Title Page

Clinical Trial Protocol

AN OPEN-LABEL, SINGLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF HM15912 IN SUBJECTS WITH RENAL IMPAIRMENT AND IN MATCHED CONTROL SUBJECTS WITH NORMAL RENAL FUNCTION

Investigational product	**:**	HM15912
Protocol number	**:**	HM-GLP2-102
Version (completion date)	**:**	1.0 (05 August 2022)
Previous version (completion date)	**:**	Not Applicable
Clinical phase	**:**	Phase 1

GENERAL INFORMATION

Protocol No.:	HM-GLP2-102
Date of the Protocol:	05-August-2022
Synopsis Version:	1.2 (29-July-2022)
Sponsor:	Hanmi Pharmaceutical Co., Ltd. 14, Wiryeseong-daero, Songpa-gu, Seoul, 05545 Korea
Sponsor Signatory & Medical Expert:	[redacted]

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of HM15912 in Subjects with Renal Impairment and Matched Control Subjects With Normal Renal Function

PROTOCOL NUMBER: HM-GLP2-102 (Version 1.0)

Hanmi Pharmaceutical Co., Ltd.

I have read the attached protocol and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable Health Authority regulations/guidelines. The human-rights and privacy of patients will be protected based on the Declaration of Helsinki.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Hanmi Pharmaceutical Co., Ltd.

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Clinical Science Director
Hanmi Pharm. Co., Ltd.
14, Wiryeseong-daero, Songpa-gu,
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Date (Day/Month/Year)
August 5, 2022

[redacted]

INVESTIGATOR SIGNATURE PAGE

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Signature of Investigator	Date (Day/Month/Year)
Investigator Name (print or type)	
Investigator's Title	

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of HM15912 in Subjects with Renal Impairment and Matched Control Subjects With Normal Renal Function	
Name of Sponsor: Hanmi Pharmaceutical Co., Ltd.	
Name of Investigational Product: HM15912	
Study Centers: Approximately 4 sites in Unite States	
Publication(s): N/A	
Planned Study Period: First subject first dose is estimated in 4Q 2022. The study is expected to be performed for about 2 years from approval of the regulatory authority and the duration may be shorten or extended depending on the study situation	**Development Phase:** Phase 1

Rationale

The primary purpose of this open-label, single-dose study is to characterize the effect of renal impairment on the pharmacokinetics (PK) of HM15912 following subcutaneous (SC) administration of a single 0.5 mg/kg dose.

Recent Food and Drug Administration (FDA) draft guidance; Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing (2020)[1], suggests that renal impairment studies be conducted in patients with decreased renal function for biologic drugs of which the molecular weight is less than 69 kDa, even if the drug or its active metabolite is not primarily eliminated by the kidneys. Furthermore, the guideline recommends that a PK study be conducted in subjects with renal impairment when the drug is likely to be used in patients with impaired renal function. While agency-specific requirements such as methodology for estimated glomerular filtration rate (eGFR) assessment differ, European Medicines Agency (EMA) also suggests quite similar guidance.[2]

HM15912 with a molecular weight of 57 kDa is intended for use in patients with short bowel syndrome (SBS). The prevalence for renal impairment in patients with SBS remain unclear, but recent study reported that 28.1% of SBS patients developed renal impairment.[3] Therefore, the present study is being conducted to evaluate whether renal impairment has an impact on PK of HM15912. Findings from this study will be used to develop dosing recommendations so that dose may be adjusted appropriately in the presence of renal impairment.

This study is a staged and parallel-group study of HM15912 in subjects with **severe** renal impairment (eGFR < 30 mL/min/1.73m^2) and subjects without renal impairment (eGFR ≥ 90 mL/min/1.73m^2) as a control group (Part 1) and in subjects with **moderate** (30 mL/min/1.73m^2 $\leq$ eGFR < 60 mL/min/1.73m^2) and **mild** (60 mL/min/1.73m^2 $\leq$ eGFR < 90 mL/min/1.73m^2) renal impairment (Part 2), matched for age, body weight and, to the extent possible, for gender to control group. The study will follow a staged approach as renal excretion is minor for HM15912 based on the results from pre-clinical study. Therefore, it is proposed that effect of renal impairment on PK of HM15912 be evaluated first in the population with severe renal impairment.

If the study results confirm that severe renal impairment does not alter PK to an extent that warrants dosage adjustment, no further study is warranted. If the results do not strongly support such a conclusion, Part 2 will be conducted in subjects with moderate and mild renal impairment.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Part 1: To evaluate the effect of severe renal impairment on the pharmacokinetics of HM15912 following single SC dose	• Maximum serum concentration (C_{max}) • Area under the concentration-time curve from extrapolated to infinity ($AUC_{0-\infty}$)
Part 2 (if applicable): To evaluate the effect of moderate and mild renal impairment on the pharmacokinetics of HM15912 following single SC dose	
Secondary	
To evaluate the safety and tolerability of a single SC dose of HM15912 in subjects between mild, moderate and severe renal impairment and normal renal function subjects.	• Incidence of adverse events (AEs), treatment-emergent AEs (TEAEs) and serious AEs (SAEs) • Changes from baseline in vital signs and 12-lead electrocardiogram (ECG) parameters
Exploratory	
To assess the immunogenicity of HM15912 after single SC dose in subjects with renal impairment and normal renal function	• Anti-drug antibody (ADA) • Neutralizing antibody (NAb) • Anti-polyethylene glycol (anti-PEG) antibody
To assess the additional PK parameters of HM15912 in subjects with renal impairment and normal renal function	• Time to maximum serum concentration (t_{max}) • Elimination half-life ($t_{1/2}$) • Volume of distribution (Vd/F) • Clearance (CL/F) • First order rate constant associated with the terminal (log-linear) portion of the curve (λ_z) • Area under the concentration-time curve from time zero to the last observable concentration (AUC_{last}) • Percentage of $AUC_{0-\infty}$ due to extrapolation from T_{last} to infinity ($AUC_{\%Extrap}$)

Methodology:

This is a Phase 1 non-randomized, open-label, single-dose, parallel-cohort study to investigate the effect of renal impairment on the pharmacokinetics of HM15912 after administrating a single 0.5 mg/kg SC dose. Subjects will be selected and categorized into normal renal function or renal impairment groups based on their eGFR calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2021).

Part 1: A total of approximately 16 subjects; approximately 8 subjects with severe renal impairment (Cohort 2) and approximately 8 with normal renal function (Cohort 1) will be enrolled. Cohort 2 will be recruited first. The demographics will be pooled across study sites to determine an average value for age and weight. Subsequently, the Cohort 1 will be recruited later such that each subject's age is within ±10 years and weight is within ±15 kg of the mean of Cohort 2.

Part 2: Part 2 will be conducted if the point estimate of geometric mean ratio (GMR) of $AUC_{0-\infty}$ for the severe renal impairment group (Cohort 2) compared to the control group (Cohort 1) [redacted] Based on whether the decision criterion to proceed to Part 2 is met, up to 8 subjects with moderate renal impairment (Cohort 3) and 8 subjects with mild renal impairment (Cohort 4) will be enrolled.

Subject screening for participation in this study will be conducted within 28 days prior to IP dosing on Day 1. At screening, eGFR will be calculated based on CKD-EPI equation (2021). Two times of blood sample will be taken during the screening period that are at least 3 days but no more than 14 days apart. The mean of the eGFR obtained from two screening visits will be used for group assignment. All subjects must have stable renal function to enter the study which is defined as ≤ 25% difference between 2 measurements of eGFR obtained. Investigator and medical monitor should sign off the eligibility check form and the document should be submitted to the sponsor before dosing the subject.

Each subject will receive a single dose of HM15912 administered SC in the abdomen on the Day 1. Blood samples will be collected from subjects to determine PK of HM15912 up to 29 days post-dose.

Subjects will be confined to the Clinical Research Unit (CRU) for PK sampling and safety assessments (as specified in the Schedule of Activities) from Day -1 to Day 8. After completion of study procedures on Day 2, if subjects request to discharge, they may be discharged from the CRU on their desired date, at the discretion of Investigator. If subjects discharge earlier than Day 8 based on the subject's request, Day 3, 4, 5, 6, and 7 procedures can be done in outpatient visits. These outpatient visit could be replaced to nurse home visit at the discretion of investigator.

After the inpatient period, outpatient visits will take place on Day 10, 15, 22 and 29 for the collection of PK samples and safety assessments. On Day 10, if subject request, outpatient visit could be replaced with nurse home visit upon the investigator's discretion. Day 29 follow up visit will mark the end of study visit.

Physical examinations, supine 12-lead electrocardiogram (ECG), vital sign measurements, and clinical laboratory tests will be conducted and adverse events (AEs) will be monitored throughout the study to assess safety.

Number of Subjects:

Up to approximately 32 subjects, divided in approximately 4 cohorts with 8 subjects per cohort, are planned for enrollment.

Criteria for Inclusion/ Exclusion:

Patients eligible for enrolment in the study must meet all of the following criteria:

Inclusion Criteria

All subjects

1. Subjects voluntarily agree to participate in this study and sign an IRB-approved informed consent prior to performing any of the Screening visit procedures.
2. Males and females ≥ 18 and ≤ 80 years of age at the Screening visit
3. Body mass index (BMI) of ≥ 17.5 to ≤ 40.0kg/m^2;
4. 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.
5. 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 contraceptive methods from the Screening visit and for a period of 60 days after the dose of IP. Acceptable methods of contraception for males are the use of condoms together with spermicidal foam/gel/film/cream/suppository. Effective contraceptives for the female partner include: surgical sterilization (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), hormonal contraception, intrauterine contraception/device or barrier methods (female condom, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. The adequacy of other methods of contraception will be assessed on a case-by-case basis by the Investigator.

Additional inclusion criteria for subjects with normal renal function (Cohort 1)

1. No clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and heart rate measurement, 12-lead ECG and clinical laboratory tests.
2. Normal renal function (eGFR≥ 90 mL/min/1.73m^2) at Screening based on the CKD-EPI equation.
3. Demographically comparable to the group of subjects with impaired renal function.
   3.1. The body weight of each subject will be within ±15kg of the mean body weight of the severe renal impairment group (Cohort 2).
   3.2. The age of each subject will be within ±10 years of the mean age of the severe renal impairment group (Cohort 2).
   3.3. Attempts will be made to ensure that the male-to-female distribution in Cohort 1 is comparable to that in Cohort 2; cohorts cannot comprise entirely of any one gender
   3.4. Other demographic characteristics, such as race and ethnicity, matched as closely as possible to the renal impairment cohort

Additional inclusion criteria for subjects with impaired renal function (Cohort 2, Cohort 3 [if applicable] and Cohort 4 [if applicable])

1. Good general health commensurate with the population with chronic kidney disease (renal impairment). “Health” is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, measurement of heart rate and 12-lead ECG as well as clinical laboratory tests (except serum creatinine and eGFR). Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease and other common co-morbidities in this population are possible exemptions, as long as, in the opinion of the investigator, the subject is medically stable, is on a stable drug regimen and can abide by the meals and dietary restrictions.
2. Meet the following eGFR criteria during the screening period based on the CKD-EPI equation:
   Severe renal impairment: eGFR < 30 mL/min/1.73m^2, but not requiring hemodialysis.
   Moderate renal impairment (Part 2 only): 30 mL/min/1.73m^2 ≤ eGFR < 60 mL/min/1.73m^2

Mild renal impairment (Part 2 only): 60 mL/min/1.73m^2 ≤ eGFR < 90 mL/min/1.73m^2
The difference of eGFR values obtained from the two screening visits (S1 and S2) should not be more than 25%.

3. Any form of renal impairment except acute nephritic syndrome (subjects with history of previous nephritic syndrome but in remission can be included).
4. Stable drug regimen, which means no change in medication within 3 months prior to the dose of IP, for the management of individual subject's medical history; on a case-by-case basis, with input from the sponsor and medical monitor; subjects receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control.

