Clinical Study Protocol

A First-in-Human, Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of HM15912 in Healthy Korean Subjects

Sponsor:	Hanmi Pharmaceutical Co., Ltd. 14, Wiryeseong-daero, Songpa-gu, Seoul, 05545, Korea
Principal Investigator:	Hyeong-Seok Lim, MD, PhD
Sponsor Study Number:	HM-GLP2-101
IP Name:	HM15912 or placebo
Development Phase:	Phase 1
Version of Final Protocol	Final 4.2, 6 Apr 2020

This clinical study will be conducted in accordance with the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (GCP) (E6), the protocol and other applicable regulatory requirements.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

Protocol Title: A First-in-Human, Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of HM15912 in Healthy Korean Subjects

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on GCP applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

_____ _____

Date

Seungjae Baek, MD, PhD

Executive Director of Clinical Science

Hanmi Pharmaceutical Co., Ltd.

14, Wiryeseong-daero, Songpa-gu, Seoul, 05545, Korea

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Declaration of the Principal Investigator

Protocol Title: A First-in-Human, Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of HM15912 in Healthy Korean Subjects

This clinical study protocol was subjected to critical review and has been released by the Sponsor. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on GCP applicable to this clinical study.

Principal Investigator

_____ _____
Date

Hyeong-Seok Lim, MD, PhD

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LIST OF STUDY STAFF

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Institution	Asan Medical Center 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Korea
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PROTOCOL SYNOPSIS

Protocol Title	A First-in-Human, Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of HM15912 in Healthy Korean Subjects
Study Number	HM-GLP2-101
Development Phase	Phase 1
Sponsor	Hanmi Pharmaceutical Co., Ltd.
Institution	Asan Medical Center 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Korea
Principal Investigator	Hyeong-Seok Lim, MD, PhD Department of Clinical Pharmacology and Therapeutics Asan Medical Center
Study Objectives	**Primary Objective:** To assess the safety and tolerability of HM15912 after single subcutaneous (SC) doses **Secondary Objective:** To assess the PK profile of HM15912 after single SC doses **Exploratory Objective:** To explore the PD properties of HM15912 after single SC doses
Study Design	This is a double-blind, randomized, placebo-controlled, single ascending dose (SAD) study to assess the safety, tolerability, PK and PD of the SC administration of HM15912 in healthy Korean subjects. The study will be conducted in approximately 5 sequential dosing cohorts, enrolling 8 subjects per cohort. Subjects will be randomized to HM15912 or placebo in a ratio of 6:2 (6 active, 2 placebo). When necessary, one dosing cohort may be added or removed. In this first-in-human (FiH) study, each cohort will be divided in 2 blocks in order to implement the sentinel dosing approach. Within each cohort, the first block will consist of 2 sentinel subjects;
	1 subject will receive HM15912, and 1 subject will receive matched placebo. The second block will consist of 6 subjects randomized to receive HM15912 (n = 5) or matched placebo (n = 1). Individual subjects in the second block will be dosed at least 24 hours after the first block when safety and tolerability are found to be satisfactory by the Principal Investigator. Following an overnight fast of at least 10 hours, each subject will receive a single dose of either HM15912 or matched placebo-administered SC in the abdomen on the morning (8:00 AM - 10:00 AM) of Day 1. Subjects will continue fasting through approximately 4 hours postdose. Water intake is also limited for approximately 1 hour before dosing and approximately 2 hours after dosing. Water intake is also limited for approximately 1 hour before dosing and approximately 2 hours after dosing. The planned maximum dose of HM15912 is 1.5 mg/kg; however, higher doses may be administered if safety is confirmed in previous cohorts. If dose is escalated to 1.5 mg/kg or above, approval of the Ministry of Food and Drug Safety (MFDS) will be obtained. After at least 6 subjects (HM15912, n ≥ 4) in each cohort have completed assessments through at least Day 17, blinded safety data will be reviewed and a dose decision/dose escalation decision for the

subsequent cohort will be made by the Principal Investigator and the Sponsor. If there are PK/PD data obtained from the preceding or current cohorts, the PK/PD data will be reviewed as well when necessary. Escalation will only proceed if safety and tolerability data related to the dose of the prior cohort are verified. Determination of whether to proceed to the next cohort will be made by the Principal Investigator and the Sponsor, and changes in the dose and the number of cohorts will be approved by the MFDS and the IRB.

PK data will only be reviewed if available. After review of the PK data from the preceding or current cohorts, changes in time points for PK collection, clinical laboratory assessments, and PD collection may be required and will be approved by the MFDS and the IRB.

If dose escalation is stopped based on available blinded safety data, the current dose level will be considered as the minimum intolerable dose (MID). The dose just below the MID will be regarded as the maximum tolerated dose (MTD). If the dose escalation is stopped due to reaching exposure limit without dose-limiting safety findings, the MTD cannot be determined. Dose de-escalation may occur in the last cohort or additional cohorts to further refine clinically relevant dose levels.

The study will be comprised of:

- A Screening visit up to 28 days before dosing
- An inpatient assessment period of approximately 8 days, with admission to the institution on Day-1, dosing on Day 1, and discharge on Day 7 once the planned schedule is completed
- Two Outpatient visits on Day 8 (± 4 hours), Day 10 (± 1 day), Day 17 (± 1 day) and Day 30 (± 3 days)
- A final Follow-up visit on Day 44 (± 3 days)

The total duration of the clinical study per subject will be up to approximately 72 days, including the Screening period.

Investigational Product

HM15912 and matching placebo will be supplied by the Sponsor as a sterile solution in prefilled syringes, manufactured by Hanmi Pharm. Co., Ltd. [redacted]

Doses will be administered via SC injection to subjects in approximately 5 dose cohorts. Additional cohorts may be enrolled and proceed at a dose higher or lower than the planned maximum dose of 1.5 mg/kg, if deemed appropriate by the Principal Investigator and the Sponsor, but cohorts are planned as follows:

Cohorts	Number of Subjects	Treatment[1]
Cohort 1	N = 6	HM15912 0.05 mg/kg
	N = 2	Placebo
Cohort 2	N = 6	HM15912 0.1 mg/kg
	N = 2	Placebo
Cohort 3	N = 6	HM15912 0.5 mg/kg
	N = 2	Placebo
Cohort 4	N = 6	HM15912 1 mg/kg
	N = 2	Placebo
Cohort 5	N = 6	HM15912 1.5 mg/kg
	N = 2	Placebo

[1] After at least 6 subjects (HM15912, n ≥ 4) in each cohort have completed assessments through at least Day 17, blinded safety data (PK/PD data from the preceding or current

	cohorts will also be reviewed when necessary) will be reviewed and a dose decision/dose escalation decision for the subsequent cohort will be made by the Principal Investigator and the Sponsor. If dose escalation is stopped, dose de-escalation may occur in additional cohorts, to further refine clinically relevant dose levels. The planned maximum dose of HM15912 is 1.5 mg/kg; however, higher doses may be administered if safety is confirmed in previous cohorts. If dose is escalated to 1.5 mg/kg or above, MFDS approval will be obtained.
Number of Subjects	Approximately 40 subjects, divided in approximately 5 cohorts with 8 subjects per cohort (6 HM15912, 2 placebo), are planned for enrollment.
Study Population	Healthy Korean male and female subjects ≥ 19 and ≤ 60 years of age with a body mass index (BMI) ≥ 18.5 kg/m^2 and ≤ 27 kg/m^2 are planned for enrollment.
Inclusion Criteria	1. Subject voluntarily agrees to participate in this study and signs an IRB-approved informed consent prior to performing any of the Screening visit procedures. 2. Korean males and females ≥ 19 and ≤ 60 years of age at the Screening visit 3. Female subjects must be non-pregnant and non-lactating and either surgically sterile (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or post-menopausal for ≥ 12 months. Postmenopausal status will be confirmed through testing of follicle-stimulating hormone (FSH) levels ≥ 40 IU/L at the Screening visit for amenorrheic female subjects ≤ 60 years of age. Male subjects must be surgically sterile (at least 1-year post vasectomy), abstinent or if engaged in sexual relations with women of child-bearing potential, the subject and his partner must be using the following acceptable effective or medically recognized dual protection contraceptive methods from the administration of IP to up to 60 days after receiving the dose of the IP. • Effective contraceptive method: Sexual partner's surgical sterilization (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), intrauterine contraception/device of the sexual partner • Dual protection contraceptive method: Combinational use of physical barrier methods (male condom, female condom and diaphragm for the sexual partner, sponge, cervical cap), spermicide for females in the form of foam/gel/film/cream/suppository, oral or hormonal contraceptives for the sexual partner The adequacy of other methods of contraception will be assessed on a case-by-case basis by the Principal Investigator. 4. Body mass index (BMI) ≥ 18.5 kg/m^2 and ≤ 27 kg/m^2 at the Screening visit and with a weight ≥ 50 kg for males and ≥ 45 kg for females Healthy, determined by pre-study medical evaluation (medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory assessments)
Exclusion Criteria	Subjects who meet 1 or more of the following criteria at the Screening visit will not be considered eligible to participate in the clinical study. Also, subjects who meet 1 or more of the following criteria 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, and 31 when they are hospitalized

	(Day-1) will not be considered eligible to participate in the clinical study. 1. Subject with a history or presence of clinically significant active diseases of the gastrointestinal, cardiovascular (including a history of arrhythmia or any clinically significant conduction delays in the ECG), hepatic, pulmonary, neurological, renal, pancreatic, immunological, dermatological, endocrine, genitourinary or hematological system 2. Subject with a history or presence of skin rashes or dermatitis 3. Subject with a history or presence of any psychiatric disorder that, in the opinion of the Principal Investigator, might confound the results of the study or pose additional risk in administering the investigational product to the subject 4. Subject who has participated in other clinical studies (including bioequivalence tests) within 6 months before the Screening visit and has received IPs 5. Subject who has received GLP-1, GLP-2, human growth hormones, or analogues in the past 6. Subject with a history of any serious adverse reaction, hypersensitivity, or intolerance to IP components 7. Subject who has any clinically significant history of allergic conditions (including drug allergies, asthma, eczema, or anaphylactic reactions, but excluding untreated, asymptomatic, seasonal allergies) prior to IP administration 8. Subject with a history of gallstones, intestinal obstruction, or surgery/surgical resection of stomach or intestine (simple appendectomy is allowed) 9. Subject with a history or presence of gastrointestinal illnesses such as malabsorption, pancreatic disease, gastrointestinal polyps, irritable bowel syndrome, Crohn's disease, or ulcerative colitis 10. Subject with a personal or family history of hypercoagulability or thromboembolic disease 11. Subject who has FPG < 70 or > 110 mg/dL at the Screening visit. 12. Subject with a history of any major surgery within 6 months prior to the Screening visit 13. Subject with a history or current diagnosis of heart diseases, defined as symptomatic heart failure (New York Heart Association class III or IV), myocardial infarction, unstable angina requiring medication, transient ischemic attack, cerebral infarct, or cerebral hemorrhage or invasive cardiovascular procedure, such as coronary artery bypass graft surgery, or angioplasty/percutaneous coronary intervention within 6 months before the Screening visit (a diagnostic cardiac catheterization without any intervention does not exclude the subject) 14. Subject with cardiac arrhythmia requiring medical or surgical treatment within 6 months prior to the Screening visit 15. Subject who has/had febrile illness or symptomatic, viral, bacterial (including upper respiratory infection), or fungal (noncutaneous) infection within 1 week prior to the Screening visit 16. Subject with daily use of more than 5 cigarettes or equivalent use of any tobacco product within 6 weeks prior to the Screening visit. Subject must be able to abstain from smoking during the confinement period. 17. Subject with a history of any active infection, except mild viral diseases,

	within 30 days prior to the Screening visit 18. Subject with a history of hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis C antibody (HCV Ab), or human immunodeficiency virus (HIV) 19. Subject with the existence of any surgical or medical condition that, in the judgment of the Principal Investigator, might interfere with the absorption, distribution, metabolism or excretion of the IP 20. Subject with the presence of clinically significant physical, clinical laboratory or ECG findings (e.g., QTcB > 450 msec for males, QTcB > 470 msec for females, left bundle branch block) at the Screening visit that, in the opinion of the Principal Investigator, may interfere with any aspect of study conduct or interpretation of results. 21. Subject who has a mean pulse < 45 or > 90 beats per minute (bpm); mean systolic blood pressure (SBP) > 140 mmHg; mean diastolic blood pressure (DBP) > 90 mmHg (measurements taken for 2 consecutive times after the subject has been resting in supine or sitting position for 5 minutes) (mean values from 2 consecutive measurements will be used). 22. Subject who has donated whole blood within 60 days before the Screening visit, who has done apheresis within 1 month before the Screening visit or who has received blood products 23. Subject who has a history of alcohol or illicit drug abuse as judged by the Principal Investigator or who reports use of recreational drugs (e.g., marijuana) within 6 weeks prior to the Screening visit 24. Subject who has a positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids, phencyclidine, etc.) at the Screening visit or on Day-1 25. Female subject who is currently pregnant or breastfeeding or who has a positive serum pregnancy test at the Screening visit or on Day-1 26. Subject who has used over-the-counter (OTC) medications (including acetaminophen and vitamins), prescription medications, or herbal remedies from 3 days prior to the Screening visit, unless it is approved by the Principal Investigator 27. Subject who is unwilling to avoid consumption of coffee and caffeine-containing beverages within 24 hours before each study visit and while the subject is confined to the institution 28. Subject who is unwilling to avoid use of alcohol or alcohol-containing foods, medications or beverages within 48 hours before each study visit and while the subject is confined to the institution 29. Subject who is unwilling to abstain from vigorous exercise from 48 hours prior to admission until the Follow-up visit 30. Subject who is unable to understand the protocol requirements, instructions, study-related restrictions, and the nature, scope and possible consequences of the clinical study or who is unlikely to comply with the protocol requirements, instructions and study-related restrictions; e.g., uncooperative attitude, inability to return for Follow-up visits and improbability of completing the clinical study 31. Subject who is deemed by the Principal Investigator to be inappropriate in conducting the clinical study Subjects who have screen failed may be allowed to re-screen once at the discretion of the Principal Investigator.

