 (11.1)	2 (22.2)	4 (44.4)	7 (25.9)	2 (22.2)

	(B) Part 2 ($N = 16$)			
	HM15136			Placebo
System organ class, *n* (%)	0.02 mg/kg ($n = 9$)	0.06 mg/kg ($n = 3$)	Pooled HM15136 ($n = 12$)	($n = 4$)
Any treatment-emergent adverse event	6 (66.7)	2 (66.7)	8 (66.7)	4 (100.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	2 (22.2)	1 (33.3)	3 (25.0)	1 (25.0)
General disorders and administration-site conditions	1 (11.1)	0 (0.0)	1 (8.3)	2 (50.0)
Infections and infestations	0 (0.0)	1 (33.3)	1 (8.3)	0 (0.0)
Injury, poisoning and procedural complications	1 (11.1)	0 (0.0)	1 (8.3)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	1 (11.1)	1 (33.3)	2 (16.7)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (22.2)	0 (0.0)	2 (16.7)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
Renal and urinary disorders	1 (11.1)	0 (0.0)	1 (8.3)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	3 (33.3)	0 (0.0)	3 (25.0)	3 (75.0)

4 | DISCUSSION

Once-weekly s.c. administration of the novel glucagon analogue HM15136 (0.02-0.06 mg/kg) was generally well tolerated in overweight and obese patients without T2D. Most TEAEs were mild, with no clinically significant laboratory test findings or changes in vital signs, and no new safety signals. Similar results were observed in overweight and obese patients with T2D receiving HM15136 0.02 mg/kg.

Raised FPG levels, including those within diabetic range, were observed in both parts of the study. This suggests a dose-dependent relationship with HM15136, although the small population size of each part precludes definitive conclusions. The possibility of increased glucose levels following administration of a glucagon analogue was

TABLE 3 Immunogenicity in A, Part 1, and B, Part 2 of the study (safety population)

	(A) Part 1 ($N = 36$)			
	HM15136			Pooled placebo
	0.02 mg/kg ($n = 9$)	0.04 mg/kg ($n = 9$)	0.06 mg/kg ($n = 9$)	($n = 9$)
Anti-HM15136 antibodies at baseline	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Anti-HM15136 antibodies at any time post treatment	1 (11.1)	2 (22.2)	2 (22.2)	0 (0.0)
Peak titre				
40.5	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
81	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)
1296	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
20 736	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Domain specificity				
GC15136	1 (11.1)	2 (22.2)	1 (11.1)	0 (0.0)
HMC001	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GC15136 and HMC001	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
Cross-reactive to rhGlucagon	1 (11.1)	2 (22.2)	2 (22.2)	0 (0.0)
Neutralizing effect (cell-based assay)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cross-reactive to endogenous glucagon (cell-based assay)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	(B) Part 2 ($N = 16$)		
	HM15136		Pooled placebo
	0.02 mg/kg ($n = 9$)	0.06 mg/kg ($n = 3$)	($n = 4$)
Anti-HM15136 antibodies at baseline	0 (0.0)	0 (0.0)	0 (0.0)
Anti-HM15136 antibodies at any time post treatment	1 (11.1)	1 (33.3)	0 (0.0)
Peak titre			
40.5	1 (11.1)	0 (0.0)	0 (0.0)
162	0 (0.0)	1 (33.3)	0 (0.0)
Domain specificity			
GC15136	1 (11.1)	1 (33.3)	0 (0.0)
Cross-reactive to rhGlucagon	1 (11.1)	2 (33.3)	0 (0.0)
Neutralizing effect (cell-based assay)	0 (0.0)	0 (0.0)	0 (0.0)
Cross-reactive to endogenous glucagon (cell-based assay)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Data presented as *n* (%).
Abbreviation: rhGlucagon, recombinant human glucagon.

anticipated, based on its physiological role,[13] and the study protocol was designed to address this by including predefined stopping criteria. While FPG increases in patients without T2D were clinically relevant, they did not exceed 180 mg/dL or higher and thus did not lead to study withdrawal. By contrast, four of 12 patients with T2D who received HM15136 experienced FPG increases of 200 mg/dL or higher, and, in three cases, these elevations met the threshold for study withdrawal (i.e. FPG ≥ 270 mg/dL). The observed increase in plasma glucose during HM15136 administration is a potential safety concern in overweight and obese patients, particularly those with pre-existing T2D.