Exclusion Criteria

All subjects

Subjects who meet any of the following criteria must not be enrolled in the study:

1. Renal transplant recipients or subjects requiring hemodialysis and peritoneal dialysis
2. Subject with a history or presence of any psychiatric disorder that, in the opinion of the Investigator, might confound the results of the study or pose additional risk in administering the IP to the subject
3. Has participated in an interventional clinical trial (investigational or marketed product) within 1 month of screening or 5 half-lives of the drug under investigation (whichever comes first), or plans to participate in another clinical trial
4. Subject with a history of any serious adverse events, hypersensitivity reactions, or intolerance to IP components
5. Subject who has any clinically significant history of allergic conditions (including drug allergies, asthma, eczema, or anaphylactic reactions, but excluding treatment not required, asymptomatic, seasonal allergies) prior to IP administration
6. Subject with a history of any major surgery within 6 months prior to the Screening visit
7. Subject with symptomatic heart failure (New York Heart Association class III or IV)
8. Subjects with clinically significant infections within the past 30 days those requiring hospitalization, or as judged by the Investigator
9. Evidence of any viral (including COVID-19), bacterial (including upper respiratory infection), or fungal (noncutaneous) infection within 1 week prior to the Screening visit
10. History of known colon polyps (if resected, the subject can be allowed to participate in the study) or family history of familial adenomatous polyposis
11. 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)
12. Subject with the existence of any surgical or medical condition that, in the judgment of the Investigator, might interfere with the absorption, distribution, metabolism or excretion of the IP
13. Any clinically significant abnormality at screening identified on ECG that in the opinion of the investigator would affect the subject's ability to participate in the trial or cardiac arrhythmia requiring any treatment among medical or surgical treatment, device implantation and catheter ablation within 6 months prior to screening
14. Subject who has done a full blood donation within 60 days before the Screening visit, who has done apheresis within 1 month before the Screening visit or who has received blood products
15. Subject who has a history of alcohol, illicit drug or recreational drug abuse as judged by the Investigator within 6 weeks prior to the Screening visit
16. Subject who has a positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines) at the Screening visit or on Day -1, except for prescribed medications as judged by the Investigator
17. 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 CRU

18. Subject who is unwilling to abstain from vigorous exercise from 48 hours prior to admission until the Follow-up visit
19. 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
20. Subject who is deemed by the Investigator to be inappropriate in conducting the clinical study

Additional exclusion criteria for subjects with normal renal function (Cohort 1)

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding treatment not required, asymptomatic, seasonal allergies at the time of dosing).
2. Subject who has a mean BP ≥140mmHg (systolic) or ≥90mmHg (diastolic). After at least 5 minutes of supine rest, measurements will be taken 2 consecutive times, at least 2 minutes apart. If mean of the 2 BP is ≥140mmHg (systolic) or ≥90mmHg (diastolic), measurement should be repeated 1 more time and the average of the 3 BP values should be used to determine the subject's eligibility.
3. Subject who has a baseline corrected QT interval using the Fridericia formula QTcF >450 msec in males or QTcF >470 msec in females

Additional exclusion criteria for subjects with impaired renal function (Cohort 2, Cohort 3 [if applicable] and Cohort 4 [if applicable])

1. Subject with clinically significant active diseases that may affect the safety of the subject or that may affect the pharmacokinetics of HM15912 (including drug allergies, but excluding treatment not required, asymptomatic, seasonal allergies at time of dosing). Subjects with any significant hepatic, cardiac, or pulmonary disease or subjects who are clinically nephrotic. Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease, etc. is not cause for exclusion as long as the subject is medically stable and any drugs that are administered for these conditions are not expected to interfere with the PK of HM15912.
2. Subject who has a mean BP ≥ 180 mm Hg (systolic) or ≥ 120 mm Hg (diastolic). After at least 5 minutes of supine rest, measurements will be taken 2 consecutive times at least 2 minutes apart. If mean of the 2 BP is ≥ 180mm Hg (systolic) or ≥ 120mmHg (diastolic), the BP should be repeated 1 more time and the average of the 3 BP values should be used to determine the subject's eligibility.
3. Subject who has a baseline corrected QT interval using the Fridericia formula QTcF > 480 msec

Test Product, Dose and Mode of Administration:

HM15912 will be supplied by the Sponsor as a sterile solution in prefilled syringes, manufactured by Hanmi Pharm. Co., Ltd. The concentration of HM15912 is 125 mg/mL as protein and the charged volume is 0.55 mL including 0.05 mL overfill. HM15912 dose will be administered subcutaneously once.

Duration of Treatment:

The total duration of the clinical study per subject will be up to approximately 57 days.

The study will be comprised of:

- Two screening visit up to 28 days before dosing.
- An inpatient assessment period of approximately 9 days, with admission to the CRU on Day -1, dosing on Day 1 and discharge in the Day 8

- Outpatient visit on Day 10, 15, 22 and 29. Day 29 follow up visit will mark the end of study visit

Statistical Methods:

The planned sample size of 8 subjects for each cohort is selected to characterize the effect of renal impairment on the PK of HM15912 based on FDA and EMA guideline rather than calculated with consideration of statistical requirements. With 8 subjects for each cohort (renal impairment cohort and normal renal function cohort), half width of two-sided 90% confidence interval of natural log scaled $AUC_{0-\infty}$ difference between two cohorts is [redacted]

PK parameter analyses such as $AUC_{0-\infty}$, AUC_{last}, and C_{max} will be conducted for PK population which is defined as all subjects who has at least 1 evaluable HM15912 serum concentration after receiving any amount of HM15912 without important protocol deviations or events through to significantly affect the PK of study drug. PK parameters will be derived by non-compartmental analysis using WinNonlin® or any available software.

After Part 1, PK parameter of HM15912 from severe renal impairment group (Cohort 2) will be estimated and compared to control group (Cohort 1). A one-way analysis of variance (ANOVA) will be used to compare log transformed PK parameter. The estimates of adjusted mean difference and corresponding 90% confidence intervals (CI), as well as each exponentiation of estimates will be presented. After statistical or clinical evaluation of results from Part 1, whether to proceed to Part 2 will be further discussed.

If Part 2 is conducted, same analysis with Part 1 will be implemented to compare of each moderate (Cohort 3) or mild (Cohort 4) renal impairment subjects and control group (Cohort 1). In case the demographics of the moderate or mild renal impairment group compared to the normal renal function group are not within the criteria specified in the protocol, it will be considered to add that demographic information as a covariate of ANOVA. If needed, further evaluation to characterize the relationship between renal function and PK parameter will be explored.

AEs, 12-lead ECG, vital signs, physical examination, and laboratory data will be summarized. Summary of AEs will be focused on treatment-emergent adverse events, and clinically significant change of 12-lead ECG, vital signs, physical examination, and laboratory data will be reported as AEs as well.

1.2. Schedule of Assessments

Table 1. Schedule of Assessments

Visit	Screening Visit[a]		Inpatient Period									Outpatient Period			
Day	S1	S2	-1	1	2	3[e]	4[e]	5[e]	6[e]	7[e]	8	10[e] (±1day)	15 (±1day)	22 (±1day)	29[m] (±1day)
Informed consent	X														
Inclusion/exclusion criteria	X		X												
Medical history	X		X												
eGFR assessment[a]	X	X													
Demographic data (age, sex, etc.)	X														
Height[b]	X														
BMI, Body weight[b]	X			X											X
Pregnancy test (female subjects with childbearing potential only)[c]	X		X												X
Serum FSH (postmenopausal females only)	X														
HbA1c	X														
Urine drugs of abuse and alcohol breath test	X		X								X[f]	X	X	X	X
Check-in			X												
Check-out[d]											X				
IP administration				X											
Adverse event assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR, tympanic body temperature, RR)[g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	Screening Visit[a]		Inpatient Period									Outpatient Period			
Day	S1	S2	-1	1	2	3[e]	4[e]	5[e]	6[e]	7[e]	8	10[e] (±1day)	15 (±1day)	22 (±1day)	29[m] (±1day)
Clinical laboratory tests (hematology, coagulation, chemistry[h], urinalysis)	X	X[i]	X	X	X						X		X	X	X
12-lead ECG[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Immune response assessments (ADA, NAb, anti-PEG antibody)			X										X		X
Injection site assessments[k]				X	X	X	X	X	X	X	X	X	X	X	X
Physical examinations[l]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling				X	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibody; anti-PEG = anti-polyethylene glycol; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; HR=heart rate; IP = investigational product; NAb = neutralizing antibody; PK = pharmacokinetics; RR = respiratory rate; SC = subcutaneous;

a. Screening will consist of two CRU outpatient visits (Screening Visit 1 and 2) -between 3 to 14 days apart, with the 1st screening visit occurring within 28 days prior to IP administration (Day 1). At each screening visit, blood sample will be taken for the eGFR assessment. The 2nd screening visit is only to demonstrate stable renal function with eGFR ≤ 25% of the value obtained at Screening visit 1. Other screening procedures completed during the first visit do not need to be repeated except eGFR, adverse event assessment and physical examinations.

b. 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. BMI will be calculated with the height measured at S1.

c. Serum pregnancy tests at the Screening visit; serum or urine pregnancy tests at the Day -1 and Day 29. A woman is considered to have childbearing potential, following menarche and until becoming post-menopausal unless permanently sterile.

d. After completion of study procedures on Day 2, if subjects request to discharge, subjects may be discharged from the CRU on their desired date, upon investigator's discretion. If subjects discharge from CRU, all the remaining procedures scheduled for inpatient period will be conducted by outpatient visit or nurse home visit as appropriate.

e. If subjects discharge earlier than Day 8 based on the subject's request, Day 3, 4, 5, 6, and 7 procedures can be done in outpatient visits. These outpatient visit could be replaced to nurse home visit at the discretion of investigator. Nurse home visit may replace outpatient visit on Day 10 as well. Outpatient visit on Day 8,15,22 and 29 are not replaceable with nurse home visit.

f. On Day 8, urine drug test and alcohol screening will be performed only if subjects discharge earlier than Day 8.

g. Supine BP and HR will be measured for 2 consecutive times, at least 2 minutes apart, after the subject has been recumbent and at rest ≥ 5 minutes, and mean values will be recorded. If abnormal, at the Screening visit, measurement will be repeated 1 more time and the average of the 3 BP values should be used to determine the subject's eligibility.

h. Samples for a chemistry test will be collected after at least 4 hours of fasting.

i. The 2nd screening visit is only to demonstrate stable renal function with eGFR ≤25% of the value obtained at Screening visit 1. Other clinical laboratory tests except serum creatinine assessment, do not need to be repeated.

j. The 12-lead ECGs will be performed after the subject has been resting supine for ≥ 5 minutes. A triplicate 12-lead ECGs will be performed at screening period and Day1. At all other times, however, single 12-lead ECGs will be performed. Limited to Day 1, ECGs will be performed at predose and at 4 hours postdose, and a ±30-minute assessment window is allowed for measurement 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.

k. Injection site assessments will be performed at predose and at 4 and 12 hours postdose on Day 1.

l. Full physical examination at Screening Visit 1 (S1); brief physical examination at all other time points.

m. At the early discontinuation visit, every effort must be made to complete the assessments planned at Day 29.