Evaluation Criteria	*Primary Endpoints* • General safety variables: Adverse event (AE) assessments, clinical laboratory tests (hematology, clinical chemistry, coagulation and urinalysis), vital signs (blood pressure [BP], pulse, tympanic temperature and respiratory rate [RR]), 12-lead electrocardiogram (ECG), physical examinations • Specific safety variables: Injection site assessments, immunogenicity assessments (ADA, NAb, anti-PEG) (performed only if analysis is necessary) *Secondary Endpoints* • C_{max}: Maximum serum HM15912 concentration determined from the concentration-time profile • T_{max}: Time of maximum serum HM15912 concentration determined from the concentration-time profile • AUC_{0-t}: Area under the concentration-time curve from predose (time 0) to the last quantifiable concentration • AUC_{inf}: Area under the concentration-time curve from predose (time 0) extrapolated to infinite time ($AUC_{0-t} + C_{last}/\lambda_z$) calculated using the linear-log trapezoidal rule • $AUC_{\%extrap}$: Percentage of AUC_{inf} that is due to extrapolation beyond t_{last} • λ_z: The terminal elimination rate constant determined by selection of at least 3 data points on the terminal phase of the concentration-time curve • $t_{½}$: Terminal elimination half-life calculated as: $\ln 2/\lambda_z$ • CL/F: Total body clearance calculated as: $Dose/AUC_{inf}$ • V_z/F: Apparent volume of distribution calculated as: $Dose/(AUC_{inf} * \lambda z)$ *Exploratory Endpoints* • Blood plasma citrulline • Albumin, prealbumin • Fasting lipid panel (total cholesterol, triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL], very low-density lipoprotein [VLDL], free fatty acid [FFA]) • Blood glucose-related panel (fasting plasma glucose, gastric inhibitory polypeptide [GIP], glucagon-like peptide-1 [GLP-1], C-peptide, glucagon, insulin) • Insulin-like growth factor-1 (IGF-1) and keratinocyte growth factor (KGF)
Statistical Methods	*Sample Size Considerations* Enrolling 8 subjects per cohort (HM15912:placebo=6:2) has been set based on the experience and the general properties of exploratory studies, and this matches the typical sample size used in similar studies conducted to assess safety and PK. Therefore, no formal sample size calculation will be performed. Safety and tolerability of the IP will be assessed based on AEs, clinical laboratory parameters, physical examinations, vital signs and ECG parameters throughout the duration of the study. Safety analysis will involve examination of the descriptive statistics and individual subject listings for any effects of study treatment on clinical tolerability and safety.

	Data Presentation/Descriptive Statistics All demographic, safety, PK and PD data will be listed and summarized in tabular format by descriptive and comparative statistics as appropriate. PK data will also be displayed graphically as appropriate. The PK/PD relationship between IP exposure and exploratory endpoints may also be analyzed by graphical displays.

Table 1 Schedule of Assessments

Table 1-1. Schedule of Assessments (Cohort 1-3)

Visit	Visit 1 Screening	Visit 2 Inpatient Treatment Period									Visit 3 Outpatient[a]	Visit 4 Outpatient[a]	Visit 5 Follow-up[b]
Day	-28 ~ -2	-1 Outpatient	-1 Inpatient	1	2	3	4	5	6	7	10 (±1 day)	17 (±1 day)	30 (±3 days)
Informed consent	X												
Inclusion/exclusion criteria	X	X[c]											
Demographic data	X												
Height[d], BMI[e]	X	X								X	X	X	X
Body weight[d]	X	X								X	X	X	X
Medical history	X	X[f]											
Prior/concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X
Pregnancy test (all females)[g]	X	X											X
Serum FSH (postmenopausal females only)	X												
Urine drugs of abuse and alcohol screening	X	X									X	X	X
Viral serology	X												
Check-in			X										
Check-out										X			
Outpatient	X	X									X	X	X
Randomization		X											
Standardized meals			X	X[h]	X	X	X	X	X				
IP administration[h]				X									
Adverse event assessments	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, pulse, tympanic temperature, RR)[i]	X	X		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X	X	X	X
Clinical laboratory tests (hematology, chemistry, coagulation, urinalysis)[j]	X	X		X[k]		X[k]	X[k]			X		X	X

Visit	Visit 1 Screening	Visit 2 Inpatient Treatment Period									Visit 3 Outpatient[a]	Visit 4 Outpatient[a]	Visit 5 Follow-up[b]
Day	-28 ~ -2	-1 Outpatient	-1 Inpatient	1	2	3	4	5	6	7	10 (±1 day)	17 (±1 day)	30 (±3 days)
12-lead ECG[l]	X	X		X[l]	X	X	X			X	X	X	X
Immune response assessments (ADA, NAb, anti-PEG)			X[m]								X		X
Injection site assessments[n]				X	X	X	X	X	X	X			
Physical examinations	X	X		X	X	X	X	X	X	X	X	X	X
PK sampling[o]				X	X	X	X	X	X	X	X	X	X
Citrulline[p]				X	X	X	X	X	X	X	X	X	X
GIP, GLP-1, C-peptide, glucagon, insulin[q]				X			X			X		X	X
IGF-1 and KGF[r]				X			X			X		X	X

ADA = anti-drug antibody; Anti-PEG = anti-polyethylene glycol; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; FFA = free fatty acid; FPG = fasting plasma glucose; FSH = follicle-stimulating hormone; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; HDL = high-density lipoprotein; IP = investigational product; LDL = low-density lipoprotein; NAb = neutralizing antibody; PK = pharmacokinetics; RR = respiratory rate; SC = subcutaneous; VLDL = very low-density lipoprotein

a. An additional Outpatient visit may be included in later cohorts, if required, after PK data are evaluated. If so, assessments scheduled on Day 17 will be performed at the additional Outpatient visit.

b. If a subject is discontinued from the study or withdraws consent, the Principal Investigator must make every possible effort to perform the evaluations described for the Follow-up visit. Efforts will be made to perform the Follow-up visit within 30 days from the date the subject is discontinued from the study or withdraws consent.

c. The criteria applicable for admission prior to randomization, i.e., exclusion criteria 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, and 31, will be checked again.

d. Height will be measured only at the Screening visit. Height and weight measurements will be performed with shoes removed. Weight will be recorded rounded to 1 decimal place. If weight is measured rounded to 2 decimal places, the number is rounded off from the second digit after the decimal point.

e. BMI will be calculated by the following formula: BMI = Weight (kg) ÷ ((Height (m) x Height (m)). The calculated BMI will be rounded to 1 decimal place. The height measured at the Screening visit will be used for BMI calculation, and if a value is calculated as 2 decimal places, the number is rounded off to the first place.

f. Medical history which will be checked on Day-1 is limited to the medical history related to exclusion criteria 1, 2, 3, 6, 8, 9, 10, 11, 13, 14, 15, and 17.

g. Serum pregnancy tests at the Screening visit and on Day-1; urine pregnancy tests at the Day 30/Follow-up visit.

h. HM15912 or placebo will be administered via SC injection into the abdomen on the morning of Day 1 after a minimum 10-hour fast. Subjects will continue fasting through approximately 4 hours postdose. Water consumption will also be limited for 1 hour before dosing and for approximately 2 hours after dosing. After the planned 4-hour post-dose blood sampling (clinical laboratory tests and analysis of citrulline) and testing (12-lead ECG) are performed, subjects will be served lunch by the institution.

i. Vital signs will be measured twice per day on Day 1 through Day 6 (AM and PM). Vital signs will be measured at predose and 6 hours postdose on Day 1. Vital signs will be measured whenever possible in the morning and afternoon between Day 2 and Day 6. All other assessments will be performed once per day whenever possible. BP and pulse will be measured for 2 consecutive times after a subject has been lying down or sitting to rest ≥ 5 minutes, and mean values will be recorded.

j. Samples for clinical laboratory tests will be collected after at least 12 hours of fasting. If the PK sampling time points are changed, the sampling times for clinical laboratory tests may be adjusted accordingly.

k. 4, 48 and 72 hours postdose

l. The 12-lead ECGs will be performed after a subject has been resting supine for ≥ 5 minutes. ECGs will be measured in triplicate in the morning during admission. Only for Day 1, however, ECGs will be measured in triplicate predose and 4 hours postdose, and a ±30-minute sampling window is allowed for measurement at 4 hours postdose. Triplicate ECGs will be recorded at least 30 seconds apart from each other, not exceeding a time period of 3 minutes for the completion of all 3 ECGs. 12-lead ECGs during the Outpatient visit will be measured once per day whenever possible.

m. Blood sampling for immunogenicity assessments will be performed only for hospitalized patients after admission on Day-1, Day 10, and Day 30.

n. Injection site assessments will be performed predose, within 1 hour postdose and at 4 and 12 hours postdose on Day 1, and then between 9:00 AM and 12:00 PM daily from Day 2 through Day 7.

o. [redacted] See Table 2-1 for the PK sampling schedule.

p. If the PK sampling time points are changed, the citrulline sampling times may be adjusted accordingly. See Table 2-1 for the citrulline sampling schedule.

q. Blood will be collected for GIP, GLP-1, C-peptide, glucagon and insulin immediately before administration and once daily on Days 4 and 7, at the Day 17 Outpatient visit and at the Day 30/Follow-up visit. If the PK sampling time points are changed, sampling times may be adjusted accordingly.

r. Blood will be collected for IGF-1 and KGF immediately before administration and once daily on Days 4 and 7, at the Day 17 Outpatient visit and at the Day 30/Follow-up visit. If the PK sampling time points are changed, sampling times may be adjusted accordingly.

Table 1-2. Schedule of Assessments (Cohort 4, 5)

Visit	Visit 1 Screening	Visit 2 Inpatient Treatment Period									Visit 3 Out patient[a]	Visit 4 Out patient[a]	Visit 5 Out patient[a]	Visit 6 Out patient[a]	Visit 7 Follow-up[b]
Day	-28 ~ -2	-1 Outpatient	-1 Inpatient	1	2	3	4	5	6	7	8 (±4 hours)	10 (±1 day)	17 (±1 day)	30 (±3 days)	44 (±3 days)
Informed consent	X														
Inclusion/exclusion criteria	X	X[c]													
Demographic data	X														
Height[d], BMI[e]	X	X								X		X	X	X	X
Body weight[d]	X	X								X		X	X	X	X
Medical history	X	X[f]													
Prior/concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (all females)[g]	X	X													X
Serum FSH (postmenopausal females only)	X														
Urine drugs of abuse and alcohol screening [s]	X	X									X	X	X	X	X
Viral serology	X														
Check-in			X												
Check-out										X					
Outpatient	X	X									X	X	X	X	X
Randomization		X													
Standardized meals			X	X[h]	X	X	X	X	X						
IP administration[h]				X											
Adverse event assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, pulse, tympanic temperature, RR)[i]	X	X		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X	X	X	X	X	X
Clinical laboratory tests (hematology, chemistry, coagulation,	X	X		X[k]			X[k]			X			X	X	X

Visit	Visit 1 Screening	Visit 2 Inpatient Treatment Period									Visit 3 Out patient[a]	Visit 4 Out patient[a]	Visit 5 Out patient[a]	Visit 6 Out patient[a]	Visit 7 Follow-up[b]
Day	-28 ~ -2	-1 Outpatient	-1 Inpatient	1	2	3	4	5	6	7	8 (±4 hours)	10 (±1 day)	17 (±1 day)	30 (±3 days)	44 (±3 days)
urinalysis)[j]															
12-lead ECG[l]	X	X		X[l]	X	X	X			X	X	X	X	X	X
Immune response assessments (ADA, NAb, anti-PEG)			X[m]										X		X
Injection site assessments[n]				X	X	X	X	X	X	X					
Physical examinations	X	X		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]				[redacted]											
[redacted]				[redacted]											
GIP, GLP-1, C-peptide, glucagon, insulin[q]				X			X			X			X	X	
IGF-1 and KGF[r]				X			X			X			X	X	

ADA = anti-drug antibody; Anti-PEG = anti-polyethylene glycol; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; FFA = free fatty acid; FPG = fasting plasma glucose; FSH = follicle-stimulating hormone; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; HDL = high-density lipoprotein; IP = investigational product; LDL = low-density lipoprotein; NAb = neutralizing antibody; PK = pharmacokinetics; RR = respiratory rate; SC = subcutaneous; VLDL = very low-density lipoprotein

a. An additional Outpatient visit may be included in later cohorts, if required, after PK data are evaluated. If so, assessments scheduled on Day 17 will be performed at the additional Outpatient visit.

b. If a subject is discontinued from the study or withdraws consent, the Principal Investigator must make every possible effort to perform the evaluations described for the Follow-up visit. Efforts will be made to perform the Follow-up visit within 30 days from the date the subject is discontinued from the study or withdraws consent.

c. The criteria applicable for admission prior to randomization, i.e., exclusion criteria 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, and 31, will be checked again.

d. Height will be measured only at the Screening visit. Height and weight measurements will be performed with shoes removed. Weight will be recorded rounded to 1 decimal place. If weight is measured rounded to 2 decimal places, the number is rounded off from the second digit after the decimal point.

e. BMI will be calculated by the following formula: BMI = Weight (kg) ÷ ((Height (m) x Height (m)). The calculated BMI will be rounded to 1 decimal place. The height measured at the Screening visit will be used for BMI calculation, and if a value is calculated as 2 decimal places, the number is rounded off to the first place.