Mean serum concentrations increased with ascending HM15136 dose from 0.02 to 0.06 mg/kg, but dose proportionality was considered inconclusive in patients without T2D, and was not assessed in patients with T2D because there were only two treatment groups. Therefore, no definite conclusions can be drawn on this point.

eGFR changes were indicative of a dose-related relationship with HM15136 treatment. Mean increases from baseline were seen in the 0.04 and 0.06 mg/kg groups in patients without T2D, and in the 0.06 mg/kg group in patients with T2D. When compared with observed decreases in mean eGFR among patients receiving placebo or 0.02 mg/kg, these findings suggest that kidney function may be improved in overweight or obese patients receiving HM15136 at doses of 0.04 mg/kg or higher; however, as previously stated, care should be taken when considering patients with existing T2D. The possibility that changes in eGFR were a result of hyperfiltration caused by hyperglycaemia was explored

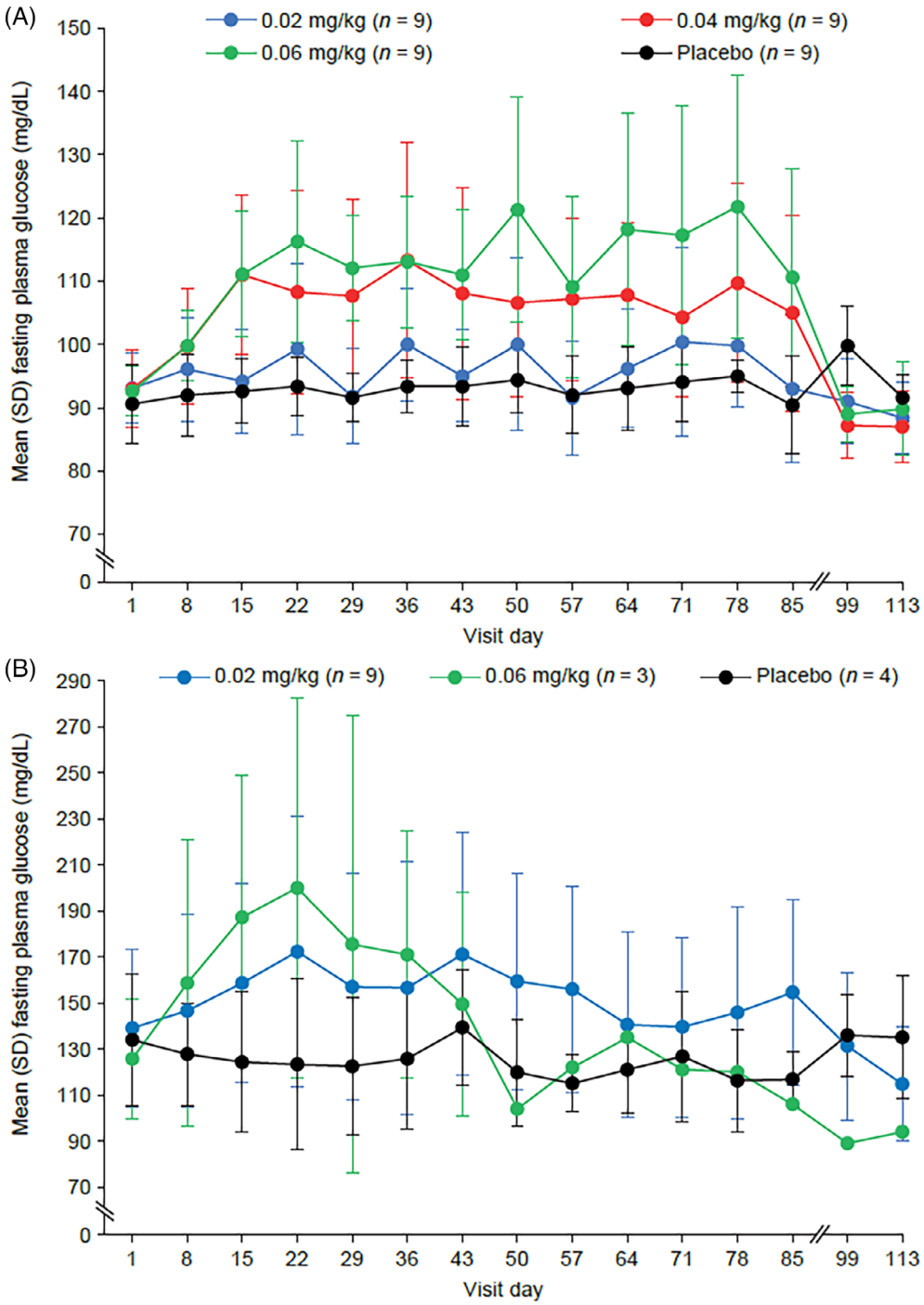

FIGURE 1 Mean fasting blood glucose levels over time by HM15136 dose in A, Part 1 ($n = 36$), and B, Part 2 ($n = 16$) of the study (PD population). PD, pharmacodynamics; SD, standard deviation

using post hoc linear regression analyses, but these provided no conclusive evidence of a relationship between fasting glucose levels and eGFR.