Table 2. Pharmacokinetic Sampling Schedule

Study Day		PK Sampling Time Point
Day 1	Inpatient Period	Predose
Day 2[a]		24 h (± 15 min)
Day 3[b]		48 h (± 60 min)
Day 4[b]		72 h (± 60 min)
Day 5[b]		96 h (± 60 min)
Day 6[b]		120 h (± 60 min)
Day 7[b]		144 h (± 60 min)
Day 8[c]		168 h (± 60 min)
Day 10[b]	Outpatient Period	216 h (± 24 h)
Day 15[c]		336 h (± 24 h)
Day 22[c]		504 h (± 24 h)
Day 29[c]		672 h (± 24 h)

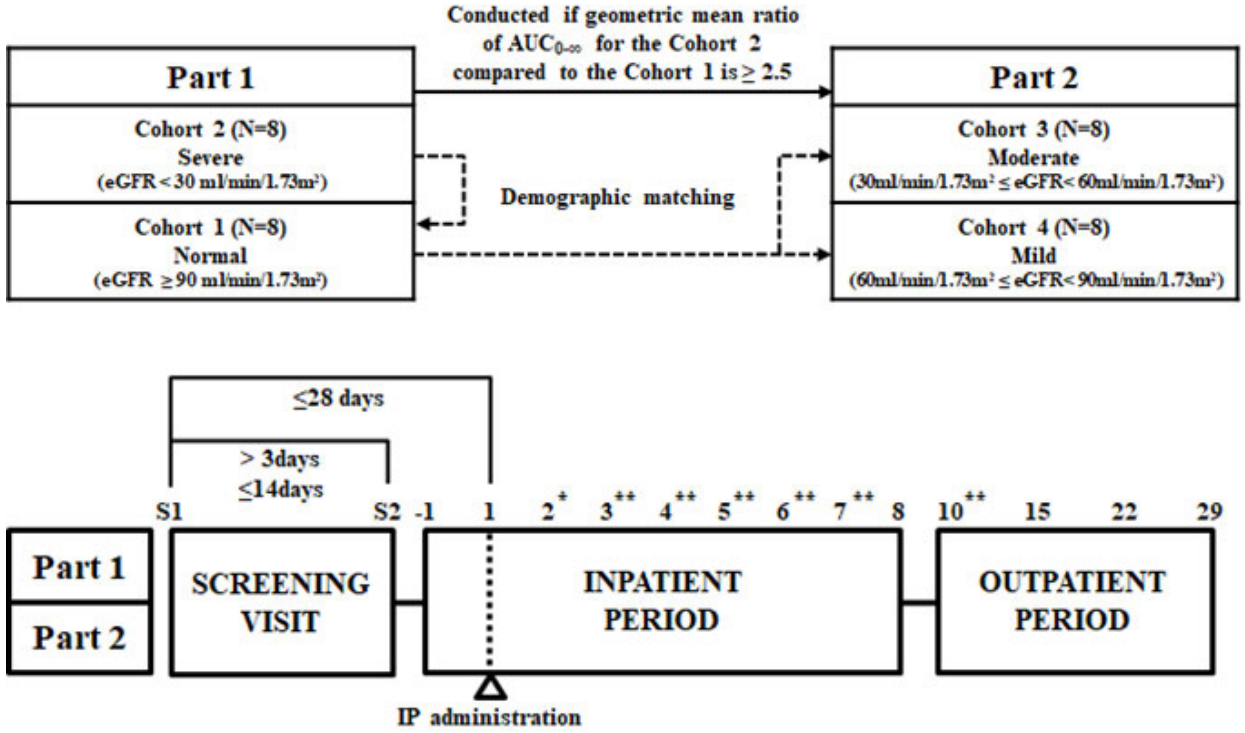
a. After completion of study procedures on Day 2, if subjects request to discharge, subjects may be discharged from the CRU on their desired date, at the discretion of investigator If subjects discharge from CRU, all the remaining procedures will be conducted by outpatient visit or nurse home visit as appropriate.

b. If subjects discharge earlier than Day 8 based on the subject's request, Day 3, 4, 5, 6, and 7 procedures can be done in outpatient visits. These outpatient visit could be replaced to nurse home visit at the discretion of investigator. Nurse home visit may replace outpatient visit on Day 10 as well.

c. Outpatient visit on Day 8, 15, 22 and 29 are not replaceable with nurse home visit.

1.3. Study Schema

Figure 1. Study Schema



Note

* After completion of study procedures on Day 2, if subjects request to discharge, subjects may be discharged from the CRU on their desired date, at the discretion of investigator. If subjects discharge from CRU, all the remaining procedures will be conducted by outpatient or nurse home visit as appropriate.
** If subjects discharge earlier than Day 8 and based on the subject's request, Day 3, 4, 5, 6, and 7 procedures can be done in outpatient visit. These outpatient visit could be replaced to nurse home visit at the discretion of investigator. Nurse home visit may replace outpatient visit on Day 10 as well. Outpatient visit on Day 8,15,22 and 29 will not be replaced with nurse home visit.

2. Introduction

HM15912 is a novel long acting chemical conjugate of a glucagon-like peptide 2 (GLP-2) analog (GT15912) and a human immunoglobulin (Ig)G4 fragment crystallizable (Fc), linked together via a bifunctional maleimide polyethylene glycol aldehyde linker molecule. HM15912 is being evaluated for treatment of subjects with short bowel syndrome (SBS).

2.1. Study Rationale

The primary purpose of this single-dose, open-label study is to characterize the effect of renal impairment on the pharmacokinetics of HM15912 in order to guide dosing recommendations in patients with renal impairment.

SBS is defined as the clinical syndrome associated with loss of residual small intestinal length due to disease or resection. A residual length of the small intestine < 200 cm meets the criteria for SBS.[4] The condition which is reduced absorption of nutrients from the gastrointestinal tract resulting in the need for parenteral nutrition for survival can be defined as intestinal failure. The patients with short bowel syndrome associated intestinal failure (SBS-IF) who requires prolonged use of PN/IV may lead to various complications, including sepsis, osteopenia, and chronic liver disease.[5] In addition, some SBS-IF patients have renal impairment because of long term dependence of PN/IV.[6,7] Moreover, ischemic bowel disease is one of the important cause of SBS-IF and renal ischemia can be easily accompanied with this condition. Though, the prevalence and risk factors for renal impairment in patients with SBS still remain unclear, but recent study showed that 28.1% of SBS patients developed renal impairment.[3] Overall, findings from previous studies in SBS patients indicate that a subpopulation of target patients of HM15912 have some degree of impaired renal function.

FDA guideline[1] suggests that a PK study should be conducted in subjects with renal impairment when the drug is likely to be used in patients with impaired renal function. The guideline also recommends that renal impairment studies needs to be conducted in patients with decreased renal function for biologic drugs of which the molecular weight is less than 69 kDa, even if the drug or its active metabolite is not primarily eliminated by the kidney. Although agency-specific requirements such as methodology for eGFR assessment differ, EMA also suggests quite similar guidance.[2]

To characterize the effect of renal impairment on the pharmacokinetics (PK) of HM15912, a pharmacokinetic study was conducted in sham rats and experimental renal failure model rats. When rats were treated with HM15912 and then assessed, there were no significant differences in PK profile between sham rats and nephrectomized rats. These data indicate that the renal pathway might not be the main elimination route of HM15912, and impaired renal function did not affect the pharmacokinetic properties of HM15912. Though kidney was not a major elimination pathway of HM15912 in the nephrectomized rat model, the molecular weight of HM15912 is 57kDa, lower than cut off value for the PK study in renal impairment subjects which is suggested by the FDA and around one third of the target population have a potential to have impaired renal function. Taken together, the present study is being conducted to evaluate

whether renal impairment has an impact on HM15912 PK. Findings from this study will be used to develop dosing recommendations so that dose may be adjusted appropriately in the presence of renal impairment.

2.2. Background

GLP-2 is a major hormone that affects many aspects of intestinal physiology such as growth, barrier function, digestion, absorption, movement, and blood flow.[8] GLP-2 is created by specific post translational proteolytic cleavage of proglucagon in a process that also liberates the related glucagon-like peptide-1 (GLP-1) from the intestinal endocrine L-cells. Intestinal GLP-2 is co secreted along with GLP-1 upon nutrient ingestion and is known to play a critical role in intestinal growth by promoting crypt cell proliferation. Because of its intestinal proliferation property, GLP-2 analog has long been used to treat people with SBS.[8,9,10]

The half-life of native GLP-2 within the human body is very short (approximately 7 minutes), so the GLP-2 based 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 complicated preparation processes to administer it to patients.[11] Thus teduglutide cannot resolve inconvenience of daily dosing and error that may occur during the preparation process so there are still big unmet needs existed for SBS-IF patients requiring long-term PN/IV.

To overcome the limitations of teduglutide and achieve a better subject quality of life, Hanmi Pharmaceutical Co. Ltd. has developed HM15912, a novel long-acting GLP-2 analog chemically conjugated, via a bifunctional polyethylene glycol linker, to a recombinant human IgG4 Fc fragment (HMC001) to prolong its duration of action. In HM15912, the amino acid sequence of the GLP-2 analog moiety is different from teduglutide, rendering a novel structure uniquely designed based on human GLP-2. The purpose of this novel design of GT15912 is to achieve a more potent activity than teduglutide. Furthermore, conjugation of GT15912 to the Fc domain of human IgG4 via a flexible non-peptidyl linker at the C-terminal position extends the half-life of GLP-2 analog by promoting neonatal Fc receptor (FcRn) mediated vascular endothelial recycling, preventing receptor-mediated clearance, and reducing renal clearance due to the increase in molecular weight.

According to pharmacodynamic (PD) studies, HM15912 dose-dependently induced human GLP 2 receptor-mediated intracellular cAMP accumulation in hGLP-2R/CHO-K1 cells and stimulated IGF-1 production in mouse primary intestinal subepithelial myofibroblasts. The secreted IGF-1 acted in a paracrine fashion on the tyrosine kinase IGF-1 receptor expressed in the proliferative compartment of the crypt. The efficacy of HM15912 has also been demonstrated in in vivo studies. Multiple subcutaneous (SC) administrations of HM15912 dose-dependently increased intestinal growth, especially the wet weight of the small intestine, showing superior intestinotrophic efficacy to teduglutide in normal mice and rats. Furthermore, the intestinal growth induced by HM15912 improved nutrition absorption in an SBS rat model, confirming as well that the intestinotrophic effects of physical improvement was strongly co-related with functional improvement.

HM15912 has been evaluated in one clinical study to date. A first–in-human study (HM-GLP2-101) was a Phase 1 double-blind, randomized, placebo-controlled, single ascending dose (SAD) study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of the SC administration of HM15912 in healthy subjects conducted in Korea. The study was conducted in 5 sequential dosing cohorts enrolling 8 subjects per cohort. Subjects were randomized to HM15912 or placebo in a ratio of 3:1 (active: 6, placebo: 2) and administered 0.05 mg/kg (Cohort 1), 0.1 mg/kg (Cohort 2), 0.5 mg/kg (Cohort 3), 1.0 mg/kg (Cohort 4) and 1.5 mg/kg (Cohort 5) of HM15912 or matching placebo. Healthy volunteers exposed to single ascending doses of HM15912 confirmed a favorable safety profile. Overall, 25 of 40 subjects reported at least one treatment emergent adverse event (TEAE) but all of the TEAEs were mild and moderate in severity. There have been no serious adverse events (SAEs) and no subjects have discontinued study due to adverse events (AEs). Plasma citrulline level, which is a biomarker for intestinal enterocyte mass, was measured to assess the PD property. The fasting plasma citrulline levels (nmol/mL) gradually increased by HM15912 administration from dose 0.5 mg/kg, and the values between 0.5 mg/kg and 1.5 mg/kg tended to be overlapped and saturated. Serum concentration of HM15912 reached its peak levels (mean t_{max}) in 71.8 to 142.9 hours. Mean terminal elimination $t_{1/2}$ of HM15912 was estimated to approximately 108 to 167.4 hours that could support a potential for once every 4-week dosing frequency. Based on these results, the Sponsor aims to develop HM15912 as a long-acting treatment option for subjects with SBS and Phase 2 trial for SBS patients is currently ongoing (NCT04775706, EudraCT: 2021-000176-11).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of HM15912 may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

The planned dose of HM15912 for this study is 0.5 mg/kg and it was selected to minimize potential risks for both subjects with normal renal function and subjects with renal impairment.

Experiences with native GLP-2 and teduglutide suggest that expected common AEs for this class of compounds include abdominal pain and distension, injection site reactions, nausea, headache, upper respiratory tract infection, and (in some studies) vomiting and fluid overload.