f. Medical history which will be checked on Day-1 is limited to the medical history related to exclusion criteria 1, 2, 3, 6, 8, 9, 10, 11, 13, 14, 15, and 17.

g. Serum pregnancy tests at the Screening visit and on Day-1; urine pregnancy tests at the Day 44/Follow-up visit.

h. HM15912 or placebo will be administered via SC injection into the abdomen on the morning of Day 1 after a minimum 10-hour fast. Subjects will continue fasting through approximately 4 hours postdose. Water consumption will also be limited for 1 hour before dosing and for approximately 2 hours after dosing. After the planned 4-hour post-dose blood sampling (clinical laboratory tests) and testing (12-lead ECG) are performed, subjects will be served lunch by the institution.

i. Vital signs will be measured twice per day on Day 1 through Day 6 (AM and PM). Vital signs will be measured at predose and 6 hours postdose on Day 1. Vital signs will be measured whenever possible in the morning and afternoon between Day 2 and Day 6. All other assessments will be performed once per day whenever possible. BP and pulse will be measured for 2 consecutive times after a subject has been lying down or sitting to rest ≥ 5 minutes, and mean values will be recorded.

j. Samples for clinical laboratory tests will be collected after at least 12 hours of fasting. If the PK sampling time points are changed, the sampling times for clinical laboratory tests may be adjusted accordingly.

k. 4 and 72 hours postdose

l. The 12-lead ECGs will be performed after a subject has been resting supine for ≥ 5 minutes. ECGs will be measured in triplicate in the morning during admission. Only for Day 1, however, ECGs will be measured in triplicate predose and 4 hours postdose, and a ±30-minute sampling window is allowed for measurement at 4 hours postdose. Triplicate ECGs will be recorded at least 30 seconds apart from each other, not exceeding a time period of 3 minutes for the completion of all 3 ECGs. 12-lead ECGs during the Outpatient visit will be measured once per day whenever possible.

m. Blood sampling for immunogenicity assessments will be performed only for hospitalized patients after admission on Day-1, Day 17, and Day 44.

n. Injection site assessments will be performed predose, within 1 hour postdose and at 4 and 12 hours postdose on Day 1, and then between 9:00 AM and 12:00 PM daily from Day 2 through Day 7.

o. [redacted]PK data show that other time points would be more beneficial. See Table 2-2 for the PK sampling schedule.

p. If the PK sampling time points are changed, the citrulline sampling times may be adjusted accordingly. See Table 2-2 for the citrulline sampling schedule.

q. Blood will be collected for GIP, GLP-1, C-peptide, glucagon and insulin immediately before administration and once daily on Days 4 and 7, at the Day 17 Outpatient visit and at the Day 30 Outpatient visit. If the PK sampling time points are changed, sampling times may be adjusted accordingly.

r. Blood will be collected for IGF-1 and KGF immediately before administration and once daily on Days 4 and 7, at the Day 17 Outpatient visit and at the Day 30 Outpatient visit. If the PK sampling time points are changed, sampling times may be adjusted accordingly.

s. Alcohol breath test procedure could be replaced with the examination by interview to avoid infection of COVID-19.

Table 2 Citrulline Sampling Schedule for Exploring PK Samples and PD

Table 2-1 Citrulline Sampling Schedule for Exploring PK Samples and PD (Cohort 1~3)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

a. Sampling times may be adjusted between the cohorts in case available PK data show that other time points would be more beneficial.

b. Samples will be collected with an empty stomach.

c. PK and citrulline samples may be collected ±1 day (24 hours) from the scheduled sampling time points at the Days 10 and 17 Outpatient visits. The samples may also be collected ±1 day (24 hours) from the scheduled sampling time points in case there is an additional Outpatient visit.

d. PK and citrulline samples may be collected ±3 days (72 hours) from the scheduled sampling time points at the Day 30 Outpatient visit.

Table 2-2 Citrulline Sampling Schedule for Exploring PK Samples and PD (Cohort 4, 5)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted][b,c]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

a. Sampling times may be adjusted between the cohorts in case available PK data show that other time points would be more beneficial.

b. Samples will be collected with an empty stomach.

c. PK and citrulline samples may be collected ±1 day (24 hours) from the scheduled sampling time points at the Days 10 and 17 Outpatient visits. The samples may also be collected ±1 day (24 hours) from the scheduled sampling time points in case there is an additional Outpatient visit.

d. PK and citrulline samples may be collected ±3 days (72 hours) from the scheduled sampling time points at the Day 30 and Day 44 Outpatient visit.

Table 3 PD Sampling Schedule

Table 3-1 PD Sampling Schedule (Cohort 1~3)

Study Day	Screening -28 ~ -2	-1	1		2	3	4	5	6	7	OP 10	OP 17	FU 30
Assessment			Predose (-30 min)	4 h (±15 min)	24 h (±15 min)	48 h (±15 min)	72 h (±15 min)	96 h (±15 min)	120 h (±15 min)	144 h (±15 min)	216 h (±24 h)	384 h (±24 h)	696 h (±72 h)
Chemistry test - albumin, prealbumin[a,b]	X	X		X		X	X			X		X	X
Chemistry test - fasting lipid panel (total cholesterol, triglycerides, LDL, HDL, VLDL, FFA)[a,b]	X	X		X		X	X			X		X	X
Chemistry test - fasting plasma glucose[a,b]	X	X		X		X	X			X		X	X
Blood GIP, GLP-1, C-peptide, glucagon, insulin[a]			X				X			X		X	X
IGF-1 and KGF[a]			X				X			X		X	X

FFA = free fatty acid; FPG = fasting plasma glucose, FU = follow-up; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; HDL = high-density lipoprotein; IGF-1 = insulin-like growth factor-1; KGF = keratinocyte growth factor; LDL = low-density lipoprotein; OP = outpatient; VLDL = very low-density lipoprotein

a. All samples will be collected after a minimum 12-hour fast. If the PK sampling time points are changed, sampling times may be adjusted accordingly between the cohorts.

b. Included in clinical laboratory tests.

Table 3-2 PD Sampling Schedule (Cohort 4, 5)

Study Day	Screening -28 ~ -2	-1	1		2	3	4	5	6	7	OP 8	OP 10	OP 17	OP 30	FU 44
Assessment			Predose (-30 min)	4 h (±15 min)	24 h (±15 min)	48 h (±15 min)	72 h (±15 min)	96 h (±15 min)	120 h (±15 min)	144 h (±15 min)	168 h (±4 h)	216 h (±24 h)	384 h (±24 h)	696 h (±72 h)	1032 h (±72 h)
Chemistry test - albumin, prealbumin[a,b]	X	X		X			X			X			X	X	X
Chemistry test - fasting lipid panel (total cholesterol, triglycerides, LDL, HDL, VLDL, FFA)[a,b]	X	X		X			X			X			X	X	X
Chemistry test - fasting plasma glucose[a,b]	X	X		X			X			X			X	X	X
Blood GIP, GLP-1, C-peptide, glucagon, insulin[a]			X				X			X			X	X	
IGF-1 and KGF[a]			X				X			X			X	X	

FFA = free fatty acid; FPG = fasting plasma glucose, FU = follow-up; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; HDL = high-density lipoprotein; IGF-1 = insulin-like growth factor-1; KGF = keratinocyte growth factor; LDL = low-density lipoprotein; OP = outpatient; VLDL = very low-density lipoprotein

a. All samples will be collected after a minimum 12-hour fast. If the PK sampling time points are changed, sampling times may be adjusted accordingly between the cohorts.

b. Included in clinical laboratory tests.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
anti-HBc	Hepatitis B core antibody
anti-PEG	anti-polyethylene glycol
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{\%extrap}$	Percentage of AUC_{inf} that is due to extrapolation beyond t_{last}
AUC_{0-t}	Area under the concentration-time curve from predose (time 0) to the time of the last quantifiable concentration
AUC_{inf}	Area under the concentration-time curve from predose (time 0) extrapolated to infinite time ($AUC_{0-t} + C_{last}/\lambda_z$)
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CHO	Chinese hamster ovary
CL/F	Total body clearance
C_{max}	Maximum serum concentration
hs-CRP	High sensitivity C-reactive protein
DBP	Diastolic blood pressure
DMP	Data Management Plan
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
EMA	European Medicines Agency
FiH	First-in-human
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C antibody
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HMC001	Human immunoglobulin G4 Fc fragment

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IGF-1	Insulin-like growth factor-1
IP	Investigational product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ISEMFs	Intestinal subepithelial myofibroblasts
KGF	Keratinocyte growth factor
LDL	Low-density lipoprotein
ALD-PEG-ALD	Aldehyde-Polyethylene glycol-Aldehyde
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimum intolerable dose
MTD	Maximum tolerated dose
MRSD	Maximum recommended starting dose
NAb	Neutralizing antibody
NOAEL	No observed adverse effect level
OTC	Over-the-counter
PD	Pharmacodynamics
PK	Pharmacokinetics
PN	Parenteral nutrition
PT	Preferred Term
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's correction
QTcF	QT interval corrected for heart rate using Fridericia's correction
RR	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SID	Subject identification
SOC	System Organ Class

Abbreviation	Definition
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination half-life
T_{max}	Time of maximum serum concentration
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
Vz/F	Apparent volume of distribution
λ_z	Terminal elimination rate constant

1. INTRODUCTION

1.1. Background

Hanmi Pharmaceutical is developing HM15912, a synthetic substance produced by combining a GLP-2 analogue [redacted] This medicinal product is developed as a new treatment for the short bowel syndrome (SBS).

The SBS is a rare disease caused by broad surgical resection of the small intestine or as a result of an inborn condition. It is characterized by a decrease in the intestinal absorption surface area and subsequent malabsorption of essential macronutrients and micronutrients[2]. There is no definitive treatment for the SBS at present, and patients with a short residual bowel are likely to rely on parenteral nutrition (PN). Long-term PN may cause life-threatening complications such as sepsis, osteopenia, and chronic liver diseases[3].

GLP-2 is known to increase the intestinal absorption surface area by promoting the growth of crypt cells within the intestine, and it has been developed as a treatment to reduce SBS patients' dependency on PN. GLP-2 is a major hormone that affects many aspects of intestinal physiology such as growth, barrier function, digestion, absorption, movement, and blood flow[4]. The half-life of GLP-2 within the human body is very short (approximately 7 minutes), so the GLP-2 medication currently on the market, teduglutide (GATTEX®), has been developed to have resistance to the dipeptidyl peptidase-4 (DPP-4) enzyme. Of note, however, that the half-life of teduglutide is 1.3~2.2 hours, which is still short, and it is provided as freeze-dried powder, thereby requiring medical staff to go through complicated preparation process to administer it to patients[5]. Thus, teduglutide cannot be a sufficient treatment option for SBS patients requiring long-term PN.

Unlike teduglutide, HM15912 is a GLP product that prolongs the half-life and enhances stability by decreasing renal excretion resulting from increased molecular weight and with recycling of vascular endothelial cells through FcRn binding. [redacted] The nonclinical PD study results show that HM15912 induced human GLP-2 receptor-mediated cAMP accumulation dose-dependently in hGLP-2R/CHO-K1 cells and stimulated IGF-1 production in mice's primary intestinal subepithelial myofibroblasts (ISEMFs). The secreted IGF-1 binds with the tyrosine kinase IGF-1 receptor in crypt and this is related to crypt cell proliferation through the paracrine signaling. The PD of HM15912 has been verified from in vivo experiments as well. When HM15912 was subcutaneously dosed multiple times to mice and rats, the growth of their intestine, especially the wet weight of their small intestine, has increased dose-dependently and shown higher intestinotrophic efficacy compared to teduglutide. Furthermore, it has been proved that there is a relationship between the physical improvement of intestinal environment and the functional improvement of intestine since the intestinal growth led by HM15912 in SBS rat models has enhanced nutrient absorption as a result. Based on such PD and PK properties, HM15912 is expected to be a promising option for treating the SBS.

Additional details can be found in the Investigator's Brochure (IB)[1].

1.2. Rationale for the Clinical Study

This first-in-human (FiH) study evaluates the safety, tolerability, PK and PD of HM15912, [redacted]

This study is conducted to define a tolerable dose range for most subjects and to provide exploratory data on the potential for prolonged intestinal absorption increase in healthy population. The results of this clinical study will provide data on design and dose selection for subsequent studies.

1.3. Risk-benefit Assessment

While HM15912 has not been evaluated in humans, clinical experiences with other GLP-2 analogues and known pharmacologic and preclinical data suggest the following expected side effects:

- Gastrointestinal: Abdominal pain, abdominal discomfort, nausea, vomiting, abdominal inflation, dysorexia, colon polyp, small intestinal tumor, intestinal obstruction, gallbladder/biliary tract disease, pancreatic disease
- Respiratory: Upper airway infection, cough
- Immunological: Hypersensitivity reaction
- General: Injection site reaction, pyrexia
- Investigational: Slight increase of amylase and lipase, slight decrease of ALP, ALT, and AST
- Nervous system: Sleep disorder
- Skin lesion: Skin hemorrhage
- Fluid overload

There will be no direct health benefit for healthy subjects from receipt of the investigational product (IP). The protocol has been designed to minimize the risk to research participants. Subjects will be monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs. Sentinel dosing will be employed within each cohort, and available blinded safety data (together with PK/PD data if possible) will be assessed after each dose level to determine if it is safe to escalate to the next planned dose.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To assess the safety and tolerability of HM15912 after single SC doses

2.2. Secondary Objective

- To assess the PK profile of HM15912 after single SC doses

2.3. Exploratory Objective

- To explore the PD properties of HM15912 after single SC doses

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1. Overview

This is a double-blind, randomized, placebo-controlled, single ascending dose (SAD) study to assess the safety, tolerability, PK and PD of the SC administration of HM15912 in healthy Korean subjects.