In general, any changes in clinical laboratory evaluations, vital signs and physical examination findings were small, in both parts of the study. Small decreases in mean diurnal ABPM were observed in all patients without T2D and in patients with T2D who received HM15136 0.06 mg/kg, suggesting that HM15136 administration may be associated with reductions in blood pressure. This is supported by the fact that glucagon is known to reduce vascular resistance in several organs, suggesting a vasodilatory effect (although the mechanism is currently unknown).[14,15]

All patients who received HM15136 showed small weight losses, in contrast to those who received placebo. However, it should be noted that the highest weight loss (seen in patients without T2D who received 0.06 mg/kg) was less than 3% of body weight. As current treatment options for obesity (e.g. semaglutide, liraglutide, tirzepatide) are associated with large reductions in body weight (≥ 10 kg or ~ 20% of total body weight),[16–18] the small reductions observed with HM15136 cannot therefore support the development of this drug as a

TABLE 4 Change from baseline at day 85 in key PD variables in A, Part 1, and B, Part 2 of the study (PD population)

	(A) Part 1 ($N = 36$)			
	HM15136			Placebo
	0.02 mg/kg ($n = 9$)	0.04 mg/kg ($n = 9$)	0.06 mg/kg ($n = 9$)	($n = 9$)
Weight (kg)				
n	8	9	8	7
Change from baseline, mean (SD)	−0.6 (1.9)	−2.1 (2.2)	−2.3 (3.7)	2.4 (4.1)
LS mean difference (95% CI)	−2.6 (−4.8, −0.4)	−4.3 (−6.4, −2.1)	−4.6 (−6.8, −2.4)	
Percentage change from baseline, mean (SD)	−0.5 (1.9)	−2.3 (2.5)	−2.6 (3.7)	2.1 (3.9)
LS mean difference (95% CI)	−2.2 (−4.4, −0.1)	−4.1 (−6.3, −1.9)	−4.5 (−6.7, −2.3)	
Liver fat via MRI-PDFF (%)				
n	4	2	1	4
Change from baseline, mean (SD)	−8.8 (2.6)	−11.0 (3.5)	9.4 (NA)	−2.1 (2.5)
LS mean difference (95% CI)	6.7 (2.2, 11.2)	8.9 (3.3, 14.5)	−11.5 (−18.7, −4.3)	
Percentage change from baseline, mean (SD)	−36.8 (9.5)	−84.7 (1.9)	61.0 (NA)	−13.0 (11.6)
LS mean difference (95% CI)	23.7 (7.3, 40.2)	71.6 (51.5, 91.8)	−74.1 (−100.1, −48.0)	
Visceral fat via MRI (L)				
n	8	8	6	7
Change from baseline, mean (SD)	−0.3 (0.3)	0.03 (0.2)	−0.3 (0.1)	0.1 (0.3)
LS mean difference (95% CI)	0.4 (0.2, 0.7)	0.1 (−0.2, 0.4)	0.4 (0.1, 0.7)	
Percentage change from baseline, mean (SD)	−11.4 (16.7)	3.4 (12.3)	−16.6 (4.0)	3.5 (13.5)
LS mean difference (95% CI)	14.9 (1.1, 28.7)	0.1 (−13.7, 13.9)	20.1 (5.3, 35.0)	
Fasting plasma glucose				
n	8	9	8	7
Change from baseline, mean (SD)	−1.0 (13.0)	12.0 (10.7)	17.9 (16.9)	0.6 (6.5)
LS mean difference (95% CI)	−0.4 (−9.8, 8.9)	12.5 (3.3, 21.7)	18.2 (8.9, 27.5)	