HM15912 has shown no adverse effect on the central nervous system, respiratory function, or cardiovascular system in GLP studies. The *in vitro* acute effects of HM15912 on hERG K+ channel current, recorded from stably transfected HEK-293 cells, were evaluated and no effect was seen with the maximum concentration of HM15912 tested. In addition, no statistically significant increased heart rate was observed in cardiovascular telemetry study in monkeys at doses 100 times higher than the expected effective dose. No meaningful or toxicologically significant findings were observed in the cardiovascular system. Additionally, there was no significant change in body temperature.

The safety of HM15912 has also been investigated in 26-week GLP toxicology studies (once weekly SC administration) in rats and monkeys. The no observed adverse effect levels

(NOAELs) were determined at 30 mg/kg for rat and 18 mg/kg for monkey in 26-week toxicology studies. The human equivalent dose converted from the animal dose based on body surface area is 4.8 mg/kg and 5.8 mg/kg, respectively.

In 26-week toxicity study in rats, elevation of liver enzymes, particularly, alkaline phosphatase (ALP), alanine aminotransferase (ALT), bile acid and fluctuation of plasma lipids parameters were observed but these findings were fully resolved during the recovery period. Minimal bile duct hypertrophic or hyperplastic response on gastrointestinal(GI) tract were observed in female rats, predominantly.

Additionally, in 26-week toxicity study in monkeys, elevated ALT and high individual bile acid and cholesterol and/or triglyceride concentrations were seen transiently in the treated groups, with no clear dose response relationship. The association of the occasionally low hematocrit and hemoglobin concentrations and the fluctuations in a few leukocytes (mainly lymphocytes, monocytes, and occasionally monocytes and basophils) to treatment with HM15912 was inconclusive in this study. The administration of HM15912 resulted in diffuse hypertrophy of the mucosa in the small intestine of treated animals and correlated with increased length, weight, and thickening of the small intestine in monkeys. These treatment-related histopathological changes were considered to be an expected pharmacological effect related to HM15912.

To investigate the effect of renal clearance on the pharmacokinetic properties of HM15912, a pharmacokinetic study was conducted in sham and nephrectomized rats. In this study, impaired renal function didn't impact pharmacokinetic properties of HM15912. This finding indicates that the renal elimination is not a main pathway in the disposition of HM15912. In other words, if HM15912 is administered in the same dose level to subjects with normal renal function and renal impaired subjects, there may be no significant differences in exposure.

In the SAD study, HM-GLP2-101, HM15912 doses of 0.05, 0.1, 0.5, 1.0 and 1.5 mg/kg were administered and, all of the TEAEs reported were mild and moderate in severity. Overall, 25 of 40 subjects reported at least one TEAE in this study. 22 of 40 subjects experienced at least one TEAE that were judged by the investigator as suspected of being related to study drug. Most common TEAEs were injection site bruising (7/40; 17.5%), nasopharyngitis (3/40; 7.5%) and headache (3/40; 7.5%). There have been no serious SAEs and no subjects discontinued treatment due to TEAEs. Dose-limiting safety finding were not noted in clinical laboratory evaluations, vital signs, blood pressure measurements, 12-lead ECG measurements, physical examination, or local tolerability assessments. Subcutaneous administration of HM15912 was well tolerated in healthy volunteers at dose levels up to and including 1.5 mg/kg. A brief summary of TEAEs was presented in Table 3.

In the SAD study, two (2) out of 30 (6.7%) HM15912 treated subjects had an anti-drug antibody (ADA) response. One (1) subject in the 0.1 mg/kg dose cohort had a treatment-induced ADA response on Day 30, that was specific to the Fc domain of HM15912 and cross-reactive to endogenous GLP-2. One (1) subject in the 1.0 mg/kg dose cohort had a positive ADA response on baseline (pre-existing antibody before treatment), Day 17 and Day 44, but titer was not increased at all, not specific to the Fc domain nor the active pharmaceutical portion of HM15912, and also not cross-reactive to endogenous GLP-2. None of these ADAs had neutralizing activities. Anti-polyethylene glycol (Anti-PEG) antibody assay as a specificity test

performed for the samples showed the post-dose titer increase by at least four (4) fold (2 titer dilution) compare to the pre-treatment. In this study, there was no subject who showed titer increase more than 4 times compared to baseline, so specificity assay did not need to be performed based on assessment rationale.

Table 3: Treatment-Emergent Adverse Events Reported to Date in Study HM-GLP2-101

System Organ Class Preferred Term, Subject (%)	HM15912 0.05mg/kg (N=6)	HM15912 0.1mg/kg (N=6)	HM15912 0.5mg/kg (N=6)	HM15912 1.0mg/kg (N=6)	HM15912 1.5mg/kg (N=6)	HM15912 (N=30)	Placebo (N=10)	All (N=40)
General disorders and administration site conditions	0	0	1 (16.7%)	2 (33.3%)	3 (50.0%)	6 (20.0%)	2 (20.0%)	8 (20.0%)
Injection site bruising	0	0	0	2 (33.3%)	3 (50.0%)	5 (16.7%)	2 (20.0%)	7 (17.5%)
Pyrexia	0	0	1 (16.7%)	0	0	1 (3.3%)	0	1 (2.5%)
Investigations	0	0	2 (33.3%)	1 (16.7%)	4 (66.7%)	7 (23.3%)	1 (10.0%)	8 (20.0%)
Blood creatine phosphokinase increased	0	0	1 (16.7%)	1 (16.7%)	0	2 (6.7%)	0	2 (5.0%)
Blood triglycerides increased	0	0	0	0	2 (33.3%)	2 (6.7%)	0	2 (5.0%)
Neutrophil count decreased	0	0	1 (16.7%)	0	0	1 (3.3%)	1 (10.0%)	2 (5.0%)
Alanine aminotransferase increased	0	0	0	0	1 (16.7%)	1 (3.3%)	0	1 (2.5%)
Aspartate aminotransferase increased	0	0	0	1 (16.7%)	0	1 (3.3%)	0	1 (2.5%)
Blood bilirubin increased	0	0	0	0	1 (16.7%)	1 (3.3%)	0	1 (2.5%)
White blood cells urine positive	0	0	0	0	1 (16.7%)	1 (3.3%)	0	1 (2.5%)
Nervous system disorders	2 (33.3%)	1 (16.7%)	0	0	0	3 (10.0%)	2 (20.0%)	5 (12.5%)
Headache	2 (33.3%)	0	0	0	0	2 (6.7%)	1 (10.0%)	3 (7.5%)
Presyncope	1 (16.7%)	1 (16.7%)	0	0	0	2 (6.7%)	0	2 (5.0%)
Somnolence	0	0	0	0	0	0	1 (10.0%)	1 (2.5%)
Gastrointestinal disorders	0	0	0	3 (50.0%)	0	3 (10.0%)	0	3 (7.5%)
Abdominal pain upper	0	0	0	1 (16.7%)	0	1 (3.3%)	0	1 (2.5%)
Paraesthesia oral	0	0	0	1 (16.7%)	0	1 (3.3%)	0	1 (2.5%)
Retching	0	0	0	1 (16.7%)	0	1 (3.3%)	0	1 (2.5%)

System Organ Class Preferred Term, Subject (%)	HM15912 0.05mg/kg (N=6)	HM15912 0.1mg/kg (N=6)	HM15912 0.5mg/kg (N=6)	HM15912 1.0mg/kg (N=6)	HM15912 1.5mg/kg (N=6)	HM15912 (N=30)	Placebo (N=10)	All (N=40)
Infections and infestations	0	2 (33.3%)	0	0	0	2 (6.7%)	1 (10.0%)	3 (7.5%)
Nasopharyngitis	0	2 (33.3%)	0	0	0	2 (6.7%)	1 (10.0%)	3 (7.5%)
Gastroenteritis	0	1 (16.7%)	0	0	0	1 (3.3%)	0	1 (2.5%)
Musculoskeletal and connective tissue disorders	1 (16.7%)	0	0	0	1 (16.7%)	2 (6.7%)	1 (10.0%)	3 (7.5%)
Back pain	1 (16.7%)	0	0	0	0	1 (3.3%)	0	1 (2.5%)
Myalgia	0	0	0	0	0	0	1 (10.0%)	1 (2.5%)
Pain in extremity	0	0	0	0	1 (16.7%)	1 (3.3%)	0	1 (2.5%)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (16.7%)	1 (3.3%)	1 (10.0%)	2 (5.0%)
Fixed eruption	0	0	0	0	0	0	1 (10.0%)	1 (2.5%)
Pruritus	0	0	0	0	1 (16.7%)	1 (3.3%)	0	1 (2.5%)
Metabolism and nutrition disorders	0	0	0	1 (16.7%)	0	1 (3.3%)	0	1 (2.5%)
Decreased appetite	0	0	0	1 (16.7%)	0	1 (3.3%)	0	1 (2.5%)
Surgical and medical procedures	0	0	0	0	0	0	1 (10.0%)	1 (2.5%)
Blepharoplasty	0	0	0	0	0	0	1 (10.0%)	1 (2.5%)

Taken together, administration of HM15912 dose of 0.5mg/kg will not likely to pose any risks to both normal and renal impaired subjects.

Potential risks associated with this study and mitigation strategies are presented in Table 4**.**

Table 4: Risks and Mitigation Strategies

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug (HM15912)		
Overall risk of fatigue, nausea, dizziness, polyuria, decreased appetite, itching, and redness	Known pharmacology for drugs of this type	Physical examination will be conducted by the investigator with every outpatient visit. If adverse event was observed, appropriate

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		medical intervention will be applied.
Gastrointestinal side effects: Nausea or vomiting, abdominal pain or distension and biliary effects	Known pharmacology for drugs of this type	Undergo laboratory assessment (total bilirubin, alkaline phosphatase, liver tests [AST, ALT, GGT], and hematology) at the time points as specified in the SoA (Section 1.2). Additional time points may be added during the study period to ensure appropriate safety monitoring.
Risk for acceleration of neoplastic growth	Known pharmacology for drugs of this type	Considering the nature of the polyp development, single dosing of HM15912 contains the minimal risk of adenoma hyperplasia.
Upper respiratory tract infections and headache	Known pharmacology for drugs of this type	Monitor the subject closely for these events and treat per local standard of care
Study Procedures		
Injection site reaction	The most frequently reported symptoms were itching and redness. The reactions were dose dependent, mild to moderate in severity and transient in nature.	Monitor the subject closely for these events and treat per local standard of care
Electrocardiograms	Minor skin irritation from the electrodes	Monitor the subject closely for these events and treat per local standard of care
Peripheral access for blood draws	Tenderness, pain, bruising, bleeding and/or infection where the needle goes into the skin and blood vein as well as light-headedness and nausea	Monitor the subject closely for these events and treat per local standard of care

2.3.2. Benefit Assessment

There will be no direct health benefit for subjects from receipt of the investigational product (IP). Participation in this study will contribute to the process of developing new therapies in areas of growing unmet need.

2.3.3. Overall Benefit: Risk Conclusion

The protocol has been designed to minimize the risk to research subjects by careful selection of dose and subjects for the study. Subjects will be monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Part 1: To evaluate the effect of severe renal impairment on the pharmacokinetics of HM15912 following single SC dose	• Maximum serum concentration (C_{max}) • Area under the concentration-time extrapolated to infinity ($AUC_{0-\infty}$)
Part 2 (if applicable): To evaluate the effect of moderate and mild renal impairment on the pharmacokinetics of HM15912 following single SC dose	
Secondary	
To evaluate the safety and tolerability of a single SC dose of HM15912 in subjects between mild, moderate and severe renal impairment and normal renal function subjects.	• Incidence of adverse events (AEs), treatment emergent AEs (TEAEs) and serious AEs (SAEs) • Changes from baseline in vital signs and 12-lead electrocardiogram (ECG) parameters
Exploratory	
To assess the immunogenicity of HM15912 after single SC dose in subjects with renal impairment and in subjects with normal renal function	• Anti-drug antibody (ADA) • Neutralizing antibody (NAb) • Anti-polyethylene glycol (anti-PEG) antibody
To assess the additional PK parameters of HM15912 in subjects with renal impairment and in subjects with normal renal function	• Time to maximum serum concentration (t_{max}) • Elimination half-life ($t_{1/2}$) • Volume of distribution (Vd/F) • Clearance (CL/F) • First order rate constant associated with the terminal (log-linear) portion of the curve (λ_z) • Area under the concentration-time curve from time zero to the last observable concentration (AUC_{last}) • Percentage of $AUC_{0-\infty}$ due to extrapolation from T_{last} to infinity ($AUC_{\%Extrap}$)

4. Study Design

4.1. Overall Design

This study is a phase 1, open-label, single-dose, parallel-group study to investigate the effect of renal impairment on the pharmacokinetics of HM15912 in subjects with severe renal impairment and subjects without renal impairment as a control group (Part 1), and in subjects with moderate and mild renal impairment (Part 2).