The study will be conducted in approximately 5 sequential dosing cohorts, enrolling 8 subjects per cohort. Subjects will be randomized to HM15912 or placebo in a ratio of 6:2 (6 active, 2 placebo). When necessary, one dosing cohort may be added or removed.

Each cohort will be divided in 2 blocks in this FiH study in order to implement the sentinel dosing approach. Within each cohort, the first block will consist of 2 sentinel subjects; 1 subject will receive HM15912, and 1 subject will receive matched placebo. The second block will consist of 6 subjects randomized to receive HM15912 (n = 5) or matched placebo (n = 1). Individual subjects in the second block will be dosed at least 24 hours after the first block when safety and tolerability are found to be satisfactory by the Principal Investigator.

Following an overnight fast of at least 10 hours, each subject will receive a single dose of either HM15912 or matched placebo-administered SC in the abdomen on the morning (8:00 AM - 10:00 AM) of Day 1. Subjects will continue fasting through approximately 4 hours postdose. Water intake is also limited for approximately 1 hour before dosing and approximately 2 hours after dosing.

The planned maximum dose of HM15912 is 1.5 mg/kg; however, higher doses may be administered if safety is confirmed in previous cohorts. If dose is escalated to 1.5 mg/kg or above, MFDS approval will be obtained. After at least 6 subjects (HM15912, n ≥ 4) in each cohort have completed assessments through at least Day 17, blinded safety data will be reviewed and a dose decision/dose escalation decision for the subsequent cohort will be made by the Principal Investigator and the Sponsor. If there are PK/PD data obtained from the preceding or current cohorts, the PK/PD data will be reviewed as well when necessary. Escalation will only proceed if safety and tolerability data related to the dose of the prior cohort are verified. Determination of whether to proceed to the next cohort will be made by the Principal Investigator and the Sponsor, and changes in the dose and the number of cohorts will be approved by the MFDS and the IRB.

PK data will only be reviewed if available. After review of the PK data from the preceding or current cohorts, changes in time points for PK collection, clinical laboratory assessments, and PD collection may be required and will be approved by the MFDS and the IRB.

If dose escalation is stopped based on available blinded safety data, the current dose level will be considered as the minimum intolerable dose (MID). The dose just below the MID will be regarded as the maximum tolerated dose (MTD). If the dose escalation is stopped due to reaching exposure limit without dose-limiting safety findings, the MTD cannot be determined. Dose de-escalation may occur in the last cohort or additional cohorts to further refine clinically relevant dose levels.

Stopping rules are described in Section 3.4.

The study will be comprised of:

- A Screening visit up to 28 days before dosing

- An inpatient assessment period of approximately 8 days, with admission to the institution on Day-1, dosing on Day 1, and discharge on Day 7 once the planned schedule is completed
- Two Outpatient visits on Day 8 (± 4 hours), Day 10 (± 1 day), Day 17 (± 1 day) and Day 30 (±3 days)
- A final Follow-up visit on Day 44 (± 3 days)

The total duration of the clinical study per subject will be up to approximately 72 days, including the Screening period.

Procedures related to the clinical study are detailed in the Schedule of Assessments, the PK Sampling Schedule, the Citrulline Sampling Schedule, and the PD Sampling Schedule (Table 1-1 and 1-2, Table 2-1 and 2-2, Table 3-1 and 3-2, respectively).

Doses will be administered via SC injection to subjects in approximately 5 dose cohorts. Additional cohorts may be enrolled and proceed at a dose higher or lower than the planned maximum dose of 1.5 mg/kg, if deemed appropriate by the Principal Investigator and the Sponsor, but cohorts are planned as follows:

Table 4 Cohorts and Dose Administration

Cohorts	Number of Subjects	Treatment[1]
Cohort 1	N = 6	HM15912 0.05 mg/kg
	N = 2	Placebo
Cohort 2	N = 6	HM15912 0.1 mg/kg
	N = 2	Placebo
Cohort 3	N = 6	HM15912 0.5 mg/kg
	N = 2	Placebo
Cohort 4	N = 6	HM15912 1.0 mg/kg
	N = 2	Placebo
Cohort 5	N = 6	HM15912 1.5 mg/kg
	N = 2	Placebo

[1] After at least 6 subjects (HM15912, n ≥ 4) in each cohort have completed assessments through at least Day 17, blinded safety data (PK/PD data from the preceding or current cohorts will also be reviewed when necessary) will be reviewed and a dose decision/dose escalation decision for the subsequent cohort will be made by the Principal Investigator and the Sponsor. If dose escalation is stopped, dose de-escalation may occur in additional cohorts to further refine clinically relevant dose levels. The planned maximum dose of HM15912 is 1.5 mg/kg; however, higher doses may be administered if safety is confirmed in previous cohorts.

3.2. Endpoints

3.2.1. Primary Endpoints

- General safety variables: Adverse event (AE) assessments, clinical laboratory tests (hematology, clinical chemistry, coagulation and urinalysis), vital signs (blood pressure [BP], pulse, tympanic temperature and respiratory rate [RR]), 12-lead electrocardiogram (ECG), physical examinations
- Specific safety variables: Injection site assessments, immunogenicity assessments (ADA, NAb, anti-PEG) (performed only if analysis is necessary)

3.2.2. Secondary Endpoints

- C_{max}: Maximum serum HM15912 concentration determined from the concentration-time profile
- T_{max}: Time of maximum serum HM15912 concentration determined from the concentration-time profile
- AUC_{0-t}: Area under the concentration-time curve from predose (time 0) to the last quantifiable concentration
- AUC_{inf}: Area under the concentration-time curve from predose (time 0) extrapolated to infinite time ($AUC_{0-t} + C_{last}/\lambda_z$) calculated using the linear-log trapezoidal rule
- $AUC_{\%extrap}$: Percentage of AUC_{inf} that is due to extrapolation beyond t_{last}
- λ_z: The terminal elimination rate constant determined by selection of at least 3 data points on the terminal phase of the concentration-time curve
- $t_{½}$: Terminal elimination half-life calculated as: $\ln 2/\lambda_z$
- CL/F: Total body clearance calculated as: $Dose/AUC_{inf}$
- Vz/F: Apparent volume of distribution calculated as: $Dose/(AUC_{inf} * \lambda_z)$

3.2.3. Exploratory Endpoints

- Blood plasma citrulline
- Albumin, prealbumin
- Fasting lipid panel (total cholesterol, triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL], very low-density lipoprotein [VLDL], free fatty acid [FFA])
- Blood glucose-related panel (fasting plasma glucose, gastric inhibitory polypeptide [GIP], glucagon-like peptide-1 [GLP-1], C-peptide, glucagon, insulin)
- Insulin-like growth factor-1 growth factor-1; IGF-1) and keratinocyte growth factor (KGF)

3.3. Rationale for the Study Design

This study evaluates the safety, tolerability, PK and PD of single ascending doses of HM15912 administered via SC injection. This study was designed to minimize bias and to obtain reference data (i.e., data from placebo-treated subjects) which will aid in the interpretation of results through double blind and placebo control.

For this FiH study, sentinel dosing will be utilized for each cohort. This will minimize the number of subjects affected by rapid side effects after HM15912 administration. The Principal Investigator and the Sponsor will review available blinded safety and tolerability data after each cohort to determine the next dose and then decide whether the dose escalation should be stopped or whether the dose should be increased/decreased in the subsequent cohort. If PK/PD data have been obtained, they can be used for reference. This is not mandatory, however.

The planned safety assessments that will be performed during the study are measures for ensuring the safety of subjects during a clinical trial. The PK sampling schedule is considered appropriate given the information obtained from the nonclinical study results of HM15912. The rationale for dose selection is discussed in Section 5.2.

Based on the in vivo effect of endogenous GLP-2, the exogenous administration of HM15912, a GLP-2 analogue, is expected to expand the mucous epithelium of the small intestine and colon resulting from the proliferation of crypt cells[1]. Plasma citrulline is a nonprotein amino acid that is mostly synthesized in the small intestine cells, and is well-known as a noninvasive plasma biomarker for intestinal cell mass[2]. Apolipoprotein AIV is also mostly synthesized in the small intestine cells, and previous studies have shown the correlation between apolipoprotein AIV and plasma citrulline levels[3]. Therefore, effect of HM15912 on expansion of the intestinal mucous membrane will be explored by measuring plasma citrulline after HM15912 administration. The serum proteins, albumin and prealbumin, and serum lipid panel will also be evaluated to observe changes in nutrient status of subjects resulting from expansion of the intestinal mucous membrane[4].

GLP-2 affects the pancreas and is involved in the secretion of glucagon and maintenance of glucose homeostasis[1]. These pancreatic hormones are balanced in a physiological condition, and this study will explore the effect of GLP-2 administration on the homeostasis.

3.4. Dose Escalation and Study Stopping Criteria

Dose escalation will be stopped if 1 of the following conditions applies:

- Death of a subject in 1 cohort, at any time, that is considered to be related to the IP, judged by the Principal Investigator
- One or more of the subjects in 1 cohort have experienced serious AE that is considered to be related to the IP, judged by the Principal Investigator.
- Two or more of the subjects in 1 cohort have experienced severe AE that is considered to be related to the IP, judged by the Principal Investigator.
- Two or more of the subjects in 1 cohort have experienced moderate AEs that persist for more than 7 days and are considered to be related to the IP, judged by the Principal Investigator.
- Two or more of the subjects in 1 cohort develop similar clinically significant laboratory, significant ECG or vital sign abnormalities, or severe AEs in the same organ class,

indicating dose-limiting intolerance. Dose escalation may proceed if after review of the data by the Principal Investigator and discussion with the Sponsor, it is concluded that the events are not drug related.

- It is determined that the limit of safety and/or tolerability has been reached. Decision will be made between the Sponsor and the Principal Investigator.

If any delayed reactions occur in subjects administered HM15912 during this study, the Principal Investigator will immediately stop the administration and take appropriate medical measures. If delayed reactions are suspected to be drug hypersensitivity reactions, appropriate medical measures will be taken in accordance with 7.9. Handling of Hypersensitivity Reactions. If Principal Investigator and Sponsor discuss and agree that administering HM15912 to other subjects is an unacceptable risk, they may stop the study as below.

The Principal Investigator and the Sponsor may stop the clinical study after an appropriate discussion if conditions or events including, but not limited to, the following occur during the study. A sufficient written statement on the reason for stopping the study will be submitted to the IRB.

- If clear risks or unacceptable risks are found in the subjects enrolled in this clinical study
- If the Sponsor decides to postpone or stop development of the IP

4. STUDY POPULATION

The study population will consist of healthy male and female volunteers. Subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.

4.1. Number of Subjects

A total of approximately 40 subjects will be enrolled in the clinical study (N = 8 per cohort with 6 randomized to HM15912 and 2 randomized to matching placebo within each group) according to the inclusion/exclusion criteria. Enrolling 8 subjects per cohort (HM15912:placebo=6:2) has been set based on the experience and the general properties of exploratory studies, and this matches the typical sample size used in similar studies conducted to assess safety and PK. Therefore, no formal sample size calculation will be performed (refer to Section 8.11).

4.2. Inclusion Criteria

Subjects who meet the following criteria will be considered eligible to participate in the clinical study:

1. Subject voluntarily agrees to participate in this study and signs an IRB-approved informed consent prior to performing any of the Screening visit procedures.
2. Korean males and females ≥ 19 and ≤ 60 years of age at the Screening visit
3. Female subjects must be non-pregnant and non-lactating and either surgically sterile (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or post-menopausal for ≥ 12 months. Postmenopausal status will be confirmed through testing of follicle-stimulating hormone (FSH) levels ≥ 40 IU/L at the Screening visit for amenorrheic female subjects ≤ 60 years of age.

   Male subjects must be surgically sterile (at least 1-year post vasectomy), abstinent or if engaged in sexual relations with women of child-bearing potential, the subject and his partner must be using the following acceptable effective or medically recognized dual protection contraceptive methods from the administration of IP to up to 60 days after receiving the dose of the IP.

   - Effective contraceptive method: Sexual partner's surgical sterilization (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), intrauterine contraception/device of the sexual partner
   - Dual protection contraceptive method: Combinational use of physical barrier methods (male condom, female condom and diaphragm for the sexual partner, sponge, cervical cap), spermicide for females in the form of foam/gel/film/cream/suppository, oral or hormonal contraceptives for the sexual partner

   The adequacy of other methods of contraception will be assessed on a case-by-case basis by the Principal Investigator.
4. Body mass index (BMI) ≥ 18.5 kg/m^2 and ≤ 27 kg/m^2 at the Screening visit and with a

weight ≥ 50 kg for males and ≥ 45 kg for females

5. Healthy, determined by pre-study medical evaluation (medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory evaluations)

4.3. Exclusion Criteria

Subjects who meet 1 or more of the following criteria at the Screening visit will not be considered eligible to participate in the clinical study. Also, subjects who meet 1 or more of the following criteria 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, and 31 when they are hospitalized (Day-1) will not be considered eligible to participate in the clinical study.