	(B) Part 2 ($N = 16$)		
	HM15136		Placebo
	0.02 mg/kg ($n = 9$)	0.06 mg/kg ($n = 3$)	($n = 4$)
Weight (kg)			
n	7	1	4
Change from baseline, mean (SD)	−1.1 (2.4)	−3.8 (NA)	0.2 (1.0)
LS mean difference (95% CI)	−1.1 (−3.1, 0.9)	−4.4 (−7.2, −1.6)	
Percentage change from baseline, mean (SD)	−0.9 (2.8)	−4.3 (NA)	0.3 (1.3)
LS mean difference (95% CI)	−1.3 (−3.6, 1.1)	−5.1 (−8.4, −1.8)	
Liver fat via MRI-PDFF (%)			
n	5	0	3
Change from baseline, mean (SD)	−1.0 (5.4)	NA	−2.7 (3.8)
LS mean difference (95% CI)	−1.7 (−10.6, 7.1)	NA	
Percentage change from baseline, mean (SD)	−8.2 (25.1)	NA	−17.0 (28.2)
LS mean difference (95% CI)	−8.8 (−55.6, 38.0)	NA	
Visceral fat via MRI (L)			
n	6	1	4
Change from baseline, mean (SD)	0.1 (0.3)	−0.3 (NA)	0.02 (0.2)
LS mean difference (95% CI)	−0.1 (−0.5, 0.3)	0.3 (−0.4, 1.0)	
Percentage change from baseline, mean (SD)	6.8 (19.0)	−16.9 (NA)	2.3 (12.3)
LS mean difference (95% CI)	−4.5 (−29.4, 21.0)	19.3 (−24.0, 62.5)	

(Continues)

TABLE 4 (Continued)

	(B) Part 2 ($N = 16$)		
	HM15136		Placebo
	0.02 mg/kg ($n = 9$)	0.06 mg/kg ($n = 3$)	($n = 4$)
Fasting plasma glucose			
n	7	1	4
Change from baseline, mean (SD)	29.6 (23.6)	6.0 (NA)	−17.3 (26.1)
LS mean difference (95% CI)	48.3 (18.5, 78.2)	49.5 (2.9, 96.1)	

Abbreviations: CI, confidence interval; LS, least squares; MRI, magnetic resonance imaging; NA, not applicable; PD, pharmacodynamics; PDFF, proton density fat fraction; SD, standard deviation.

therapeutic option for obesity (the observed increase in plasma glucose would also be a safety concern in the T2D population). An alternative option might be to consider the combined use of HM15136 and another incretin (e.g. a GLP-1 RA). Because GLP-1 RAs are known to counterbalance glucagon-induced hyperglycaemia,[19] this approach of dual agonism may offer better control over both weight reduction and plasma glucose level in overweight/obese patients with co-morbidities (as shown in recent phase 2 studies)[20,21] and also leverage potential synergies between the GLP-1 RA and glucagon receptor pathways.

The small population size in this study is a recognized limitation of phase I trials. The disruption to scheduled visits caused by the COVID-19 pandemic (resulting in protocol deviations) is also recognized, although it should be noted that all data were reviewed for potential impact on study findings and no singular anomalies were reported. The strengths of the study include the assessment of patients with multiple co-morbidities and at risk from other health conditions because of high BMI.[22]

In conclusion, this study has established a safety and tolerability profile for the novel long-acting glucagon analogue, HM15136, noting the potential for hyperglycaemia. HM15136 monotherapy may not be a suitable choice in the treatment of obesity because of the observed uncontrolled elevation in plasma glucose, particularly in patients with co-morbid diabetes. However, HM15136 may be of utility (potentially in combination with other therapies) in treating chronic hypoglycaemia-related diseases such as postbariatric hypoglycaemia and congenital hyperinsulinism. Recruitment is currently underway in the latter disease area for a phase 2 trial in patients aged 2 years or older.[23]

AUTHOR CONTRIBUTIONS

Research design: WS, MH and SB. Conduct of research: WS, MH and SB. Data analyses: WS, MH and SB. Manuscript writing and critical review: all authors.

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CONFLICT OF INTEREST

JB, SK and JC are current employees of Hanmi Pharmaceutical Co., Ltd; WS and SB are former employees of Hanmi Pharmaceutical Co., Ltd. MH is an employee and shareholder at ProSciento. Wonjung Shin and Seungjae Baek were employees of Hanmi Pharmaceutical Co., Ltd at the time of preparation of the manuscript.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15162.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author (SB) upon reasonable request.