At Screening, subjects will be enrolled to the appropriate groups based on the classification as defined in the Food and Drug Administration (FDA) draft guidance for industry, "Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling" (2020).[1] Subjects with normal renal function and subjects with renal impairment will be classified based on the estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2021).

- $eGFR(mL/min/1.73m^2) = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

  where: S_{cr} = serum creatinine in mg/dL
  $\kappa = 0.7$ (females) or 0.9 (males)
  $\alpha = -0.241$ (female) or -0.302 (male)
  $\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0
  $\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0
  Age (years)

Subject screening for participation in this study will be conducted within 28 days prior to IP dosing on Day 1. The mean of the eGFR obtained from two screening visits will be used for group assignment. Second baseline eGFR sample will be taken during the screening period, that are at least 3 days but no more than 14 days apart from the first eGFR assessment. All subjects must have stable renal function to enter the study which is defined as ≤ 25% difference between 2 measurements of eGFR during the screening period. Subjects will be selected and categorized according to their eGFR as shown in Table 5. Investigator and medical monitor should sign off the eligibility check form and the document should be submitted to the sponsor before dosing the subject.

Table 5. Renal Function Categories by eGFR ranges

Cohort	Renal Impairment	eGFR ($mL/min/1.73m^2$)	Number of Subjects
1	Normal	≥ 90	8
2	Severe	< 30	8

3	Moderate	≥ 30 to < 60	8
4	Mild	≥ 60 to < 90	8

Approximately 16 subjects will be enrolled in Part 1; 8 subjects with severe renal impairment (Cohort 2) and approximately 8 with normal renal function (Cohort 1). The 8 subjects of Cohort 2 will be recruited first. After the end of recruitment of Cohort 2, the demographics will be pooled to determine an average value for age and weight which will be used as a reference value for Cohort 1. The subjects with normal renal function in Cohort 1 will be recruited later such that each subject's age is within ±10 years and weight is within ±15 kg of the mean of the Cohort 2. An attempt will be made to maintain a similar male/female ratio between Cohort 1 and Cohort 2. Care will be taken when recruiting the subjects with normal renal function such that the entire group is not younger and of lower body weight than the impaired subjects.

Part 2 will be conducted if the point estimate of geometric mean ratio (GMR) of $AUC_{0-\infty}$ for the severe renal impairment group (Cohort 2) compared to the control group (Cohort 1) [redacted] Based on whether the decision criterion to proceed to Part 2 is met, up to 8 subjects with moderate renal impairment (Cohort 3) and 8 subjects with mild renal impairment (Cohort 4), matched for demographic character to control group will be enrolled.

For both Parts 1 and 2, subjects who withdraw from the study for non-safety related reasons and who are considered to be non-evaluable with respect to the primary objective may be replaced at the discretion of the sponsor but the maximum number of meaningfully evaluable patients will be not more than planned 8.

Each subject will receive a single dose of either HM15912 administered SC in the abdomen on the Day 1. Blood samples will be collected from subjects to determine PK of HM15912 up to 29 days post-dose.

Subjects will be confined to the unit PK sampling and safety assessments (as specified in the Table 2). Inpatient period will be approximately 8 days, with admission to the Clinical Research Unit (CRU) on Day -1, dosing on Day 1 and discharge in the Day 8. After completion of study procedures on Day 2, if subjects request to discharge, they may be discharged from the CRU, on their desired date, at the discretion of Investigator. If subjects discharge earlier than Day 8 and based on the subject's request, Day 3, 4, 5, 6, and 7 procedures can be done in outpatient visit. These outpatient visit could be replaced to nurse home visit at the discretion of investigator.

After the inpatient period, outpatient visits will take place on Day 10, 15, 22 and 29 for the collection of PK samples and safety assessments. On Day 10, if subjects request, outpatient visit could be replaced with nurse home visit upon the investigator's discretion. Day 29 follow up visit will mark the end of study visit.

Physical examinations, supine 12-lead electrocardiogram (ECG), vital sign measurements, and clinical laboratory tests will be conducted and AEs will be monitored throughout the study to assess safety.

4.2. Scientific Rationale for Study Design

This study is designed to evaluate the PK of HM15912 in subjects with renal impairment, based on recommendations given in the FDA draft guidance[1] for industry. Pharmacokinetic studies of investigational products intended for chronic use and with a molecular weight less than 69 kDa are recommended by global regulatory agencies. The molecular weight of HM15912 is approximately 57 kDa, and a subset of the target population may have renal impairment. As a result, the present study is being conducted to determine whether renal impairment affects HM15912 PK. The findings from this study will be used to develop dosing recommendations for patients with renal impairment.

When the drug is substantially eliminated by the kidney (ie, if the fraction of dose excreted unchanged in the urine is at least 30%), a dedicated renal impairment study is recommended. The full pharmacokinetic study design of renal function is to include subjects with varying degrees of renal impairment, including mild, moderate and severe impairment, with corresponding matched control subjects. However, if renal elimination is a minor route of elimination of the drug, then a reduced study design which includes only severe impairment and matched control subjects is warranted for consideration. To investigate the effect of renal clearance on the pharmacokinetic properties of HM15912, a pharmacokinetic study was conducted in male sham and nephrectomized rats. In this study, impaired renal function didn't impact pharmacokinetic properties of HM15912. These data indicate that the renal pathway might not be the main elimination route of HM15912, and impaired renal function did not affect the pharmacokinetic properties of HM15912. Overall, these results indicate that a full PK study design as outlined by FDA and the European Medicines Agency (EMA) guidances[1,2] on studies with subjects with renal impairment is not warranted, and a reduced design can be applied. Therefore, the proposed study will assess the effect of HM15912 only in subjects with severe renal function and demographically matched subjects with normal renal function. If the study results confirm that severe renal impairment does not alter PK to an extent that warrants dosage adjustment, no further study is warranted. If the results do not strongly support such a conclusion, Part 2 will be conducted in subjects with mild and moderate renal impairment.

4.3. Justification for Dose

The planned dose of HM15912 for this study is 0.5 mg/kg. In the first in human SAD study (HM-GLP2-101) with healthy subjects, HM15912 doses of 0.05, 0.1, 0.5, 1.0 and 1.5 mg/kg were investigated. Safety results of doses up to 1.5 mg/kg suggested that HM15912 was safe and well-tolerated and no dose-limiting safety findings were noted during the Phase 1 study. This dose selection also takes into account safety considerations for subjects with severe renal impairment in whom an increase in exposure of HM15912 may be observed. In study HM-GLP2-101, 0.5mg/kg doses of HM15912 led to C_{max} of 3,740 ng/ml and $AUC_{0-\infty}$ of 1,237,890 ng·h/ml. 1.5mg/kg doses of HM15912 led to C_{max} of 9,463 ng/ml and $AUC_{0-\infty}$ of 3,609,894 ng·h/ml. GMR of $AUC_{0-\infty}$ for the dose 1.5mg/kg to dose of 0.5mg/kg, the ratio was approximately 3.0 and the ratio of C_{max} was 2.5. Thus, based on the safety data of prior study, with the single dose of 0.5 mg/kg, exposure increases up to 2.5 fold if observed, will not likely to pose any safety risks.

HM15912 is currently undergoing evaluation in clinical trials with SBS patients; therefore, the clinical dose has not yet been established. However, in the SAD study, dose of 0.5 mg/kg was sufficient to increase intestinal enterocyte mass. The fasting plasma citrulline levels which is a biomarker for intestinal enterocyte mass, increased from dose 0.5 mg/kg, and the values between 0.5 mg/kg and 1.5 mg/kg tended to be overlapped and saturated. Thus, 0.5 mg/kg dose is selected for this study on the grounds that it is minimum effective dose and close to the clinical dose so as to enable prediction of pharmacokinetic at the clinical dose.

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the Schedule of Activities. The end of the study is defined as the date of the last visit of the last subject in the study or last scheduled procedure for the last subject in the trial globally.

4.5. Study Termination

Monitoring of subject safety data will be performed by the sponsor and medical monitor. Study conduct may be interrupted or terminated by the sponsor at any time if there appears to be an undue risk to the study subjects' health or well-being after a thorough review of all clinical, laboratory, PK, and other available safety data.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Subjects who meet all the following criteria at screening will be eligible to participate in the clinical study. Note: Subjects not eligible because of laboratory result(s) may have the laboratory test(s) (hematology, clinical chemistry including liver function tests, and ECG) repeated once during the screening period at the discretion of the investigator to determine eligibility.

5.1.1. All Subjects

1. Subjects voluntarily agree to participate in this study and sign an IRB-approved informed consent prior to performing any of the Screening visit procedures.
2. Males and females ≥ 18 and ≤ 80 years of age at the Screening visit
3. Body mass index (BMI) of ≥17.5 to ≤40.0kg/m^2
4. 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.
5. 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 contraceptive methods from the Screening visit and for a period of 60 days after the dose of IP. Acceptable methods of contraception for males are the use of condoms together with spermicidal foam/gel/film/cream/suppository. Effective contraceptives for the female partner include: surgical sterilization (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), hormonal contraception, intrauterine contraception/device or barrier methods (female condom, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. The adequacy of other methods of contraception will be assessed on a case-by-case basis by the Principal Investigator.

5.1.2. Additional Inclusion Criteria for Subjects with Normal Renal Function (Cohort 1)

1. No clinically relevant abnormalities identified by a detailed medical history, full physical examination, including BP and heart rate measurement, 12 -lead ECG and clinical laboratory tests.
2. Normal renal function (eGFR ≥ 90 mL/min/1.73m^2) at Screening based on the CKD-EPI equation.
3. Demographically comparable to the group of subjects with impaired renal function.

A. The body weight of each subject will be within ±15kg of the mean body weight of the severe renal impairment group (Cohort 2).
B. The age of each subject will be within ±10 years of the mean age of the severe renal impairment group (Cohort 2).
C. Attempts will be made to ensure that the male-to-female distribution in Cohort 1 is comparable to that in Cohort 2; cohorts cannot comprise entirely of any one gender
D. Other demographic characteristics, such as race and ethnicity, matched as closely as possible to the renal impairment cohort

5.1.3. Additional Inclusion Criteria for Subjects with Impaired Renal Function (Cohort 2, Cohort 3 [if applicable] and Cohort 4 [if applicable])

1. Good general health commensurate with the population with chronic kidney disease (renal impairment). "Health" is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, measurement of heart rate and 12-lead ECG as well as clinical laboratory tests (except serum creatinine and eGFR). Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease and other common co-morbidities in this population are possible exemptions, as long as, in the opinion of the investigator, the subject is medically stable, is on a stable drug regimen and can abide by the meals and dietary restrictions.
2. Meet the following eGFR criteria during the screening period based on the CKD-EPI equation:
   A. Severe renal impairment: eGFR < 30 mL/min/1.73m^2, but not requiring hemodialysis.
   B. Moderate renal impairment (Part 2 only): 30 mL/min/1.73m^2 ≤ eGFR < 60 mL/min/1.73m^2
   C. Mild renal impairment (Part 2 only): 60 mL/min/1.73m^2 ≤ eGFR < 90 mL/min/1.73m^2
   D. The difference of eGFR values obtained from the two screening visits should not be more than 25%
3. Any form of renal impairment except acute nephritic syndrome (subjects with history of previous nephritic syndrome but in remission can be included).
4. Stable drug regimen, which means no change in medication within 3 months prior to the dose of IP, for the management of individual subject's medical history; on a case-by-case basis, with input from the sponsor and medical monitor; subjects receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control.