1. Subject with a history or presence of clinically significant active diseases of the gastrointestinal, cardiovascular (including a history of arrhythmia or any clinically significant conduction delays in the ECG), hepatic, pulmonary, neurological, renal, pancreatic, immunological, dermatological, endocrine, genitourinary or hematological system
2. Subject with a history or presence of skin rashes or dermatitis
3. Subject with a history or presence of any psychiatric disorder that, in the opinion of the Principal Investigator, might confound the results of the study or pose additional risk in administering the investigational product to the subject
4. Subject who has participated in other clinical studies (including bioequivalence tests) within 6 months before the Screening visit and has received IPs
5. Subject who has received GLP-1, GLP-2, human growth hormones, or analogues in the past
6. Subject with a history of any serious adverse reaction, hypersensitivity, or intolerance to IP components
7. Subject who has any clinically significant history of allergic conditions (including drug allergies, asthma, eczema, or anaphylactic reactions, but excluding untreated, asymptomatic, seasonal allergies) prior to IP administration
8. Subject with a history of gallstones, intestinal obstruction, or surgery/surgical resection of stomach or intestine (simple appendectomy is allowed)
9. Subject with a history or presence of gastrointestinal illnesses such as malabsorption, pancreatic disease, gastrointestinal polyps, irritable bowel syndrome, Crohn's disease, or ulcerative colitis
10. Subject with a personal or family history of hypercoagulability or thromboembolic disease
11. Subject who has FPG < 70 or > 110 mg/dL at the Screening visit.
12. Subject with a history of any major surgery within 6 months prior to the Screening visit
13. Subject with a history or current diagnosis of heart diseases, defined as symptomatic heart failure (New York Heart Association class III or IV), myocardial infarction, unstable angina requiring medication, transient ischemic attack, cerebral infarct, or cerebral hemorrhage or invasive cardiovascular procedure, such as coronary artery bypass graft surgery, or angioplasty/percutaneous coronary intervention within 6 months before the

Screening visit (a diagnostic cardiac catheterization without any intervention does not exclude the subject)

14. Subject with cardiac arrhythmia requiring medical or surgical treatment within 6 months prior to the Screening visit
15. Subject who has/had febrile illness or symptomatic, viral, bacterial (including upper respiratory infection), or fungal (noncutaneous) infection within 1 week prior to the Screening visit
16. Subject with daily use of more than 5 cigarettes or equivalent use of any tobacco product within 6 weeks prior to the Screening visit. Subject must be able to abstain from smoking during the confinement period.
17. Subject with a history of any active infection, except mild viral diseases, within 30 days prior to the Screening visit
18. Subject with a history of hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis C antibody (HCV Ab), or human immunodeficiency virus (HIV)
19. Subject with the existence of any surgical or medical condition that, in the judgment of the Principal Investigator, might interfere with the absorption, distribution, metabolism or excretion of the IP
20. Subject with the presence of clinically significant physical, clinical laboratory or ECG findings (e.g., QTcB > 450 msec for males, QTcB > 470 msec for females, left bundle branch block) at the Screening visit that, in the opinion of the Principal Investigator, may interfere with any aspect of study conduct or interpretation of results.
21. Subject who has a mean pulse < 45 or > 90 beats per minute (bpm); mean systolic blood pressure (SBP) > 140 mmHg; mean diastolic blood pressure (DBP) > 90 mmHg (measurements taken for 2 consecutive times after the subject has been resting in supine or sitting position for 5 minutes) (mean values from 2 consecutive measurements will be used).
22. Subject who has donated whole blood within 60 days before the Screening visit, who has done apheresis within 1 month before the Screening visit or who has received blood products
23. Subject who has a history of alcohol or illicit drug abuse as judged by the Principal Investigator or who reports use of recreational drugs (e.g., marijuana) within 6 weeks prior to the Screening visit
24. Subject who has a positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids, phencyclidine, etc.) at the Screening visit or on Day-1
25. Female subject who is currently pregnant or breastfeeding or who has a positive serum pregnancy test at the Screening visit or on Day-1
26. Subject who has used over-the-counter (OTC) medications (including acetaminophen and vitamins), prescription medications, or herbal remedies from 3 days prior to the Screening visit, unless it is approved by the Principal Investigator
27. Subject who is unwilling to avoid consumption of coffee and caffeine-containing beverages within 24 hours before each study visit and while the subject is confined to the institution
28. Subject who is unwilling to avoid use of alcohol or alcohol-containing foods, medications

or beverages within 48 hours before each study visit and while the subject is confined to the institution

29. Subject who is unwilling to abstain from vigorous exercise from 48 hours prior to admission until the Follow-up visit
30. Subject who is unable to understand the protocol requirements, instructions, study-related restrictions, and the nature, scope and possible consequences of the clinical study or who is unlikely to comply with the protocol requirements, instructions and study-related restrictions; e.g., uncooperative attitude, inability to return for Follow-up visits and improbability of completing the clinical study
31. Subject who is deemed by the Principal Investigator to be inappropriate in conducting the clinical study.

Subjects who have screen failed may be allowed to re-screen once at the discretion of the Principal Investigator.

4.4. Subject Withdrawal and Replacement

Subjects may withdraw consent to participation in the clinical study at any time without penalty and for any reason without prejudice to his or her future medical care. The subject does not need to give a reason for withdrawal of consent to participation in the clinical study. Subject participation may be terminated prior to completing the study and the reason recorded as follows:

- Adverse event
- Protocol violation
- Loss to follow-up
- Subject withdraws consent.
- Study discontinuation by the Sponsor
- Withdrawn by the Principal Investigator
- Pregnancy
- Other

In all cases, the reason(s) for withdrawal must be recorded. Should the randomization code be broken for a subject, the date, time and reason must be recorded.

If a subject is withdrawn, or chooses to withdraw, from the clinical study for any reason, the Principal Investigator must make every possible effort to perform the evaluations described for the Follow-up visit.

Once a subject who was administered IP is withdrawn by the Principal Investigator, the subject may not re-enter the study.

A subject who has been withdrawn from the study before IP administration may be replaced with a candidate subject. Subjects withdrawn from the study for reasons unrelated to safety may be replaced at the discretion of the Investigator and the Sponsor. The study results obtained until their withdrawal may be reviewed for final evaluation. The numbers given to replaced subjects are described in Section 5.5.2.

4.5. Termination of the Clinical Study

If the Principal Investigator or the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, the clinical study may be terminated after appropriate consultation between the involved parties. The clinical study may be terminated at the Sponsor's discretion also in the absence of such a finding.

In case the safety of subjects is jeopardized, the study must be interrupted/terminated. For the stopping criteria, please refer to Section 3.4.

The Sponsor reserves the right to discontinue this clinical study at any time for failure to meet expected enrollment goals, for safety or for any administrative reasons.

The Sponsor will report in writing to all principal investigators, the regulatory authorities and the IRB regarding the early termination of the clinical study, including reasons.

5. INVESTIGATIONAL PRODUCT

5.1. Identity of the Investigational Products

5.1.1. Study Drug

The study drug will be provided by Hanmi Pharmaceutical Co., Ltd. in a prefilled syringe. [redacted] overfill.

5.1.2. Control Drug

The control drug is a placebo matching the study drug HM15912. It is a sterile solution in a prefilled syringe without the main components of the study drug and is identical to the study drug in terms of formulation and appearance. [redacted] and it is provided by Hanmi Pharmaceutical Co., Ltd.

5.2. Dose Rationale Including Time of Dosing

The proposed starting dose of HM15912 is 0.05 mg/kg based on the results of the 4-week toxicology assessment in rats and monkeys. [redacted]
As suggested in the *2005 FDA Guidance for Industry Estimating Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*, the maximum recommended starting dose (MRSD) applying a safety factor of 10 to the human equivalent dose calculated in rats and monkeys is [redacted] compared to the MRSD.

The planned maximum dose of HM15912 is 1.5 mg/kg; however, higher doses may be administered based on the safety results of previous cohorts. [redacted] The similar GLP-2 analogue, Gattex®, has shown appropriate tolerability up to 80 mg (SC, administered once per day for 8 days) with repeated doses in healthy subjects; another GLP-2 analogue, ZP1848 (Zealand Pharma, under clinical development), has shown appropriate tolerability up to 96 mg with single doses in healthy subjects.[6,7]

Following an overnight fast of at least 10 hours, each subject will receive a single dose of either HM15912 or matched placebo administered SC in the abdomen on the morning of Day 1 in order to permit time for postdose safety, PK and PD assessments throughout the day. Subjects must continue fasting for approximately 4 hours after administration. Water consumption will also be limited for 1 hour before dosing and for approximately 2 hours after dosing. After the planned blood sampling (clinical laboratory tests) and testing (12-lead ECG) are performed 4 hours postdose, subjects will be served lunch by the institution.

5.2.1. Rationale for Dose Escalation

After at least 6 subjects (HM15912, n ≥ 4) in each cohort have completed assessments through at least Day 17, blinded safety data will be reviewed and a dose decision/dose escalation decision for the subsequent cohort will be made by the Principal Investigator and the Sponsor. If PK/PD data have been obtained, they can be reviewed as well. This is not mandatory, however. The parties will decide about the next dose level taking into consideration the outcome from the blinded safety review, the stopping rules (Section 3.4), and the available PK/PD data.

Depending on the nature, frequency and severity of the safety profile observed in the clinical study, the Principal Investigator and the Sponsor will decide one of the followings. If dose is escalated to 1.5 mg/kg or above or dose is reduced from the planned dose, approval of the MFDS and the IRB will be obtained.

1. Proceed with dose escalation and determine the next higher dose;
2. Stop dose escalation (i.e., no further dosing);
3. Investigate a lower dose level (intermediate between the current and prior ones).

5.2.2. Definition of the Maximum Tolerated Dose

If dose escalation is stopped based on available safety data, the current dose level will be considered as the MID. The dose just below the MID will be regarded as the MTD. If the dose escalation is stopped due to reaching exposure limit without dose-limiting safety findings, the MTD cannot be determined.

5.3. Supply, Packaging, Labelling and Storage

The IPs will be packaged by Hanmi Pharm. Co., Ltd. according to local legal requirement and labelled according to applicable health authority requirements.

All supplies of IPs must be stored in accordance with the manufacturer’s instructions, refrigerated between 2°C and 8°C and protected from light (i.e., kept in cartons until ready for use). HM15912 is stable up to 12 hours at room temperature. The Investigator and the institution's staff in charge will check every day if the temperature for IP storage is appropriately maintained and the thermometer is properly functioning. If temperature excursions are found, it should be reported immediately. IPs must be handled and retained properly and safely by the clinical research pharmacist at the institution and stored in a secure area accessible only to the Investigator and clinical research pharmacist.

5.4. Drug Preparation, Dispensing, Accountability and Destruction

The IPs will be provided in prefilled syringes. Dose administration will be based on the body weight of a subject rounded to 1 decimal place as measured on the day before dosing. The injection volume will also be determined by dose level. HM15912 concentration is 30 mg/mL. The determined injection volume will be prepared in dosing syringes in accordance with the instructions contained in the pharmacy manual.

Each administered IP will be recorded, and used syringes and needles will be discarded.

The Investigator or clinical research pharmacist is responsible for maintaining accurate

records regarding transportation and dispensing of IPs. The IPs must be used only for this clinical study. The unblinded monitor will check IP accountability during the clinical study period and at completion of the study.

All unused IPs must be destroyed by the Sponsor according to IP destruction-related guidelines, and documents regarding the destruction must be managed. Therefore, unused IPs, packages, and IP labels must be returned to the Sponsor upon completion of the study or during the study if needed. Used or opened IPs will be destroyed properly according to the institution's SOP. The Investigator or clinical research pharmacist will provide one copy of IP accountability records for the Sponsor.

5.5. Subject Identification and Randomization

5.5.1. Screening Numbers

All screened subjects are assigned a unique subject identification (SID) number. The SID numbers are sequentially assigned in the order of obtaining written consent, and contain 4 digits (e.g., the numbers are sequentially allocated from X001 and X represents an institute) that identify subjects from the time of Screening until the time of randomization. Enrolled subjects who drop out of the clinical study before randomization after consent has been obtained will retain their SID number.

5.5.2. Randomization Numbers

Randomization numbers are assigned to subjects after completing the Screening and re-checking the inclusion/exclusion criteria on Day-1. Randomization numbers are assigned in the order that subjects who meet all the inclusion/exclusion criteria of this study get hospitalized on Day-1. Randomization will be performed through the EDC, and randomization numbers will be assigned by the system. The randomization code (study drug or control drug) of each randomization number will be maintained in a room with restricted access to the non-blinded clinical research pharmacist only, and will be accessed by other personnel only in case of unblinding, as described in Section 5.8. A randomization number will include 3-digit subject numbers as shown in Table 5.

Table 5 Randomization Numbers and Treatment Assignment

Cohort	Randomization Numbers	Treatment Assignment	
1	101-108	0.05 mg/kg HM15912 (N = 6)	Placebo (N = 2)
2	201-208	0.1 mg/kg HM15912 (N = 6)	Placebo (N = 2)
3	301-308	0.5 mg/kg HM15912 (N = 6)	Placebo (N = 2)
4	401-408	1.0 mg/kg HM15912 (N = 6)	Placebo (N = 2)
5	501-508	1.5 mg/kg[1] HM15912 (N = 6)	Placebo (N = 2)

[1] The planned maximum dose of HM15912 is 1.5 mg/kg; however, higher doses may be administered if safety is confirmed in previous cohorts.

Once a randomization number has been allocated to one subject, it may not be assigned to another subject. If subjects withdraw prematurely from the study and are replaced under the direction of the Sponsor, then a replacement randomization number will be assigned when a replaced subject has successfully completed Screening. A replacement randomization code will be generated such that replacement subjects are assigned to the same treatment as the discontinued subjects. The replacement randomization code will differ only in randomization numbers. It is composed of 4 digits by adding "1" in front of the randomization number for a withdrawn subject. For example, if Subject 202 withdraws and is replaced, then the randomization number for the replacement subject will be 1202.

5.6. Administration of Investigational Products

HM15912 or placebo will be administered via SC injection into the abdomen on the morning of Day 1 after a minimum 10-hour overnight fast. Subjects will continue fasting through approximately 4 hours postdose. Water intake is also limited for approximately 1 hour before dosing and approximately 2 hours after dosing. After the planned blood sampling (clinical laboratory tests) and testing (12-lead ECG) are performed 4 hours postdose, subjects will be served lunch by the institution.