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REFERENCES

1. Porcellati F, Di Mauro S, Mazzieri A, et al. Glucagon as a therapeutic approach to severe hypoglycemia: after 100 years, is it still the antidote of insulin? *Biomolecules*. 2021;11:1281.
2. Arnoux JB, Verkarre V, Saint-Martin C, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. *Orphanet J Rare Dis*. 2011;6:63.
3. Lobato CB, Pereira SS, Guimarães M, et al. A potential role for endogenous glucagon in preventing post-bariatric hypoglycemia. *Front Endocrinol (Lausanne)*. 2020;11:608248.
4. Al-Massadi O, Ferno J, Dieguez C, Nogueiras R, Quinones M. Glucagon control on food intake and energy balance. *Int J Mol Sci*. 2019;20(16):3905.
5. Sánchez-Garrido MA, Brandt SJ, Clemmensen C, Müller TD, DiMarchi RD, Tschöp MH. GLP-1/glucagon receptor co-agonism for treatment of obesity. *Diabetologia*. 2017;60:1851-1861.
6. Müller TD, Finan B, Clemmensen C, DiMarchi RD, Tschöp MH. The new biology and pharmacology of glucagon. *Physiol Rev*. 2017;97:721-766.
7. Choi J, Lee SM, Kim JK, Lee J, Kim YH, Choi IY. Sustained glucagon effect on blood glucose and improvements of insulin resistance mediated by a novel long-acting glucagon analog, HM15136, in animal models. *Diabetes*. 2019;68(Suppl_1):108-LB.
8. Huh KY, Hwang JG, Shin W, et al. 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. *Diabetes Obes Metab*. 2022;24:411-420.
9. Heo YH, Kim JK, Lee JS, et al. A novel glucagon analog with an extended half-life, HM15136, normalizes glucose levels in rodent models of congenital hyperinsulinism. *Sci Rep*. 2022;12:16765.
10. Choi JHKJ, Kim JY, Lee SM, Jongsoo L, Lee SH, Choi IY. Potential of a novel long-acting glucagon analogue, HM15136, for the treatment of obesity. Abstract 766, EASD Virtual Meeting 2019. Accessed October 12, 2022. https://www.easd.org/virtualmeeting/home.html#!resources/potential-of-a-novel-long-acting-glucagon-analogue-hm15136-for-the-treatment-of-obesity-382d2efb-7663-40c2-a7bc-e969258c861a
11. Food and Drug Administration. Guidance for industry developing products for weight management. Accessed May 3, 2023. https://www.fda.gov/media/71252/download
12. American Diabetes Association. Standards of medical care in diabetes, chapter 2: classification and diagnosis of diabetes. *Diabetes Care*. 2022;45:S17-S38.
13. Rix I, Nexoe-Larsen C, Bergmann NC, Lund A, Knop FK. Glucagon physiology. In: Feingold KR, Anawalt B, Boyce A, et al., eds. *Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc*.; 2000.
14. Sélley E, Kun S, Szijártó IA, Kertész M, Wittmann I, Molnár GA. Vasodilator effect of glucagon: receptorial crosstalk among glucagon, GLP-1, and receptor for glucagon and GLP-1. *Horm Metab Res*. 2016;48:476-483.
15. Lee JS, Lee SM, Kim JK, et al. Sustained glucagon effect on cardiovascular renal and metabolic disorders mediated by a long-acting glucagon analog, HM15136, in animal disease models. *Diabetes*. 2021;70(Suppl_1):658.
16. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA*. 2015;314:687-699.
17. Deng Y, Park A, Zhu L, Xie W, Pan CQ. Effect of semaglutide and liraglutide in individuals with obesity or overweight without diabetes: a systematic review. *Ther Adv Chronic Dis*. 2022;13:1-14.
18. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387:205-216.
19. Hinnen D. Glucagon-like peptide 1 receptor agonists for type 2 diabetes. *Diabetes Spectr*. 2017;30:202-210.
20. Di Prospero NA, Yee J, Frustaci ME, Samtani MN, Alba M, Fleck P. Efficacy and safety of glucagon-like peptide-1/glucagon receptor co-agonist JNJ-64565111 in individuals with type 2 diabetes mellitus and obesity: a randomized dose-ranging study. *Clin Obes*. 2021;11:e12433.
21. Alba M, Yee J, Frustaci ME, Samtani MN, Fleck P. Efficacy and safety of glucagon-like peptide-1/glucagon receptor co-agonist JNJ-64565111 in individuals with obesity without type 2 diabetes mellitus: a randomized dose-ranging study. *Clin Obes*. 2021;11:e12432.
22. Kivimäki M, Strandberg T, Pentti J, et al. Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study. *Lancet Diabetes Endocrinol*. 2022;10:253-263.
23. Clinicaltrials.gov. NCT04732416. HM15136 Treatment for 8 Weeks in Subjects Aged ≥2 Years with Congenital Hyperinsulinism (CHI). Accessed September 21, 2022. https://clinicaltrials.gov/ct2/show/NCT04732416?term=HM15136&draw=1&rank=1.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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