5.2. Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in the study:

5.2.1. All Subjects

1. Renal transplant recipients or subjects requiring hemodialysis and peritoneal dialysis
2. Subject with a history or presence of any psychiatric disorder that, in the opinion of the Investigator, might confound the results of the study or pose additional risk in administering the IP to the subject
3. Has participated in an interventional clinical trial (investigational or marketed product) within 1 month of screening or 5 half-lives of the drug under investigation (whichever comes first), or plans to participate in another clinical trial
4. Subject with a history of any serious adverse events, hypersensitivity reactions, or intolerance to IP components
5. Subject who has any clinically significant history of allergic conditions (including drug allergies, asthma, eczema, or anaphylactic reactions, but excluding treatment not required, asymptomatic, seasonal allergies) prior to IP administration
6. Subject with a history of any major surgery within 6 months prior to the Screening visit
7. Subject with symptomatic heart failure (New York Heart Association class III or IV))
8. Subjects with clinically significant infections within the past 30 days those requiring hospitalization, or as judged by the Investigator
9. Evidence of any viral (including COVID-19), bacterial (including upper respiratory infection), or fungal (noncutaneous) infection within 1 week prior to the Screening visit
10. History of known colon polyps (if resected, the subject can be allowed to participate in the study) or family history of familial adenomatous polyposis
11. 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)
12. Subject with the existence of any surgical or medical condition that, in the judgment of the Investigator, might interfere with the absorption, distribution, metabolism or excretion of the IP
13. Any clinically significant abnormality at screening identified on ECG that in the opinion of the investigator would affect the subject's ability to participate in the trial or cardiac arrhythmia requiring any treatment among medical or surgical treatment, device implantation and catheter ablation within 6 months prior to screening
14. Subject who has done a full blood donation within 60 days before the Screening visit, who has done apheresis within 1 month before the Screening visit or who has received blood products
15. Subject who has a history of alcohol, illicit drug or recreational drug abuse as judged by the Investigator within 6 weeks prior to the Screening visit
16. Subject who has a positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids) at the Screening visit or on Day -1, except for prescribed medications as judged by the Investigator

17. 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 CRU
18. Subject who is unwilling to abstain from vigorous exercise from 48 hours prior to admission until the Follow-up visit
19. 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
20. Subject who is deemed by the Investigator to be inappropriate in conducting the clinical study

5.2.2. Additional exclusion Criteria for Subjects with Normal Renal Function (Cohort 1)

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding treatment not required, asymptomatic, seasonal allergies at the time of dosing).
2. Subject who has a mean BP ≥ 140mmHg (systolic) or ≥ 90mmHg (diastolic). After at least 5 minutes of supine rest, measurements will be taken for 2 consecutive times at least 2 minutes apart. If mean of the 2 BP is ≥ 140mmHg (systolic) or ≥ 90mmHg (diastolic), the BP should be repeated 1 more time and the average of the 3 BP values should be used to determine the subject's eligibility.
3. Subject who has a baseline corrected QT interval using the Fridericia formula QTcF >450 msec in males or QTcF > 470 msec in females

5.2.3. Additional Exclusion Criteria for Subjects with Impaired Renal Function (Cohort 2, Cohort 3 [if applicable] and Cohort 4 [if applicable])

1. Subject with clinically significant active diseases that may affect the safety of the subject or that may affect the pharmacokinetics of HM15912 (including drug allergies, but excluding treatment not required, asymptomatic, seasonal allergies at time of dosing). Subjects with any significant hepatic, cardiac, or pulmonary disease or subjects who are clinically nephrotic. Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease, etc. is not cause for exclusion as long as the subject is medically stable and any drugs that are administered for these conditions are not expected to interfere with the PK of HM15912.
2. Subject who has a mean BP ≥ 180 mm Hg (systolic) or ≥ 120 mm Hg (diastolic) After at least 5minutes of supine rest, measurements will be taken for 2 consecutive times at least 2 minutes apart. If mean of the 2 BP is ≥ 180mm Hg (systolic) or ≥ 120mmHg

(diastolic), the BP should be repeated 1 more time and the average of the 3 BP values should be used to determine the subject's eligibility.

3. Subject who has a baseline corrected QT interval using the Fridericia formula QTcF > 480 msec

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

1. Abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.
2. Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study intervention until after the final dose.
3. Water consumption will also be limited for 1 hour before dosing and for approximately 2 hours after dosing, after which time, water is allowed ad libitum.

5.3.2. Caffeine, Alcohol, and Tobacco

1. Abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.
2. Abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.
3. Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

5.3.3. Activity

Subjects will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Subjects should refrain from unusual physical training before participating in the study and maintain usual lifestyle during study participation. 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., watching television, reading).

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. If a subject does not meet all inclusion criteria or meets one or more exclusion criterion, the subject may rescreen for the study once after discussion with the investigator and medical monitor. In the event that the subject is rescreened, a new informed consent form (ICF) must be signed, a new screening number assigned, and all screening procedures repeated.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), or medical device(s) intended to be administered to a study subject according to the study protocol.

6.1. Study Drug Administered

The study drug HM15912 is a chemical conjugate of a GLP-2 analog and a human IgG4 Fc fragment linked via a flexible bifunctional polyethylene glycol linker. Details of investigational product are provided in Table 6.

Table 6. Study Drug (HM15912)

Investigational Product	HM15912
Type	Drug
Dose Formulation	Injection
Identity of Study Drug	HM15912 will be provided as a sterile, clear, and colorless solution and free of visible particles in prefilled syringe (PFS). The concentration of HM15912 is 125 mg/mL as protein and the charged volume is 0.55 mL including 0.05 mL overfill. The needle is covered with a needle shield.
Dosage Level(s)	0.5mg/kg, once
Route of Administration	Subcutaneous
Site of Administration	Abdominal wall
Use	Experimental
Sourcing	HM15912 will be manufactured and supplied by Hanmi Pharm. Co., Ltd. The sponsor should pack the study drug so that it is not contaminated or deteriorated during transportation or storage.
Packaging and Labeling	The study drug will be labeled and packaged according to local legal requirement and applicable health authority requirements.

6.2. Preparation/Handling/Storage/Accountability

1. All supplies of study drug must be stored in accordance with the manufacturer's instructions, refrigerated between 2℃ and 8℃, and protected from light (i.e., kept in the carton until ready for use). Avoid shaking HM15912 syringes during storage and handling. The instructions of how to proceed in case temperature deviations are observed (i.e., excursions above or below the allowed temperature range) are provided in the Pharmacy Manual.
2. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
3. Only subjects enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
5. Further guidance and information for the destruction and final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study.

6.4. Study Drug Compliance

Subjects will be administered study drug at the study center by the investigator or trained, qualified personnel designated by the principal investigator, under medical supervision at a scheduled timepoint. The date and time of the dose administered will be recorded in the source documents and recorded in the electronic case report form (eCRF). Deviation from the prescribed dosage regimen or planned dosing procedures should be recorded in the eCRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency and route of administration

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Subjects must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the study drug administration until Day 29, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Since the mechanism of action of study drug may increase absorption of orally administered drugs (e.g., motility medications, warfarin, benzodiazepines, phenothiazines, and thyroid medications), consideration is advised when modifying concomitant oral medication regimens.

Down-titration of concomitant medications should be considered when drugs, including those with a narrow therapeutic range or those requiring titration, are given at dosages that are higher than usual. Investigators should monitor all subjects carefully, since some of them have not previously been treated with a GLP-2 analog.

The GLP-1, other GLP-2 analogs (teduglutide or similar drug), and DPP-4 inhibitors are not allowed to be used by the subjects during the course of the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required.

6.5.1. Subjects with Normal Renal Function (Cohort 1)

In general, subjects will abstain from all concomitant treatments (prescription or over-the-counter [OTC] medications) as described in the Exclusion Criteria section of the protocol, except for the treatment of AEs.

Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis after approval by the sponsor or medical monitor.

6.5.2. Subjects with Impaired Renal Function (Cohort 2, Cohort 3 [if applicable] and Cohort 4 [if applicable])

Subjects are permitted to be on stable doses of background medications (including herbal supplements) if they are considered necessary for the welfare of the study subjects (i.e., standard therapy for the underlying disease), are not contraindicated with the study drug and are unlikely to interfere with the PK of the study drug. Whenever possible, attempts must be made to not alter the doses and regimens of the concomitant medications after Day 1 and until the end of study.

6.6. Intervention After the End of the Study

No interventions are planned after the end of the study.

7. Discontinuation of Study Intervention and Subject Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a subject to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the subject will remain in the study to be evaluated for AEs. See the Schedule of assessments (SoA) (Section 1.2) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

As any new study drug may have unexpected AEs, the following potential toxicities for HM15912 should be considered while making a decision to put the study drug on temporary hold or permanently discontinue. The details on grading and management for these toxicities are provided in Appendix 5.

- cardiovascular toxicity
- rash/inflammatory dermatitis and other skin disorders
- liver toxicity
- gastrointestinal events

Other reasons for discontinuation of study drug include the following:

- subject request
- safety concern
- pregnancy
- lost to follow up
- death
- decision by sponsor or investigator
- protocol-specified criteria

7.2. Subject Discontinuation/Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.2). See SoA (Section 1.2) for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed.

- At the early discontinuation visit, every effort must be made to complete scheduled assessments. However, lack of completion of all or any of the early discontinuation/withdrawal procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.
- The subject will be permanently discontinued both from the study intervention and from the study at that time.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Study Subject Replacement

- For both Parts 1 and 2, subjects who withdraw from the study for non-safety related reasons and who are considered to be non-evaluable with respect to the primary objective may be replaced at the discretion of the sponsor but the maximum number of meaningfully evaluable patients will be not more than planned 8.

7.4. Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with medical monitor or the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.2).
- The maximum amount of blood collected from each subject over the duration of the study will be in line with local regulations. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Efficacy is not assessed in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.2). All clinically significant abnormalities from the safety assessments will be recorded as AEs.

8.2.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of general appearance Skin, Head, Ears, Eyes, Nose and throat, Cardiovascular, Respiratory, Gastrointestinal and Neurological, Lymph nodes, Extremities, Musculoskeletal and Psychiatric systems.
- A brief physical examination will include, at a minimum, assessments of the skin, respiratory, cardiovascular system, and abdomen (liver and spleen).
- Height, Weight and BMI will also be measured according to the SoA (Section 1.2). And BMI will be calculated using Height assessed at the screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Tympanic body temperature, heart rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and heart rate will be measured after the subject has been lying down or sitting to rest for ≥ 5 minutes in a quiet setting without distractions. Blood pressure and heart rate will be measured at 2 consecutive times at least 2 minutes apart. Each measurement and the mean value will be recorded on the eCRF. Completely automated devices will be used. Manual techniques will be used only if an automated device is not available.

8.2.3. Electrocardiograms

- A 12 lead ECG will be obtained at scheduled timepoints in the SoA (Section 1.2) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Additional ECGs will be performed for cause as needed to evaluate AEs.
- The 12-lead ECGs will be performed after the subject has been resting supine for ≥ 5 minutes.
- A triplicate 12-lead ECGs will be performed at screening period and Day1. At all other times, however, single 12-lead ECGs will be performed as outlined in the SoA (Section 1.2).
- Limited to Day 1, ECGs will be performed at predose and at 4 hours postdose, and a ±30-minute assessment window is allowed for measurement 4 hours postdose.
- The 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.
- Investigator's assessment of clinical significance ('abnormal, not clinically significant' or 'abnormal, clinically significant') will be recorded in the eCRF. Centralized ECG vendor will be used for ECG measurement and independent reading.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.2) for the timing and frequency. Blood sample collection, processing, and shipping details will be outlined in a separate laboratory manual.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or up to last follow-up visit should be repeated until the values

return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.2).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded as narration in the eCRF.