5.7. Compliance

Dosing will be performed by the Investigator, but if a nurse administers, that will be carried out under the Investigator's supervision. Comments will be recorded if there are any deviations from the planned dosing procedures.

5.8. Blinding and Breaking the Blind

The clinical study will be performed in a double-blind manner with the exception of the persons involved in the preparation of the IPs. These persons will not be involved in any other study activities.

The study blind should not be broken except in a medical emergency (where knowledge of the IP administered would affect the treatment of the emergency), or if dose limiting toxicities occur or if it is necessary for dose escalation decisions as described in Section 3.4. The decision to break the blind will be made by the Principal Investigator on a case-by-case basis. The Investigator or the Principal Investigator will contact Hanmi Pharmaceutical Co., Ltd. and deliver related documents when breaking the blind. The results of breaking the blind for each subject will not be revealed. The Investigator or the Principal Investigator will record blind-breaking dates and reasons in the CRF.

If blinding is not maintained in the Investigator, the institution's staff or subjects, the subject must be withdrawn. If blinding is accidently broken during the study or blinding is broken before completion of the study due to SAEs, the Investigator must record this and rapidly report to Hanmi Pharmaceutical Co., Ltd. However, if blinding is broken for ethical reasons or blind breaking is seen to have little effect on the subject's safety, the subject may continue to participate in the clinical study in the judgment of the Investigator after discussing with Hanmi Pharmaceutical Co., Ltd.

After database lock, the overall randomization code will be broken.

5.9. Prior and Concomitant Medications

Use of prescription, herbal, OTC (including acetaminophen and vitamins) medications is prohibited from 3 days prior to the Screening visit until the Follow-up visit, unless approved by the Principal Investigator. Use of dietary supplements is prohibited from Inpatient Treatment Period until the Follow-up visit. Use of concomitant medication is permitted if deemed by the Principal Investigator to be necessary for treatment of an AE.

Other IPs cannot be used concurrently during the study, and there are no other concurrent drugs prohibited.

5.10. Overdose of Investigational Product

Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. No antidotes are available.

6. VARIABLES, PARAMETERS AND METHODS OF ASSESSMENT

Variables and parameters are listed per time point in the Schedule of Assessments, the PK Sampling Schedule, the Citrulline Sampling Schedule, and the PD Sampling Schedule (Table 1-1 and 1-2, Table 2-1 and 2-2, Table 3-1 and 3-2, respectively).

PK blood sampling will be performed nearest to the specified time.

6.1. Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history
- Medication history
- Birth history (female subjects only)

The following demographic information will be recorded:

- Date of birth
- Sex
- Height, without shoes (cm)
- Body weight, without shoes (kg) (rounded to 1 decimal place for calculation of IP dose)
- Body mass index (kg/m^2)

Other baseline characteristics will be recorded as follows:

- History of drug abuse
- History of alcohol abuse
- Smoking history
- History of caffeine use (or other stimulating beverages)
- Special diet (vegetarian)
- History of blood or plasma donation

6.2. Safety Variables

6.2.1. Adverse Events

AE reporting will begin for each subject from the date he/she signs the ICF and will continue until the Follow-up visit.

6.2.1.1. Definitions

6.2.1.1.1. Definition of Adverse Event

Any untoward medical occurrence in subjects and which does not necessarily have a causal relationship with the IP. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease, whether or not it is related to the IP.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g., those occurring during treatment-free periods (including post-treatment Follow-up periods), in association with study-related procedures and assessments, or under placebo.

Concomitant illnesses that existed prior to entry into the clinical study will not be considered as AEs unless they worsen during the treatment period. If a subject is withdrawn prior to randomization, AEs occurring in him/her will not be collected.

6.2.1.1.2. Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening; this means that a subject was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation in existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect, or
- Is another important medical event (see below)

Important medical events that do not result in death, are not life-threatening or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize a subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

6.2.1.2. Recording of Adverse Events

AEs should be collected and recorded for each subject from the date he/she signs the ICF until the end of their participation in the study, i.e., the subject has discontinued or completed the study. If a subject is withdrawn prior to randomization, AEs occurring in him/her will not be

collected.

All AEs and SAEs will be recorded in source documents and, if applicable, in relevant eCRF pages and SAE forms. The Investigator is responsible for reporting AEs or SAEs using medical terms if possible.

AEs may be volunteered spontaneously by a subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as "How have you been feeling since you were last asked?" All AEs and any required remedial action will be recorded. The type of AE, date (and time, if known) of AE onset, date (and time, if known) of AE end, severity and action taken of the AE will be documented together with the Investigator's assessment of the seriousness of the AE and causal relationship to IP and/or study procedure.

All AEs should be recorded using standardized medical terms. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

6.2.1.3. Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the categories discussed in the following sections.

6.2.1.3.1. Severity

The Investigator will assess all AEs for severity in accordance with the following standard ratings.

- Mild: Ordinarily transient symptoms, does not influence performance of a subject's daily activities. Treatment is not ordinarily indicated.
- Moderate: Marked symptoms sufficient to make a subject uncomfortable. Moderate influence on performance of a subject's daily activities. Treatment may be necessary.
- Severe: Symptoms cause considerable discomfort. Substantial influence on performance of a subject's daily activities. May be unable to continue in the study and treatment may be necessary.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade, and the date (and time, if known) of the change.

6.2.1.3.2. Causality

The Investigator will assess the causality/relationship between the IP and the AE. One of the categories described in Table 6 should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 6 Assessment of Relationship of Adverse Events to Investigational Product

Related	The AE follows a reasonable temporal sequence from IP administration, and cannot be reasonably explained by a subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications). The AE follows a reasonable temporal sequence from IP administration, and

	represents a known reaction to the drug under study or other drugs in its class, or is predicted by the known pharmacological properties of the drug. The AE cannot be judged because of insufficient or contradictory information. The AE cannot be supplemented or verified.
Not related	The AE does not follow a reasonable temporal sequence from IP administration, or can be reasonably explained by a subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

6.2.1.3.3. Seriousness

Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2.1.1.2.

6.2.1.4. Reporting of Serious Adverse Events

All SAEs that occur during the period of observation (from the date the subject signs on the ICF until the follow-up visit), whether they are considered to be related to the IP or not, must be reported to the Sponsor within 24 hours after becoming aware of the occurrence by fax or email via the completed SAE report.

Serious AEs occurring after the Follow-up visit (end of the clinical study) should be reported to the Sponsor by the Principal Investigator if the Principal Investigator considers there is a reasonable causal relationship with the IP.

The minimal information required for an initial report is:

- Sender of report (name, address of Principal Investigator)
- Subject identification (Screening/randomization number, **NOT** subject name)
- Protocol number
- Description of SAE (Start date, seriousness)
- Details of the IP (Dosage, frequency, start date, end date)
- Causality assessment

However, as far as possible all points on the SAE form should be covered in the initial report, and the completed SAE form must be faxed or emailed to the Sponsor.

After receipt of the initial report, the Sponsor will review the information and, if necessary, contact the Principal Investigator to obtain further information for assessment of the event. The Principal Investigator will be responsible for informing the IRB of the SAE, and the Sponsor will be responsible for informing the regulatory authorities of the SAE as per local requirements.

Serious Adverse Event Reporting:

Hanmi Pharmaceutical Co., Ltd. Drug Safety & PV Team

Telephone number: +82-2-410-0342

Fax number: +82-50-2260-0479

Email: newdrugsafety@hanmi.co.kr

6.2.1.5. Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Principal Investigator, until there is a satisfactory explanation for the changes observed or until the subject is lost to follow-up.

If there are any changes of condition in subjects reported with SAEs (e.g., discharge after admission, situation worsened) or if any additional information is collected, the Investigator will complete an SAE report and send it to the Sponsor by fax or email within 24 hours after becoming aware of the occurrence.

6.2.1.6. Suspected Unexpected Serious Adverse Reactions

Any AE that is considered to be a suspected unexpected serious adverse reaction (SUSAR) has additional reporting requirements, as described below:

- If the SAE is fatal or life-threatening, associated with the use of the IP, and unexpected, the Sponsor will report it to the regulatory authorities within 7 calendar days after the Sponsor learns of the event, and the Principal Investigator will report it to the IRB in accordance with the institution regulations. If the required information in the SAE report is not fully reported, however, the Sponsor will report additional follow-up information to the regulatory authorities within 15 calendar days after the Sponsor first learns of the event, and the Principal Investigator will make an additional report in accordance with the institution regulations.
- If the SAE is not fatal or life-threatening but is otherwise serious, associated with the use of the IP, and unexpected, the Sponsor will report it to the regulatory authorities within 15 calendar days after the Sponsor learns of the event, and the Principal Investigator will report to the IRB in accordance with the institution regulations.

The Sponsor will notify the Principal Investigator of relevant information about SUSARs that could adversely affect the safety of subjects in a timely fashion. Follow-up information may be submitted if necessary.

6.2.1.7. Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical study.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the IP may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

If a female subject is confirmed to be pregnant, IP administration will be stopped and her participation in the clinical study will be terminated. Immediately after becoming aware of a subject's pregnancy, the Investigator should report to the Sponsor the fact that she is pregnant together with the subject number and receive her consent that her pregnancy information will be collected and shared with the Sponsor. If the subject agrees, the Investigator must report to the Sponsor via the completed Clinical Trial Pregnancy Report; initial report within 24 hours after obtaining the subject's consent. Any pregnancy of a male subject's partner must also be reported to the Sponsor in the same manner as the pregnancy in a female subject. The Principal Investigator must follow-up and document the course and the outcome of all pregnancies even if the subject has been withdrawn from the clinical study or if the clinical study has finished. All outcomes of pregnancy (e.g., the normal delivery or elective abortion) must be reported by the Principal Investigator to the Sponsor via the completed Clinical Trial Pregnancy Report; follow-up report within 24 hours after becoming aware of the outcome.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours (based on the calendar day) in accordance with the procedure for reporting SAEs.

6.2.2. Clinical Laboratory Assessments

The clinical laboratory tests specified in Table 7 will be determined at time points specified in the Schedule of Assessments (Table 1-1 and 1-2).

Clinical laboratory tests will be performed by the laboratories specified in the Laboratory Manual(s). Samples will be collected in appropriate tubes and handled according to standard procedures of the applicable laboratory.

Table 7 Clinical Laboratory Assessments

Hematology	
• White blood cell (WBC) count	• Neutrophils (percentage and absolute count)
• Red blood cell (RBC) count	• Lymphocytes (percentage and absolute count)
• Hemoglobin (Hb)	• Monocytes (percentage and absolute count)
• Hematocrit (HCT)	• Eosinophils (percentage and absolute count)
• Mean corpuscular volume (MCV)	• Basophils (percentage and absolute count)
• Mean corpuscular hemoglobin (MCH)	• Platelet count
• Mean corpuscular hemoglobin concentration (MCHC)	• RBC distribution width (RDW)

Clinical Chemistry	
[Blood glucose-related panel]	
• Fasting plasma glucose (FPG)	
[Lipid-related panel]	
• Total cholesterol	• Triglyceride
• Low-density lipoprotein (LDL)	• Free fatty acid
• High-density lipoprotein (HDL)	
• Very low-density lipoprotein (VLDL)	
[Liver function test]	
• Alanine aminotransferase (ALT)	• Total bilirubin
• Aspartate aminotransferase (AST)	• Direct bilirubin
• Alkaline phosphatase (ALP)	• Total protein
• Lactate dehydrogenase (LDH)	• Albumin
• Gamma glutamyl transferase (GGT)	• Prealbumin
	• Albumin/globulin ratio (A/G ratio)
[Pancreas function test]	
• Amylase	• Lipase
[Kidney function test]	
• Blood urea nitrogen (BUN)	• Creatinine
• Sodium	• Potassium
• Calcium	• Chlorine
• Uric acid	• Phosphorus
• Creatine kinase (CK)	
• hs-CRP	
• Follicle-stimulating hormone (FSH) (Screening visit only; postmenopausal female subjects only)	

Coagulation	
• Activated partial thromboplastin time (PTT)	• International normalized ratio (INR)
• Prothrombin time (PT) (sec)	

Urinalysis	
• Bilirubin	• Blood (Occult blood)
• Glucose	• pH and specific gravity (SG)
• Ketone	• Albumin
• White blood cell (WBC)	• Urobilinogen
• Nitrite	
• Microscopic (WBC, RBC and squamous cell)	

Viral Serology	
• Hepatitis B core antibody (anti-HBc)	• Human immunodeficiency virus (HIV) antibody
• Hepatitis B surface antigen (HBsAg)	• Syphilis reagin
• Hepatitis C antibody (HCV Ab)	

Urine Drug Screening	
• Amphetamines (AMP)	• Cocaine (COC)
• Barbiturates (BAR)	• Opiates (OPI)
• Benzodiazepines (BZO)	• Phencyclidine (PCP)
• Cannabinoids (THC)	

Pregnancy Testing
• Serum/urine human beta chorionic gonadotrophin (all females)

The Principal Investigator or the Investigator at the institution will indicate whether or not any value outside the normal range is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during the Screening period is indicated as clinically significant, the subject's participation in the study will be decided based on the Principal Investigator's medical judgment. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken from the date the ICF is signed until the Follow-up visit, it should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized, at the discretion of the Principal Investigator.

6.2.3. Vital Signs

Vital signs will be assessed at the time points specified in the Schedule of Assessments (Table 1-1 and 1-2). The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg])
- Pulse (bpm)
- Tympanic temperature (°C)
- Respiratory rate (breaths per minute)

BP and pulse will be measured for 2 consecutive times after a subject has been lying down or sitting to rest ≥ 5 minutes, and mean values will be recorded.