8.2.5. Injection Site Assessment

Injection site assessments will be performed at the timepoints specified in the SoA (Section 1.2).

- After administration of study drug, the injection site will be marked with a pen. The local reaction from the injection site will be evaluated quantitatively using a Draize scale or similar scale. If an injection site reaction like pain on palpation, itching, erythema, edema, induration is observed, it must be recorded as an AE.
- 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. The diameter of the affected area will be measured with a paper measuring tape in centimeters and the condition of the injection site will be recorded. Digital photography will be used to document all positive injection site reactions.

- 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.

8.3. Adverse Events and Serious Adverse Events

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AE and SAEs will be collected from the signing of the ICF until the last visit at the time points specified in the SoA (Section 1.2).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 10.3.

The Investigator must record follow-up information. Follow-up information is reported in the eCRF as with initial AE/SAEs. Follow-up questions to Investigators regarding SAEs are queried directly to the Investigator.

Follow-up information must be reported according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the events is "recovered/resolved", "recovered/resolved with sequelae", or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer, or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the Investigator to recover.

The SAE follow-up information should only include new (e.g., corrections or additional) information and must be reported **within 24 hours** of receipt of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs**: Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved", or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer, or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome of "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when subject has completed the follow-up period and is expected by the Investigator to recover.

If a potential hypersensitivity reaction is observed, additional blood samples may be required to further characterize the potential hypersensitivity reaction. If anaphylactic shock is suspected, blood samples may be taken for the measurement of tryptase. In this case, a blood sample should be taken 3 to 4 hours after the event and again approximately 1 to 2 weeks later to determine tryptase baseline levels. In addition, assessments for elevated histamine levels may be considered.

The Investigator must ensure that the worst-case severity and seriousness of an event is kept throughout the study, i.e., if the severity of an AE changes over time then it should be reported as a single AE with the most severity. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

If an AE is resolved and reappears later then it should be reported as a new AE.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study drug under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to

safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of study drug and until last follow-up visit. All subjects must be instructed to notify the Investigator immediately if she or his partner becomes pregnant or suspects to be pregnant during the study.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE form.

8.3.6. Cardiovascular and Death Events

The guidance for AEs indicating cardiovascular toxicity is provided in Appendix 5.

8.3.7. Adverse Events of Special Interest

In this study, the following events are to be regarded as adverse events of special interest (AESIs) should they occur: neoplasms (malignant and benign), suspicion of liver injury, and cholecystitis.

If the event is reported as an SAE, the timelines for SAE reporting apply. If the event is reported as non-serious AE, it should be reported on the dedicated eCRF page within 24 hours of Investigator's first knowledge.

The event-specific information that needs to be captured in addition to the standard AE information is presented in the subsections below.

8.3.7.1. Neoplasms

Information on histopathology (date of examination and results), imaging (if imaging is performed), TNM staging, history of cancer (for the subject and the subject's family), treatment

received for this event, and an event narrative. Copies of images (if performed) could be stored at each site. A retrospective imaging review may be performed if deemed necessary.

8.3.7.2. Suspicion of Liver Injury

Suspicion of liver injury is defined as:

- ALT or AST >3 times baseline value lasting more than 2 weeks*, or
- ALT or AST >5 × upper limit of normal (ULN) and total bilirubin >2 × ULN*, or
- ALT or AST >5 × ULN and International normalized ratio (INR) >1.5*, or
- ALT or AST >5 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)*.

  * where no other etiology exists

If liver injury is suspected, the tests should be repeated in 48 to 72 hours for evaluation of the event course/confirmation. Additional information will need to be provided by the site, e.g., physical examination, information on alcohol consumption, concomitant therapy (including herbals).

The narrative of the event should include:

- Clinical signs and symptoms and how they developed over time. Aspects such as abdominal pain, nausea, vomiting, jaundice, fever, rash, abdominal tenderness, hepatomegaly, splenomegaly, BP, peripheral edema, jugular venous distension, signs of ascites, and recent weight gain should be considered and described.
- Information on relevant medical history, alcohol consumption, and relevant concomitant therapy (including herbals).
- Laboratory tests (at local laboratory, if needed): as a minimum ALT, AST, bilirubin (direct and total) and INR. Other tests may be warranted as clinically indicated.
- Imaging diagnostic (ultrasound/CT scan/MRI/other imaging modality). Copies of images (if performed) should be stored at each site.
- Biopsy results (if performed).

8.3.7.3. Cholecystitis

The narrative of the event should include

- Clinical signs and symptoms and how they developed over time. Aspects such pain (character of the pain including the anatomical region [e.g. sudden, after a large meal, in upper right or center abdomen] +/- irradiating pain to right shoulder or back), tenderness of the abdomen, nausea, vomiting, and fever should be considered and described.
- Information on relevant medical history, alcohol consumption, and relevant concomitant therapy (including herbals).

- Laboratory tests (at local laboratory, if needed): liver function tests, including ALT, AST, bilirubin, and ALP. Other tests may be warranted as clinically indicated.
- Imaging diagnostic (ultrasound/ CT scan/MRI/other imaging modality). Details such as the presence of gall bladder stones and common bile duct diameter should be reported, if available.

8.4. Treatment of Overdose

HM15912 will be administered once at the clinic, thus limiting the risk of overdose. For this study, any dose of study drug greater than the recommended dose for the assigned cohort will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose. Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. No antidotes are available.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until study drug can no longer be detected systemically.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

8.5. Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of study drug as specified in the Table 2.
- If PK data are available indicating that other timepoints would be more advantageous, the timing of sample collection for PK analysis may be adjusted between cohorts. Details of the collection, handling, and transport of blood samples are separately summarized in the laboratory manual. The blood for the sample will be processed and the serum analyzed using a fully validated method.
- The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of study drug serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Immunogenicity Assessments

Antibodies to study drug including ADAs, Neutralizing antibodies (Nabs), and anti-PEG antibodies will be evaluated in serum samples collected from all subjects according to the SoA (Section 1.2). Additionally, serum samples may be collected at the final visit from subjects who discontinued study drug or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee. Detailed sampling method and volume will be indicated in separate documents (i.e., Lab Procedure Manual).

The serum samples will be analyzed using a tiered approach (screening, confirmation, and titration of confirmed ADA positive samples), followed by characterization of ADA-positive samples for in vitro HM15912-neutralizing potential and cross-reactivity to the major metabolite (HM15912) and GLP-2. Results will not be revealed to the sites.

The detection and characterization of antibodies to study drug will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to study drug will also be evaluated for study drug serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of study drug.

Samples may be stored for a maximum of 5 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to study drug. Sponsor could destroy stored sample before the 5 years without notification if there is no longer need to store.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The study is not powered for formal hypothesis testing. As such there are no hypotheses for testing.

9.2. Sample Size Determination

The planned sample size of 8 subjects for each cohort is selected to characterize the effect of renal impairment on the PK of HM15912 based on FDA and EMA guideline rather than calculated with consideration of statistical requirements. With 8 subjects for each cohort (renal impairment cohort and normal renal function cohort), half width of two-sided 90% confidence interval of natural log scaled $AUC_{0-\infty}$ difference between two cohorts is [redacted]

As stated in the study design part, approximately 16 subjects will be enrolled in Part 1 (8 subjects with severe renal impairment and approximately 8 subjects with normal renal function). If Part 2 is conducted, 8 subjects with moderate renal impairment and 8 subjects with mild renal impairment will be enrolled.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Safety Population	All subjects who received any amount of HM15912. All analyses other than that specified will be performed based on safety population.
PK Population	All subjects who have at least one evaluable HM15912 serum concentration after receiving any amount of HM15912 without important protocol deviations or events (i.e. significantly affect the PK of study drug). PK parameter analyses will be conducted with PK population.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary/exploratory endpoints. Any changes from the analyses planned in SAP will be detailed in the Clinical Study Report (CSR).

9.4.1. General considerations

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation (SD), minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints unless other specified. Where appropriately, change from baseline will also be summarized. Baseline values will be defined as the most recent non-missing measurements collected prior to the first study drug administration. The data summaries will be presented by cohort. Individual subject data used for the analysis will be listed.

Pharmacokinetic parameter will be calculated using WinNonlin® or any available softwarefor the pharmacokinetic analysis, and the other analysis will be performed using SAS version 9.4 (or above).

9.4.2. Pharmacokinetic Analyses

Summary of PK concentration and PK parameter will be presented for PK population, and all available individual data will be listed for safety population.

PK concentration will be summarized using mean, SD, min, median, max, geometric mean, and geometric CV (%) by planned timepoint, and the concentration-time profiles will be depicted appropriately.

PK parameters of HM15912 following single dose administration will be derived from the concentration-time profiles as detailed below tables. PK parameters will be derived by non-compartmental analysis based on actual PK sampling times. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Primary endpoint

Parameter	Description
$AUC_{0-\infty}$ *	Area under the serum concentration-time profile from time zero extrapolated to infinite time.
C_{max}	Maximum serum concentration

* As data permit

Exploratory endpoint

Parameter	Description
t_{max}	Time to maximum serum concentration
$t_{1/2}$ *	Elimination half-life

Vd/F *	Volume of distribution
CL/F *	Clearance
λ_z *	First order rate constant associated with the terminal (log-linear) portion of the curve
AUC_{last}	Area under the concentration-time curve from time zero to the last observable concentration
$AUC_{\%Extrap}$	Percentage of $AUC_{0-\infty}$ due to extrapolation from T_{last} to infinity

* As data permit

After Part 1, PK parameter of HM15912 from severe renal impairment group (Cohort 2) will be estimated and compared to control group (Cohort 1). A one-way analysis of variance (ANOVA) will be used to compare log transformed PK parameter. The estimates of mean difference and corresponding 90% confidence intervals (CI), as well as each exponentiation of estimates will be presented to provide the estimates of geometric mean ratio. After statistical or clinical evaluation of results from Part 1, whether to proceed to Part 2 will be further discussed.

If Part 2 is conducted, same analysis with Part 1 will be implemented to compare of each moderate (Cohort 3) or mild (Cohort 4) renal impairment subjects and normal renal function subjects in Cohort 1. In case the demographics of the moderate or mild renal impairment group compared to the normal renal function group are not within the criteria specified in the protocol, it will be considered to add that demographic information as a covariate of ANOVA. If needed, further evaluation to characterize the relationship between renal function and PK parameter will be explored.

9.4.3. Safety Analyses

All safety analyses will be performed in the safety population.

AE analyses will focus on TEAEs which are defined as any AE that begins, or worsens in severity on or after the date of first study drug administration until the last follow up visit. Incidence of TEAEs will be summarized using System Organ Class (SOC) and Preferred Term (PT) of MedDRA coding dictionary. Additional summary of TEAEs by maximum severity using NCI-CTCAE version 5.0 will also be presented. Incidence of treatment related AEs (TRAEs), AESIs, SAEs or TEAEs leading to death also be summarized respectively. Injection site reactions will be documented as AEs. Additional summary for the quantitative assessment will be provided. All AEs, including those occurred between informed consent and first study drug administration, will be provided in a listing.

The results of laboratory tests, vital signs and 12-lead ECG will be summarized descriptive statistics for the actual value and the change from baseline by planned time point. Frequency analyses also be performed as appropriately. If applicable, the shift tables for the investigator's

abnormality assessment between baseline and post-baseline will be present. Abnormal physical examination findings will be reported as a list.

Immunogenicity test results will be listed by subject and summarized.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study.

9.6. Data Monitoring Committee (DMC)

Not applicable.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the stud.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

After completion of the study, a clinical study report will be written by the sponsor following the guidance in ICH E3 and will be submitted in accordance with local regulations.

10.1.6. Data Quality Assurance

- All subject data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Current Food and Drug Administration guidelines require records to be retained for a period of 2 years following the date a marketing application is approved for the drug, for the indication for which it is being investigated. If no application is filed or if the application for the investigated indication is not approved, documents will be kept until 2 years after the investigation is discontinued and the FDA is notified. It is the sponsor's responsibility to inform the contract research organization as to when essential documents are no longer needed to be retained.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study drug administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study drug administration decision or response evaluation, the results must be entered as narration in the eCRF.
- The alcohol breath test will be performed according to the site's SOP at designated time points as specified in the SoA (Section 1.2)
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 7: Protocol-Required Safety Laboratory Assessments

Hematology	**Coagulation**	**Clinical Chemistry**	**Urinalysis**

• RBC count
• WBC count (with differential)
  ° Neutrophils
  ° Eosinophils
  ° Basophils
  ° Lymphocytes
  ° Monocytes
• Platelet count
• Hemoglobin
• Hematocrit
• RBC indices:
• MCV
• MCH
• %Reticulocytes
	• PT (INR)
	• aPTT
		• Fasting plasma glucose
		• BUN
		• Creatinine
		• Potassium
		• Sodium
		• AST
		• ALT
		• GGT
		• Alkaline phosphatase
		• Total and direct bilirubin
			• Specific gravity
			• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
			• Microscopic examination (if blood or protein is abnormal)
			• Pregnancy test

Additional Tests	• Immunogenicity (ADA, NAb, anti-PEG antibody)		

Other Screening Tests	• HbA1c • eGFR • Urine drug screen • Serum hCG pregnancy test • Serology (HIV antibody, HbsAg, and hepatitis C virus antibody)

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; HbsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PEG = polyethylene glycol; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical drug to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by regulatory authorities. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to regulatory authorities. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The CTCAE Version 5.0 Grades 1 through 5 are described below: • Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. • Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a]

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE.

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.Other measures to evaluate AEs and SAEs may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor's with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor via an Electronic Data Collection Tool (Primary method)

- The primary mechanism for reporting an SAE to sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in safety management plan.

SAE Reporting to Sponsor via Paper SAE form (Back-up method)

- Facsimile transmission of the paper SAE form is the preferred method to transmit this information to the medical monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the paper SAE form within the designated reporting time frames.
- Contacts for SAE reporting can be found in safety management plan.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as >52 years of age and no menses for 12 months or more and/or as follicle-stimulating hormone (FSH) level >30 mIU/mL (as measured at site) without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Females aged ≥12 years must have a negative urine/serum pregnancy test and must use an acceptable method of contraception, including abstinence, a barrier method (diaphragm or condom), Depo-Provera, or an oral contraceptive for the duration of the study

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

- Any post-study pregnancy related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study.

10.5. Appendix 5: Adverse Event Guidance

As any new study drug may have unexpected AEs, the following guidance is offered for potential toxicities for HM15912. The following diagnostic work-up and procedures are suggested actions and should be tailored to the clinical presentation as assessed by the investigator.

1. Cardiovascular Toxicity

Definitions:

Signs and symptoms may include the following: chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, and fatigue.

Diagnostic workup:

At baseline:

- Electrocardiogram
- Cardiac biomarkers (creatine kinase-MB and troponin-I)

Depending on presentation:

- Inflammatory biomarkers (erythrocyte sedimentation rate, C-reactive protein, white blood cell count)
- O_2 saturation
- B-type natriuretic peptide
- Emergency room/hospital transfer
- Cardiology consultation
- Chest x-ray

Additional testing to be guided by cardiology and may include the following:

- Echocardiography
- Stress test
- Cardiac catheterization
- Cardiac magnetic resonance imaging (MRI)

<table>
<tr><th>Grading[a]</th><th>Management</th></tr>
<tr><td>G1: Asymptomatic abnormal cardiac biomarker testing, including abnormal ECG</td><td rowspan="3">All grades (G1-G4) warrant workup and intervention given for potential cardiac compromise.
Please consider the following:
• Hold therapy and permanently discontinue after G1
• Management of cardiac symptoms according to ACC/AHA guidelines
• Transfer subject to the emergency room at the hospital for further evaluation and management for any grade >G1
• Cardiology consultation</td></tr>
<tr><td>G2: Mild symptoms consistent with cardiotoxicity with or without abnormal cardiac biomarkers</td></tr>
<tr><td>G3: Moderate symptoms consistent with cardiotoxicity and/or clinically significant abnormal cardiac biomarkers</td></tr>
<tr><td>G4: Moderate to severe decompensation, intravenous medication or intervention required, life-threatening conditions</td><td></td></tr>
<tr><td colspan="2">Qualifying statement: Treatment recommendations are based on local standards of care and the life-threatening nature of cardiovascular complications. Holding therapy is recommended for complication grades >G2. The appropriateness of re-challenging remains unknown.</td></tr>
</table>

Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; G = grade.
[a] Not associated with CTCAE grading system

2. Rash/Inflammatory Dermatitis and Other Skin Disorders

Definitions:

- Erythema multiforme major and minor (a targetoid reaction in the skin and mucous membranes, usually triggered by infections such as herpes simplex virus, but can be associated with an immune-related drug eruption; if progresses to erythema multiforme major, it can be a harbinger of severe cutaneous adverse reaction such as Stevens–Johnson syndrome)
- Lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen planus)
- Eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection)
- Psoriasiform (resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis)
- Morbilliform (a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as 'maculopapular' and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia
- Palmoplantar erythrodysaesthesia (hand-foot syndrome) (redness, numbness/burning/itching and superficial desquamation of the palms and soles)
- Neutrophilic dermatoses (eg, sweet's syndrome)
- Others

Diagnostic workup for skin disorders above and others which are considered to be possibly study drug-related:

- Pertinent history and physical examination
- Rule out any other etiology for the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder
- If needed, consider a checkup including a blood cell count, liver, and kidney tests.
- Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis:
  - a screening antinuclear antibody test, SSA/Anti-Ro, SS-B/Anti-La
  - if predominantly photodistributed/photosensitivity, antihistone, ds-DNA and other relevant serologies
  - consider expanding serologic studies or diagnostic work up if other autoimmune conditions are considered based on signs, symptoms
- Dermatology consultation with or without skin biopsy

- Consider clinical monitoring with use of serial clinical photography, if IRB approved and subject has consented
- Review full list of subject medications to rule out other drug-induced cause for skin lesion

Grading Grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on body surface area, tolerability, morbidity, and duration.	**Management**
G1: Symptoms do not affect the quality of life or are controlled with topical regimen and/or oral antipruritics	• Consider continuing therapy for mild localized reaction (eg, injection site erythema) • Consider treatment with topical emollients and/or mild-moderate potency topical corticosteroids • Counsel subjects to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	• Dermatology consultation for proper management plan • Consider holding therapy and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to G1. • Consider initiating prednisone (or equivalent) at 0.5 to 1 mg/kg/day and tapering over at 4 weeks • In addition, treat with topical emollients, oral antihistamines, and medium-to-high potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G2 dermatitis.	• Hold the therapy and consult with dermatology to determine appropriateness of management plan and resuming • Initiate oral prednisone or equivalent (0.5 to 1 mg/kg/day) and tapering over at least 4 weeks • Treat with topical emollients, oral antihistamines, and high potency topical corticosteroids

Page 1 of 2

Footnotes are provided on the last page of the table.

Grading Grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on body surface area, tolerability, morbidity, and duration.	**Management**
G4: All severe rashes not manageable with prior intervention	• Immediately hold therapy and urgently admit the subject with consultation to a dermatology specialist for proper management of skin lesion • For resuming the therapy upon the resolution of skin toxicity, the dermatologic consultation should be conducted when the corticosteroids are reduced to prednisone (or equivalent) 10 mg or less • Systemic steroids: intravenous (methyl) prednisolone (or equivalent) at a dose of 1 to 2 mg/kg with slow tapering when the toxicity resolves • Monitor closely for progression to severe cutaneous adverse reaction

Abbreviation: AE = adverse event.

3. Liver Toxicity Monitoring Guideline

Following evaluations should be undertaken if on treatment liver function tests (LFT) increase to either #1 or #2 below:

1. If baseline LFTs are normal, further evaluation is needed if ALT or AST >3 x ULN
2. If baseline LFTs are abnormal, further evaluation is needed if ALT or AST >2 x ULN

Evaluations to be performed if trigger ALT/AST reached:

Step 1: Repeat and confirm trigger ALT/AST elevation

Step 2: If elevation confirmed, consider below in addition to hepatology/GI referral:

1. Take history to evaluate for intercurrent infection/illness
2. Obtain a history of new medications, new supplements, current alcohol use, recreational drug use, or new special diet started
3. Obtain history of exposure to environmental chemical agents
4. Rule out new liver diseases or biliary disease
    a) Acute hepatitis panel (HAV IgM, hepatitis B surface antigen, core IgM, HCV Ab or HCV RNA [better])
    b) Antinuclear antibody, anti-smooth muscle antibody
    c) Iron, ferritin
    d) Abdominal ultrasound
    e) Gamma-glutamyl transferase
    f) Alcohol level
    g) Drug screen
5. Monitor weekly LFTs until levels fall to baseline or new stable level is established
6. Study drug status should be discussed with medical monitor

Immediate study drug discontinuation

1. If normal ALT/AST
    a) ALT or AST >5 x ULN
    b) ALT or AST >3 x ULN + total bilirubin >2 x ULN
2. If abnormal baseline ALT/AST
    a) ALT or AST >5 x baseline
    b) ALT or AST >3 baseline and bilirubin >2 x baseline
    c) Absolute ALT or AST >500

4. Gastrointestinal Events

Definition:

Nausea and vomiting are anticipated AEs with this protocol. The initial assessment needs to include consideration of other differentials including pancreatitis and cholelithiasis. Laboratory assessments of amylase, lipase, and LFTs (ALT, AST, alkaline phosphatase, and bilirubin) or imaging (ultrasound, computed tomography, or MRI) should be considered and pursued if indicated.

Severity of symptoms should be assessed as following:

Grading (Not associated with CTCAE grading system)	**Management**
G1: Mild symptoms that do not interfere with quality of life	• No intervention
G2: Mild-to-moderate symptoms that may need intervention based on investigator	• Patient observation • Consider initiating antiemetic medication
G3: Moderate–to-severe symptoms that need medical intervention	• Consider holding therapy: resume therapy only if symptoms are resolved to tolerate the therapy • Treatment with antiemetic medication and intravenous fluid as needed • Treat with parenteral nutrition if no oral intake sustained
G4: Life-threatening symptoms	• Immediately discontinue therapy • Systemic intravenous fluids • Treat with antiemetic medication as indicated • Treat with parenteral nutrition • Should admit subject immediately with an urgent consult

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

10.6. Appendix 6: Abbreviations

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
Anti-PEG	Anti-polyethylene glycol
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve extrapolated to infinity
AUC_{last}	Area under the concentration-time curve from time zero to the last observable concentration
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulations
CI	Confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
C_{max}	Maximum serum concentration
CKD-EPI	Chronic kidney disease-epidemiology collaboration
CRU	Clinical research unit
CSR	Clinical Study Report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram

Abbreviation or Specialist Term	**Explanation**
EMA	European Medicines Agency
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GLP-1	Glucagon-like peptide 1
GLP-2	Glucagon-like peptide 2
GMR	Geometric mean ratio
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
NAb	Neutralizing antibody
NOAEL	No observed adverse effect level
PD	Pharmacodynamic

Abbreviation or Specialist Term	**Explanation**
PEG	Polyethylene glycol
PK	Pharmacokinetic
PN/IV	Parenteral nutrition/Intravenous fluid
PT	Prothrombin time
RR	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBS	Short bowel syndrome
SBS-IF	Short bowel syndrome-associated intestinal failure
SC	Subcutaneous
SD	Standard deviation
SoA	Schedule of assessments
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment emergent AE
TRAE	Treatment related AE
t_{max}	time to maximum serum concentration
$t_{1/2}$	elimination half-life
ULN	Upper limit of normal
Vd	volume of distribution
WOCBP	Woman of Childbearing Potential

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