6.2.4. 12-lead Electrocardiograms

12-lead ECGs will be performed at the time points specified in the Schedule of Assessments (Table 1-1 and 1-2). ECGs will be measured 3 times repeatedly predose and 4 hours postdose each on Day 1 only. A deviation of ± 30 minutes from the collection time points is allowed in case of measurement 4 hours after dosing.

The 12-lead ECGs will be performed after a subject has been resting supine for ≥ 5 minutes. Triplicate ECGs will be recorded at least 30 seconds apart from each other, not exceeding a time period of 3 minutes for the completion of all 3 ECGs. The following ECG parameters will be collected: Ventricular rate, PR interval, QRS interval, RR interval, QT interval and QT interval corrected for heart rate (QTc) (QTc using Bazett's correction [QTcB] and QTcF).

All ECGs must be evaluated by the Investigator for the presence of abnormalities. If any clinically significant abnormality is observed, it must be recorded as an AE.

6.2.5. Injection Site Assessments

Injection site assessments will be performed at the time points specified in the Schedule of Assessments (Table 1-1 and 1-2).

After injection of the study drug, the injection site will be marked with a pen. Injection site assessments will be performed predose, within 1 hour postdose and at 4 and 12 hours postdose on Day 1, and then once per day between 9:00 AM and 12:00 PM from Day 2 through Day 7. A deviation of ± 30 minutes from the assessment time points is allowed in case of measurements 4 and 12 hours after dosing.

It will be checked whether the injection site mark is well-maintained during injection site assessments. If the pen mark fades, it will be marked again to show clearly the injection site. If patients who show injection site reactions are discharged, they will be separately guided to maintain their injection site marks.

Erythema and edema among the local reactions of injection sites will be evaluated quantitatively using the Draize scale described below. If an injection site reaction like pain on palpation, itching, erythema, edema, induration is observed, it must be recorded as an AE. Note, however, that pain during injection is a natural response, so it is not considered an AE. Local reactions of the injection sites will be evaluated and recorded by one Investigator using the following scale:

Erythema will be evaluated as follows:

- 0 – No erythema
- 1 – Very slight erythema (barely perceptible)
- 2 – Well-defined erythema
- 3 – Moderate to severe erythema
- 4 – Severe erythema (beet redness) to slight eschar formations (injuries in depth)

Edema will be evaluated as follows:

- 0 – No edema
- 1 – Very slight edema (barely perceptible)
- 2 – Slight edema (edges of area well defined by definite raising)
- 3 – Moderate edema (raised approximately 1 mm)
- 4 – Severe edema (raised more than 1 mm and extending beyond the area of exposure)

For the irritation assessment, all irritation events will be documented as AEs. If AEs occur, the diameter of affected sites will be measured in centimeters (cm) and the condition of the injection sites will be recorded. In case of clinically significant injection site reactions, subjects may undergo a dermatological consultation and/or cutaneous biopsies for further histological examination of the injection site reaction.

6.2.6. Immunogenicity Assessments

Blood for assessment of ADA, anti-PEG and NAb will be collected at the time points specified in the Schedule of Assessments (Table 1-1 and 1-2).

Immunogenicity assessments will be performed when deemed necessary by the Principal Investigator or the Sponsor in any of the following cases:

- When ADA formation is suspected based on PD analysis results
- When biomarker changes related to drug efficacy are not observed at expected pharmacologically effective doses
- When AEs suspected as immune responses occur after administration
- When necessary for other clinical/scientific reasons

Details of collection, processing, shipping, and storage of the blood samples collected for immune response assessments will be outlined in a separate Laboratory Manual.

6.2.7. Physical Examinations

Physical examinations will be performed at the time points specified in the Schedule of Assessments (Table 1-1 and 1-2).

The physical examination includes assessment of general appearance and review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic and psychiatric systems).

Other evaluations may be performed as deemed necessary by the Principal Investigator.

6.3. Pharmacokinetics Variables

Blood for analysis of HM15912 will be collected at the time points specified in the Schedule of Assessments and the PK Sampling Schedule (Table 1-1 and 1-2, Table 2-1 and 2-2, respectively). PK sampling times may be adjusted between the cohorts in case available PK data show that other time points would be more beneficial.

Blood sample collection, processing and shipping details will be outlined in a separate Laboratory Manual. In brief, blood will be processed and serum will then be analyzed using a validated assay.

6.4. Pharmacodynamics Variables

6.4.1. Blood Sample Collection

Blood for analysis of citrulline, albumin, prealbumin, fasting lipid panel (total cholesterol, triglycerides, LDL, HDL, VLDL, FFA), FPG, GIP, GLP-1, C-peptide, glucagon, insulin, IGF-1, and KGF will be collected at the time points specified in the Schedule of Assessments, the Citrulline Sampling Schedule for Exploring PD, and the PD Sampling Schedule (Table 1-1 and 1-2, Table 2-1 and 2-2, Table 3-1 and 3-2, respectively). If the PK sampling time points are changed, sampling times may be adjusted accordingly between the cohorts.

Blood sample collection, processing and shipping details will be outlined in a separate Laboratory Manual. In brief, blood for samples will be processed, and plasma and serum will then be analyzed using a validated assay.

7. STUDY CONDUCT

7.1. Screening Visit

The pre-screening will be performed according to the institution's SOP using IRB-approved recruitment documents.

Subjects will be fully informed of their responsibilities (in terms of attending the study visits, dietary and lifestyle restrictions), of all the procedures expected to be performed in the study, the possible risks and benefits of being dosed with HM15912 and their rights while participating in the study. They will have the opportunity to ask questions and have time to consider participation. If a subject wishes to participate in the study, he/she will be asked to sign and date an ICF. Written informed consent will be obtained from all subjects before any Screening procedures are performed.

Subjects will be asked to comply with study precautions and to attend the Screening visit fasted apart from water (duration of fast is at least 12 hours).

Screening tests and Day-1 tests may be conducted again in the judgment of the Investigator. Subjects who have screen failed may be allowed to re-screen once at the discretion of the Principal Investigator, and they are given a new SID in such case.

Screening assessments are listed in the Schedule of Assessments (Table 1-1 and 1-2).

7.2. Admission

The subjects who successfully complete the Screening visit, meet all the inclusion criteria, do not demonstrate any exclusion criteria and comply with the precautions in the protocol will be allowed for admission after they complete planned tests at the Outpatient visit on Day-1 and are approved to participate in the study following randomization. The inclusion/exclusion criteria (applicable for admission only i.e., exclusion criteria 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, and 31) will be reviewed to confirm subject eligibility for admission (refer to Section 4.3).

7.3. Inpatient Treatment Period

Administration of the IP will be on Day 1, and safety monitoring and serial blood sampling for PK and PD assessments will be conducted throughout the inpatient assessment period (from Day-1 to Day 7).

7.4. Outpatient Visits

Outpatient visits will be on Day 8 (± 4 hours), Day 10 (± 1 day), Day 17 (± 1 day) and Day 30 (± 3 days) with safety, PK and PD assessments. An additional Outpatient visit may be included in later cohorts, if required, after PK data are evaluated. In this case, the additional Outpatient visit will proceed after approval from the MFDS and the IRB.

7.5. Follow-up

The Follow-up visit will occur on Day 44 (± 3 days) of the clinical study.

7.6. Termination Visit

Subjects who withdraw consent or are withdrawn from the clinical study should, if possible, have a termination visit. This visit should take place as soon as possible after the subject withdrew consent or was withdrawn from the clinical study. For patients who have been dosed with the IP, they will make a termination visit within 30 days after the administration, if possible. The assessments and procedures scheduled for the Follow-up visit should be performed at the termination visit.

7.7. Restrictions

7.7.1. Dietary and Fluid Restrictions

Subjects will be required to fast from all food or drink (except water) for at least 12 hours before admission, Outpatient and Follow-up visits.

During the in-house stay at the institution, only meals and fluid provided by the institution will be allowed.

Food will not be allowed within 10 hours before dosing and for approximately 4 hours after dosing. Water consumption will also be limited for 1 hour before dosing and for approximately 2 hours after dosing.

Breakfast, lunch and dinner will be served daily, except on Day 1 and admission and discharge days. On Day 1 (IP dosing day), subjects will not receive breakfast; lunch will be served after 4-hour postdose assessments/collections are performed.

Breakfast will be served after fasting samples are collected on Day 2 through Day 7.

No food or drink containing grapefruit, pomelo or Seville orange (including marmalade) will be allowed within 48 hours before admission and while subjects are confined to the institution.

Quinine-containing products (e.g., tonic water) will not be allowed within 7 days before admission and while subjects are confined to the institution.

7.7.2. Alcohol and Caffeine

Consumption of any alcoholic foods, medications, and drinks must be avoided within 48 hours before any study visit except the Screening visit and while subjects are confined to the institution. Subjects should not consume more than 3 units per day during the off-site days during the study (1 unit is equal to approximately ½ pint [250 mL] of beer, 1 small glass [125 mL] of wine, 1 measure [25 mL] of spirits, or 250ml of Korean rice wine).

No food or drink containing caffeine (e.g., chocolate, coffee, tea, cola, Red Bull) will be allowed within 24 hours before each study visit except the Screening visit and while subjects are confined to the institution.

7.7.3. Smoking and Tobacco

Heavy smokers (smoke more than 5 cigarettes per day or equivalent use of any tobacco products) are excluded from the clinical study. Subjects must abstain from smoking during the confinement period.

7.7.4. Activity and Exercise

Subjects should refrain from carrying out heavy physical training (e.g., long-distance running, weight lifting or any physical activity to which the subject is not accustomed) 48 hours before admission until the Follow-up visit. Subjects should neither start any new physical training nor increase the intensity of their usual training during study participation. Subjects may participate in light recreational activities during studies (e.g., watch television, play computer games, read).

7.7.5. Other Restrictions

Subjects must neither donate whole blood within 60 days before the Screening visit nor participate in apheresis nor get injected with blood products within 1 month before the Screening visit, and they must be guided not to donate blood or plasma > 400 mL for at least 3 months after completion of the clinical study.

Male subjects must not donate sperm for at least 60 days after receiving the dose of the IP. Female subjects must not donate eggs or breastfeed for at least 60 days after receiving the dose of the IP.

To prevent a female partner of a male subject exposed to the IP from getting pregnant or getting exposed to his semen, he must be surgically sterile (at least 1-year post vasectomy), abstinent or if engaged in sexual relations with women of child-bearing potential, the subject and his partner must be using effective or medically recognized dual protection contraceptive methods from the administration of IP to up to 60 days after receiving the dose of the IP.

- Effective contraceptive method: Sexual partner's surgical sterilization (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), intrauterine contraception/device of the sexual partner
- Dual protection contraceptive method: Combinational use of physical barrier methods (male condom, female condom and diaphragm for the sexual partner, sponge, cervical cap), spermicide for females in the form of foam/gel/film/cream/suppository, oral or hormonal contraceptives for the sexual partner

The adequacy of other methods of contraception will be assessed on a case-by-case basis by the Principal Investigator.

All female subjects participating in this study must not have any possibility of being pregnant. Having no possibility of being pregnant is defined as being surgically sterile (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or being menopausal. For females who went through uterus removal or became surgically sterile, the institution will try to obtain medical records and document their sterile state. Note, however, that having no such records is not a requirement for excluding the subjects from the study. Serum or urine pregnancy tests will be conducted for all female subjects. Being post-menopausal is defined as being amenorrheic for more than 12 months before the Screening visit and having an FSH level exceeding 40 U/mL.

7.8. Handling of Hypersensitivity Reactions

7.8.1. Anaphylaxis

Anaphylaxis, a rapid and serious allergic reaction all over the body, is a life-threatening acute immunoreaction.

If any symptoms suggesting anaphylaxis shock (functional impairment of periphery organs, allergic reactions in skin-mucous membrane tissues, etc. due to worsening respiratory symptoms, decreased respiration or low-blood pressure) are observed within minutes after IP administration, IP administration must be stopped immediately. The subject will then be laid and stabilized with his/her legs in the air to prevent further problems from dyspnoea or vomiting. IP administration will be immediately stopped.

If it is confirmed that the symptoms resulted from anaphylaxis, an intramuscular injection of epinephrine will be performed. The Investigator may also conduct clinical laboratory tests, such as serum tryptase, to screen for anaphylaxis in his/her judgment. Respiratory treatments, such as oxygen supply, or low-blood pressure/shock treatments, such as IV drips, may be performed when necessary. Monitoring of blood pressure, pulse, respiration, and oxygen saturation may also be done.

7.8.2. Subacute Hypersensitivity Reactions (Type III Hypersensitivity Reactions)

Type III hypersensitivity reactions are defined as subacute hypersensitivity reactions caused by the immune-complex of an antigen and an antibody, which induce arthralgia, skin rash, and pruritus accompanying myalgia and fever.

If symptoms (arthralgia, skin rash, and pruritus accompanied by myalgia and fever, etc.) suggesting delayed hypersensitivity reactions are confirmed within a few weeks after IP administration, the IP administration will be immediately stopped. The Principal Investigator may perform clinical laboratory tests necessary for differential diagnosis.

If the symptoms are confirmed to have been caused by delayed hypersensitivity reactions due to the IP administration, medical treatment will be carried out depending on the subject's condition with the judgment of the Principal Investigator. Any medical products may be used to ease the symptoms when necessary, and the Principal Investigator may allow administration of steroids, etc.

8. STATISTICAL METHODS

Before database lock, a statistical analysis plan (SAP) will be issued and finalized, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the clinical study report.

8.1. Definition of Analysis Populations

Prior to unblinding, analysis populations will be defined through blinded data review.
In this clinical study, the PK population is subject to PK assessments whereas the PD population is subject to PD assessments. The safety population is subject to all other analyses unless described otherwise. Each analysis population is included in the analyses, based on the actually administered IP and dosage.

Safety population: All randomized subjects who received at least 1 dose of the IP

PK population: All randomized subjects with at least one quantifiable HM15912 concentration

PD population: All randomized subjects who received at least 1 dose of the IP

8.2. General Considerations

Continuous data will be summarized using descriptive statistics (number, mean, standard deviation [SD], minimum, median and maximum). Where appropriate, change from baseline will also be summarized. Categorical data will provide the number of subjects and percentage by category. All summarized data will be presented by dose level, and the subjects administered with placebo will be analyzed as a separate pooled group. Individual subject data used for the analysis will be listed by analysis item.

8.3. Subject Disposition

Subject disposition will be summarized into the numbers and percentages of subjects dosed after randomization, subjects included in each analysis population, subjects completing the study, subjects who were withdrawn (including reasons for withdrawal) and subjects who have seriously violated the protocol.

8.4. Demographic Data and Predose Assessments

Demographic data, such as age, sex, height, weight, and BMI, and descriptive statistics of baseline characteristics or the number and percentage of subjects by category will be provided.

By using MedDRA, data related to medical history will be presented as a list standardized by the System Organ Class (SOC) and preferred terms (PT).

8.5. Prior and Concomitant Medication and Drug Administration

Prior medications are those that started and stopped prior to the dose of the IP. Concomitant medications are those taken after IP dosing (including medications that started prior to IP dosing and continued after).

Prior and concomitant medications will be standardized and listed according to the World Health Organization Drug Dictionary (WHODD), and a summarized table will also be presented for concomitant medications.

8.6. Exposure

A listing of IP administration will be created by subject and will include the date and time of administration and dosage, etc.

8.7. Safety Analyses

8.7.1. Adverse Events

Summarization and analysis of AEs will be conducted for treatment emergent adverse events (TEAE). TEAEs are defined as AEs that did not exist before IP administration but occurred after IP administration, or AEs that worsened after IP administration even if they existed before IP administration.

The reported AEs will be coded according to the SOC and PT of MedDRA, and the number of subjects and percentage for AEs after IP administration, AEs related to the IP, SAEs, severe AEs, AEs that caused study withdrawal, and AEs coded for injection site reactions will be provided.

All AEs, SAEs, AEs that caused study withdrawal, and injection site reactions will be listed by subject.

8.7.2. Clinical Laboratory Tests

Clinical laboratory test results will provide descriptive statistics for each category and collection time point, and change of clinical significance from baseline will be presented as a shift table.

8.7.3. Vital Signs

Vital sign measurement results and descriptive statistics by category and collection time point for change from baseline will be provided.

8.7.4. 12-lead Electrocardiogram

12-lead ECG measurement results and descriptive statistics by category and collection time point for change from baseline will be provided. The mean values and individual values from the triplicate ECG measurement results will be all listed by category and collection time point.

8.7.5. Immune Response Assessments

When an immunogenicity test was conducted, it will be summarized into the number of subjects and percentage according to the results (ADA, anti-PEG, NAb).

8.7.6. Physical Examinations

Abnormal physical examination findings will be listed.

8.7.7. Injection Site Assessments

All injection site reactions will be documented as AEs and included in AE analysis.

8.8. Pharmacokinetics Analyses

PK parameters will be summarized by using descriptive statistics, and concentration-time data will be summarized descriptively with tables and graphs by dose level (linear and log scale). The noncompartmental PK parameters listed in Section 3.2.2 will be calculated using R, SAS, or Phoenix® WinNonlin®.

Dose proportionality will be evaluated using the linear regression approach for the log-transformed PK parameters $AUC_{0\text{-}t}$, AUC_{inf}, C_{max} values and the log-transformed dose value. Graphical presentation of dose proportionality will also be provided. Additional analyses will be performed as deemed necessary upon review of the data as exploratory analyses.

8.9. Pharmacodynamics Analyses

Descriptive statistics by collection time point for PD parameters will be provided, and the PK/PD relationship between IP exposure and PD endpoints will be analyzed by graphical displays or by PK/PD modelling, as applicable.

8.10. Interim Analyses

No formal interim analysis is planned. However, available blinded safety and tolerability (including PK/PD data if available) from each cohort (Day-1 to Day 17) will be evaluated in a dose escalation review meeting by the Principal Investigator and the Sponsor. The data review will take place before dose escalation can proceed. Screening for the next cohort may be conducted even before proceeding to the next cohort is determined, but the IP should be administered after proceeding to the next cohort is determined.

8.11. Determination of Sample Size

Enrolling 8 subjects per cohort (HM15912:placebo=6:2) has been set based on the experience and the general properties of exploratory studies, and this matches the typical sample size used in similar studies conducted to assess safety and PK. Therefore, no formal sample size calculation has been performed. Safety and tolerability of the IP will be assessed based on AEs, clinical laboratory parameters, physical examinations, vital signs and ECG parameters throughout the duration of the study. Safety analysis will involve examination of descriptive statistics and individual subject listings for any effects of study treatment on clinical tolerability and safety.

9. DATA MANAGEMENT

9.1. Data Management

Details of data management will be described in the Data Management Plan (DMP).

AEs and medical history will be coded using the current version of MedDRA. Concomitant medications will be coded using the medication dictionary of the WHO.

Serial numbers will be used to identify subjects and their biological data. Subjects' information will be encrypted or deleted in all published data and publications according to regulations of regions/countries to protect their identity.

The information on subjects who failed the Screening will also be added to the database.

The laboratory data of the central laboratory will be electronically transmitted for database reconciliation. Electronic laboratory data will be considered source data. If sensitive data other than PK data are transmitted to an unsecured network, the data will be encrypted before transmission.

9.2. Electronic Case Report Form

9.2.1. Process of Clinical Data Management

The development, maintenance and data management of eCRFs will be performed by the contract research organization (CRO) designated by Hanmi Pharmaceutical Co., Ltd. The data manager will describe the data management process in the DMP. After data input, the monitor will verify data by comparing the source data and the eCRF. Queries may be created to clarify the input data. The Principal Investigator will sign electronically the eCRF after all data are input, all queries are solved, and the reconciliation of external data is completed. If queries need to be revised after the Principal Investigator's approval, the Principal Investigator will sign again the data affected by the change. Database lock may be conducted when the Principal Investigator's approval is completed.

9.2.2. Data Input in eCRF

The data required for safety assessments and analyses for subjects will be input in source documents through the eCRF. Data input will be described according to the Completion Guideline developed by the CRO designated by Hanmi Pharmaceutical Co., Ltd. All personnel who input data in the eCRF will be trained before accessing the study database.

9.2.3. Modification of eCRF Data

Queries may be automatically created in the eCRF system during data input, and the data management personnel, monitor, or data reviewer may create queries manually. Only the specific personnel will be authorized to modify the eCRF. The monitor will train the personnel. Data modification (revising existing data, adding new data, or deleting data) will be directly performed in the eCRF, and all data modifications will be saved in the electronic audit trail.

9.2.4. eCRF Data Approval of the Principal Investigator

The Investigator or the personnel with investigator authorization will check if all information in source data matches the eCRF data and if it is accurately reflected. The Investigator will confirm that the information is complete and accurate by signing the eCRF electronically.

9.3. Document Storage

All records created under the Principal Investigator's supervision will be maintained according to the supervision authorities' guidelines and the GCP guideline when the study is completed. Clinical study documents will be stored for at least 3 years after the study is completed or for the period indicated in the local regulation and the applicable regulatory authorities' guideline, whichever is longer (up to 25 years).

10. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

10.1. Quality Control and Quality Assurance

The Sponsor or its representatives will perform activities for quality assurance and control of this clinical trial. However, the responsibility for accuracy, integrity and reliability of study data provided to the Sponsor will be taken by the Principal Investigator who creates such data.

The Sponsor can conduct audits as part of quality assurance activities to ensure that the clinical trial is performed in accordance with the protocol, SOP, GCP and all related regulations. The Sponsor will conduct an institution visit to verify the qualifications of the Principal Investigator, to inspect the facilities and to inform the Principal Investigator of responsibilities and procedures that will ensure appropriate and accurate documentation. Audits will be carried out independently apart from routine monitoring and quality control activities.

Monitoring will be performed to ensure that the study is conducted and documented according to the protocol, GCP and all related regulations. The institution will be visited at an appropriate time during the study. The monitor must have direct access to source documents to check consistency of the data recorded in eCRFs.

The Principal Investigator must prepare and maintain adequate and accurate records on all observations and other data pertinent to the clinical study for each subject. The Principal Investigator will allow monitoring of source documents, medical records and source data required for completion of eCRFs. Frequent communication between the institution and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Principal Investigator will cooperate closely with the monitor and provide appropriate evidence that the clinical study is performed according to related regulations and the GCP guideline, when necessary. The Principal Investigator will make all appropriate safety assessments on an ongoing basis. The Responsible Medical Expert of the Sponsor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to Good Clinical Practice (GCP) and SOPs for compliance with applicable government regulations. The monitor will be an authorized individual designated by the Sponsor. The monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

10.2. Subject Safety Assurance

The Investigator must be sufficiently aware of the AEs and precautions described in this protocol in advance to ensure subject safety, and he/she must enable subjects to receive appropriate medical treatment for all AEs (including clinically significant laboratory findings) occurring during or after the study. If medical treatment is needed for concurrent diseases of subjects, the Investigator must let the subject know the fact as rapidly as possible. If SAEs or other events occur during the study, they must be reported immediately to the IRB and Hanmi Pharmaceutical Co., Ltd.

The institution must be perfectly prepared to conduct the study appropriately with necessary equipment and professional personnel.

The Sponsor will review all AEs and new information related to the IP and regularly share them with the Principal Investigator to ensure subject safety. In addition, the Sponsor will

prepare compensation measures in case of possible damage of subjects and get the Investigator to fully understand compensation subjects and procedures and to guide subjects about them.

10.3. Finance and Insurance

Financial issues of the clinical study will be described in a separate contract. The Sponsor will provide insurance for the clinical study as required by national regulations.

10.4. Access to Source Data/Documents

An electronic data capture system will be used to manage data collection during this trial. The electronic data capture system is a software tool designed to ensure quality assurance and facilitate data capture during clinical trials. This system complies with all related regulations including GCP of Korea's Pharmaceutical Affairs Act (Article 30, Clause 1, attached Table 4).

The Principal Investigator will ensure the accuracy, completeness and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability and consistency. A complete audit trail will be maintained for all data changes. The Principal Investigator or designee will cooperate with the Sponsor’s representative(s) for periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to each institution by means of electronic or manual queries.

The Principal Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECG, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving the IP. Originals of source documents will be stored, but copies that are clearly recorded identically to originals along with signatures of persons who copied and dates will also be considered as source documents.

The Principal Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors and the IRB to have direct access to all documents pertaining to the study.

10.5. Archiving Study Documents

Hanmi Pharmaceutical Co., Ltd. and the Principal Investigator are responsible for storing clinical study data even if the trial is completed or closed, and it is mandatory to store the documents related to the clinical study for at least 3 years after the last reporting (approval date of result reporting). Note, however, that the storage period may be prolonged if deemed necessary by Hanmi Pharmaceutical Co., Ltd., Hanmi Pharmaceutical Co., Ltd. will inform the Principal Investigator and the head of the institution of the need to store data and storage period in writing. If Hanmi Pharmaceutical Co., Ltd. decides that there is no need to store the data anymore, it will inform the Principal Investigator and the head of the institution of this fact in writing.

10.6. Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Principal Investigator abide by the principles of the ICH guidelines on GCP. The clinical study will also be carried out in keeping with national and local legal requirements.

10.7. Informed Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained from the subject according to the regulatory and legal requirements of the participating country. As part of this procedure, the Principal Investigator or Investigator must explain to groups of subjects or individual subjects the IRB-approved ICF orally and in writing with regard to the nature, duration and purpose of the study and the action of the drug in such a manner that the subject is aware of potential risks, inconveniences or AEs that may occur. The subject is allowed to review study information and ask questions through one-on-one interviews in a separate room. The subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by relevant regulations and ICH guidelines.

The ICF must be signed and dated including time; 1 copy will be handed to the subject, and the Principal Investigator will retain 1 original as part of clinical study records. The Principal Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of consent and date and time when it was obtained must also be documented.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB, and signed by all subjects subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

10.8. Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the IRB in accordance with local legal requirements. The Sponsor must ensure that the clinical study will proceed ethically and legally before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, which must be released by the responsible staff and receive IRB approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment, but will also be mentioned in the integrated clinical study report. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

10.9. Confidentiality Data Protection

All clinical study findings and documents will be regarded as confidential. The study staffs participating in the study, the MFDS, the Sponsor, clinical study inspectors, monitors, and the IRB and the Human Research Protection Center of the institution will be allowed to access study-related documents under the condition that they ensure confidentiality of subjects. Study documents (protocols, IBs, and other materials) will be stored appropriately in areas with a locking device to ensure their confidentiality. The Principal Investigator and members of his/her research team (including the IRB) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified in study documents by their subject number or initial, not by name. Documents that identify subjects (e.g., signed ICF) must be maintained in confidence by the Principal Investigator.

10.10. Publication Policy

By signing the clinical study protocol, the Principal Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the regulatory authorities will be notified of the Principal Investigator’s name, address, qualifications and extent of involvement.

The Principal Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

11. REFERENCE LIST

1. HM15912 Investigator's Brochure, Version 1.0, dated 19 April 2019.
2. Buchman AL. Short Bowel Syndrome: In: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th ed. Philadelphia, PA: Saunders; 1832-1848 (2016)
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5. European medicines agency: EMA/CHMP/525255/2012 – Assessment report of Revestive® (teduglutide)
6. Marier J et al. Pharmacokinetics, safety, and tolerability of teduglutide, a glucagon-like peptide-2 (GLP-2) analog, following multiple ascending subcutaneous administration in healthy subjects
7. Zealand annual report, 2017